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Cambridge Structural Database as a tool for studies of general structural features of organic molecular crystals

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Abstract. The review surveys and generalises data on the use of the Cambridge Structural Database (CSD) for studying and revealing general structural features of organic molecular crystals. It is demonstrated that software and facilities of the CSD allow one to test the applicability of a number of known concepts of organic crystal chemistry (the principle of close packing, the frequency of occurrence of space groups, the preferred formation of centrosymmetrical molecular crystals, *etc.*) on the basis of abundant statistical data. Examples of the use of the Cambridge Structural Database in engineering of molecular crystals and in the systematic search for compounds with specified properties are given. The bibliography includes 122 references.

I. Introduction

Presently, the Cambridge Structural Database (CSD) is one of the most powerful information databases, which contains exhaustive data (atomic coordinates, molecular geometry and crystal symmetry) on crystal and molecular structures of organic, bioorganic, organoelement and organometallic compounds and to a large extent coordination compounds which have been studied by X-ray diffraction and/or neutron diffraction analysis. (The term organic crystals is used to denote crystals containing at least one 'organic' carbon atom, *i.e.*, that involved in formation of C–C or C–H bonds.) Data on crystals which can hardly be called true organic molecular crystals (for example, data on inorganic alkylammonium salts, *etc.*) are also included in the CSD.

Therefore, the CSD involves information on diversified organic crystals. Hence, the correct choice and rejection of compounds in the search for structural regularities in series of related and structurally similar crystals is one of the most important problems in the use of the CSD. Presently, the CSD

contains data on 181 000 crystal structures and the body of information in the CSD increases annually by 7000–8000 new structures. Clearly, the availability of the sizable database gave impetus to a search for various special structural features of particular classes of compounds as well as to a search for general regularities of organic crystal structures with the use of the CSD on the basis of statistically reliable analysis of large samples. The first line of investigation began actually after the first CSD release has appeared. Studies of the general regularities of organic crystal structures using statistical analysis became possible only with the appearance of computer versions of the CSD and with the development of special programmes for statistical treatment of a large body of data.

There are two approaches to the elucidation of the general rules and regularities of organisation of crystalline solids from isolated structural elements (atoms, molecules and their associates and ions). The first approach involves the use of computational methods, in particular, those used for *a priori* prediction of new crystal structures. In recent years, much progress in this field has been achieved.^{1–4} The second approach is based on the correct statistical analysis of numerous crystal-structural data accumulated in information databases. We dwell on the results and prospects of the second approach with the use of modern tools and facilities of the CSD.

Useful new crystal-chemical information can be obtained by performing correct systematic statistical analysis of the large available body of experimental structural data. This idea appeared rather long ago. Thus many chemists and crystal chemists still use the values of the van der Waals radii which were determined by Pauling⁵ and Bondi⁶ based on the analysis of scarce crystal-structural and other (in particular, gas-kinetic) data available at that time. The fundamental principles of structures of organic molecular crystals (among them, the principle of close packing), which have been explicitly stated for the first time by Kitaigorodskii,⁷ were also established on the basis of relatively scarce statistical data. In the 1970's and in the early 1980's, these systematic studies were believed to be very promising. However, as the experimental published data on crystal structures were accumulated, these investigations became more complicated. The major obstacle (which is believed to be insurmountable) lay in the fact that non-computerised search and processing of abundant numerical data were extremely tedious procedures.

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It is worth noting that since the early days of crystallography (crystal chemistry), the researchers involved in this field have realised that data obtained in their studies are of fundamental importance and can have a wide use. Consequently, they were the first to systematically amass results of their studies. Thus as soon as 16 years after the development of the X-ray diffraction method, a beginning has been made in systematically reviewing X-ray structural data.⁸ In this country, results of X-ray diffraction studies of organic crystals were first surveyed by Struchkov and were reported by Kitaigorodskii⁷ in 1955. More recently, the well-known handbooks by Kitaigorodskii, Zorky and Belsky were issued.^{9,10} The complete bibliography concerning these sources was published by Watson.^{11,12}

First computer databases were compiled based on the available publications. Two of them, *viz.*, 'Powder Diffraction File'¹³ and 'NBS Crystal Data: Database Description and Applications'¹⁴ became available totally as a computer version. These banks contain exhaustive (from the chemical standpoint) information but do not include atomic coordinates and were primarily used (and are still used) for identification and comparative studies of unit cell parameters and crystal symmetry.

The compilation of structure databases which contain atomic coordinates along with crystallographic data, details of chemical structures and bibliographic description dates back to the mid-1960's. When creating these databases, one would have to process information from current publications and to collect data on structures which have been studied previously and which are scattered over numerous literature sources. Therefore, in the initial stage, priority was given to works on the development of software for collecting, testing, processing and depositing data. Subsequently, programmes were developed for the search, selection and statistical analysis of information as well as for the distribution of databases. Systematic statistical studies with the use of all the data accumulated in databases appeared only in the last decade.

Presently, information on virtually all types of chemical compounds can be found in four structure databases: the Cambridge Structural Database (University of Cambridge, UK) contains data on 181 000 structures, the Inorganic Crystal Structure Database (University of Bonn, Germany) contains data on 41 500 structures, the Metals Data File (National Research Council of Canada, Ottawa, Canada) contains data on more than 11 000 structures and the Protein Data Bank (Brookhaven National Laboratories, USA) contains data on more than 1500 structures.

Presently, the CSD¹⁵ is the biggest database. Using the information bases of the CSD, one can perform statistically reliable systematic studies of structural data. The knowledge of precise molecular geometry is necessary for the understanding of the nature of chemical bonds and chemical structures. Therefore, early studies were devoted to the determination of mean ('typical') values of bond lengths and bond angles in various classes of chemical compounds^{16,17} and the acquisition of data on structural features of particular fragments or classes of chemical compounds as a whole.^{18–20}

Systematic investigations into the mutual arrangement of molecules in crystals were begun with studies of geometrical characteristics of intermolecular interactions. In particular, statistical values of van der Waals atomic radii^{21,22} and geometrical characteristics of specific interactions (hydrogen bonds,^{23–27} and the CH...O(N), Hal...Hal and some other contacts^{28–33}) were determined.

More recently, with the increase in the size of the CSD and the perfection of software for correct selection and statistical analysis of results, some researchers formulated problems based on the belief that the CSD contains, in some form, information on general regularities of molecular crystal structures. In this respect, noteworthy is the paper by Motherwell³⁴ in which distributions of positions of geometrical centres in molecular crystals were analysed and the preference for the realisation of

the principle of close packing was statistically confirmed. Recently, some researchers have cast doubt on the firmness of this principle.³⁵ The doubts were substantiated by the fact that the principle of close packing should contradict a tendency of molecules to form strong intermolecular hydrogen bonds and by the fact that experimental crystal structures do not necessarily correspond to the calculated global energy minima.

The question of the frequency of occurrence of space groups has received the most study based on the CSD data. Numerous statistical studies were devoted to this problem.^{36–44} Admittedly, the most detailed investigations were carried out by Belsky⁴² and by Brock and Dunitz.⁴⁵ The considerable attention given to this problem is quite justified because many physical properties of crystals depend on the symmetry of the molecular arrangement and hence, the *a priori* estimation of the crystal symmetry is an important practical problem. For example, this is of importance in the design of materials with nonlinear-optical properties, which are constructed using organic chromophore molecules.^{46,47}

Often, in studies using the CSD researchers attempt to establish the reasons for which compounds crystallise preferentially in centrosymmetrical (achiral) space groups rather than restrict themselves to simple statement of the facts (for example, about the considerable predominance of racemic crystals.⁴⁸) Thus efforts to estimate the effect of molecular dipoles on the crystal packing were applied,⁴⁹ a comparative analysis of densities and stabilities of compounds that crystallise in both racemic and chiral space groups was carried out⁵⁰ and the correlations between densities, calculated packing energies and some thermodynamic properties of crystals were considered for pairs of polymorphic modifications existing at room temperature.³

In recent works devoted to analysis of the frequency of occurrence of space groups,⁴⁵ much attention was given to the number of formula units per asymmetric unit (Z'). Belsky and Zorky were the first to note the importance of the consideration of this parameter.^{51,52} Studies of crystals with $Z' > 1$ brought up many questions. For example: are conformations of independent molecules in the unit cell identical or not? Are independent molecules related by any symmetry transformations? What is meant by pseudosymmetry? How do pseudosymmetry elements and true symmetry of real crystals relate to each other? Do crystals with $Z' > 1$ possess any characteristic properties? Abrahams attempted to give the answer to the last question.⁵³ He suggested that if pseudosymmetry is present, phase transitions of the second kind can occur in crystals of a number of inorganic compounds as the temperature is increased.⁵³ This hypothesis provided the basis for the development of a procedure for the search for new potential ferroelectrics,⁵⁴ which is successfully used for predicting inorganic compounds with high-temperature phase transitions.⁵⁵

Interestingly, unit cells with $Z' > 1$ are more frequent in crystals containing molecules that can form stable associates through hydrogen bonds.⁵⁶ The occurrence of unit cells with $Z' > 1$ and the existence of pseudosymmetry are highly probable for compounds exhibiting liquid-crystal properties on melting.^{57–59}

The results of studies of characteristic types of supramolecular fragments (supramolecular synthons) that formed in crystals through the strongest nonbonded intermolecular interactions for molecules of similar types or for molecules containing similar chemical functional groups may be very useful in revealing general regularities of organisation of crystal structures.^{60–62} These studies fall within the realms of crystal engineering (a new intensively developing branch of science that appeared at the borderline between materials technology and crystal chemistry), which involves the development of procedures for the design of organic crystalline materials with predetermined properties. The crystal symmetry describes the topology of molecules in crystals and determines many physical properties of solids, namely, electrical, magnetic, linear-optical and nonlinear-optical properties, electronic and ionic conductivity, *etc.* Therefore, the current prime objective of crystal engineering is to reveal factors that

affect the formation of crystal structures with a particular molecular architecture, which causes the manifestation of a desirable physical property.

An important role of databases, in particular of the CSD, in the design of new materials was discussed in the review by Aakeroy.⁶³ It was noted that the development of software of the CSD (new algorithms and statistical and cluster analyses) and the incorporation (wherever possible) of a number of thermodynamic and/or other physicochemical characteristics of compounds into the CSD will favour the directed search and design of new compounds with preset properties.

Therefore, the use of the CSD has promise in the search for fundamental structural features of organic molecular crystals. However, it should be borne in mind that even very large statistical samples cannot assure automatically that statistically reliable characteristics and properties will be obtained without appropriate rejection and processing of the data. Therefore, when considering examples of the use of the CSD, we concentrated most attention on the analysis of schemes applied in the original publications cited for creating representative statistically significant samples. Modern versions of the CSD allow one to compile and reject particular data on the basis of a series of criteria and indications, each being a subject of special discussions in the literature.

The present review is the first attempt to consider the CSD as a tool in studying general structural regularities of organic molecular crystals.

II. Organisation and software of the Cambridge Structural Database

As has been mentioned above, the CSD contains results of complete three-dimensional X-ray and neutron diffraction studies of organic, bioorganic, organometallic and coordination compounds. The CSD is compiled by reviewing original publications in 1025 scientific journals and other sources (data as of 1988). Presently, the majority of crystal chemists and crystallographers as well as many chemists consistently use the above-mentioned databases in their routine work. For example, the 1998 version of the CSD is employed by researchers at about 40 scientific institutes of Russia and Newly Independent States of the Former Soviet Union. About 150 articles were devoted to the use of the CSD. The major principles of selection and systematic numerical analysis of information in crystallographic databases were considered and analysed in detail in one of the latest papers, namely, in the review by Allen⁶⁴ 'Crystallographic Data Bases: Samples and Analysis of Precise Structure Information from the Cambridge Structural Database'. Therefore, we mention only briefly the essentials of organisation and software of the CSD.

The use of the CSD requires special software, namely, the programme package developed for the search, selection of required data, analysis of geometrical parameters of molecules and crystal structures and their representation with the use of computer graphics tools. The search for the required information in the CSD is performed using the QUEST programme, which specifies the query. This query can be formulated in the form of three major packages, *viz.*, 1D, 2D and 3D.

A query specified by the QUEST1D option allows one to obtain bibliography, the name of a compound, the molecular formula or the amino acid sequence, unit cell parameters, the *R* factor and required comments (the presence of disorder, errors, *etc.*).

A query specified by the QUEST2D option allows one to obtain information on the atom and bond properties, the formal chemical type of the bond, tables of atom connectivities and the structural formula.

A query specified by the QUEST3D option allows one to obtain the description of a crystal structure, *i.e.*, the space group, symmetry operations, three-dimensional atomic coordinates,

crystallographic connectivity determined by the covalent radii and data on the correspondence between the 'crystallographic' and 'chemical' atoms from tables of connectivities of 2D diagrams.

Queries are specified with the use of special menus (BILD, SEARCH and QUEST). Information can be rejected by specifying a set of BITSCREEN indications.

The QUEST3D option compiles a data file FDAT from information selected according to the query. This file serves as an input file for the GSTAT(VISTA) and/or PLUTO programmes. The GSTAT programme was originally developed for calculations of intra- and intermolecular geometry and geometry of molecular fragments.⁶⁵ Presently, GSTAT is a programme package which allows one to analyse geometrical characteristics with the use of statistical and numerical methods.⁶⁶ The VISTA programme (graphical supplement to GSTAT) is destined mainly for numerical, statistical and graphical analysis of the geometrical information extracted from the CSD.

The PLUTO programme is applied not only by crystallographers but also by chemists. This programme is destined for the preparation of various graphical illustrations, including visualisation of both molecular structure and crystal packing based on three-dimensional coordinate data sets.

The most precise data in the CSD are used in the analysis of geometrical characteristics. In the simplest case, entries containing errors and disordered structures are rejected. The CSD contains two major parameters characterising the accuracy of the crystal structure, namely, the *R* factor and the *AS* parameter. The former characterises the overall discrepancy between the diffraction data and the crystal structure solved on the basis of these data. The latter characterises the average standard deviation of bond lengths. These parameters can be used both in QUEST (for preliminary rejection in the course of the search) and GSTAT (in statistical averaging).

Calculations of average molecular geometrical parameters used in statistical analysis were discussed in many papers (see, for example, Refs 67–69). Generally, either an average or a weighted average is calculated. A weighted average is better suited for cases where environmental effects are insignificant (for example, for rigid parameters, such as bond lengths). If environmental effects are substantial (torsion angles and bond angles), simple unweighted averages should preferably be determined. It is desirable to use an unweighted average also in statistical verifications of hypotheses. The absence of standard deviations of parameters for the majority of structures in the CSD does not allow one to calculate weighted averages without recourse to the original literature. However, Taylor and Kennard⁶⁹ demonstrated that an unweighted average can be sufficient even for rigid parameters provided the scatter of the experimental values is limited by the *AS* criterion. The authors believe that when the value of *AS* is 1.2, estimates of, for example, bond lengths in organic structures are quite correct. An unweighted average is used in the GSTAT programme for calculations of standard statistical characteristics.

It should be noted that only selected crystal-structural data, which are obtained by X-ray diffraction analysis of single crystals, are included in the CSD. In particular, atomic anisotropic displacement parameters (previously, they were called thermal ellipsoids) cannot be analysed. These parameters contain unique information on the dynamics of crystal structures and characteristics of atomic movements and/or disorder in crystals. Unfortunately, these data are absent in the CSD. Trueblood and Dunitz⁷⁰ were the first to call attention to this disappointing fact. They have demonstrated how information on the dynamics of crystal structures can be used for estimating energy characteristics (for example, barriers) of slow intramolecular movements in crystals, which is important in studies of properties of organic crystals.

III. Van der Waals atomic radii and nonbonded intermolecular distances in organic crystals

The atoms of elements can be, in a rather rough approximation, represented by rigid spheres with radii which are geometrical characteristics of the corresponding elements.⁷ The effective values of these characteristics are called van der Waals radii (WR) of elements. Needless to say these concepts are very simplified because atoms in molecules (the more so, in molecules in crystals) cannot be rigid, and their effective sizes depend also on the nearest environment as well as on the hybrid state of the atom. The first studies^{71,72} carried out with the use of the CSD have demonstrated that some bound atoms are flattened rather than spherical.⁷³ However, the simple 'rigid' spherical model appears to be a very persistent and extremely useful formalism.

Frequent application of WR stems from the necessity of comparing lengths of expected nonbonded intermolecular atom–atom contacts in crystals, which are determined as the sum of the corresponding WR, with the corresponding distances observed in crystal structures. Besides, in early work⁷ WR were used for choosing force-field parameters in calculations of the energy of intermolecular interactions in crystals. Presently, the CSD is finding increasing use for choosing these parameters,^{1–4} and the parameters of pairwise $X \cdots Y$ interactions are chosen based on the analysis of statistical distributions of bond lengths of the corresponding contacts retrieved from a large body of data in the CSD.

Several systems of WR are known. They were suggested by Pauling,⁵ Kitaigorodskii,⁷ Bondi,⁶ Zefirov and Zorky,⁷⁴ Nyburg and Faerman,⁷⁵ and Batsanov.⁷⁶ Bondi's system (table) of WR⁶ is most commonly used in spite of the fact that it has been repeatedly criticised in more recent works.^{71,74,77} In this country, the system of radii suggested by Zefirov and Zorky⁷⁴ has gained acceptance.

Rowland and Taylor performed systematic analysis of nonbonded contacts in organic molecular crystals.^{23–26,78} In one of their recent works, the authors decided to test the compatibility between the commonly accepted systems of WR of nonmetals H, C, N, O, F, P, S, Cl, Br and I and the observed nonbonded interatomic distances in crystals studied over a period of the last 30 years.²² Studies were carried out with the use of the 1995 version of the CSD containing 126 353 crystal structures. Only precise (R factors < 5%) and ordered structures that contained exclusively the above-listed atoms were considered. Structures containing charged groups were also rejected to exclude the effect of electrostatic interactions on interatomic distances. A total of 28 403 structures satisfying all the above-mentioned requirements were selected. For a pair of atoms A and B under consideration, all intermolecular distances falling within the interval $(R_A + R_B) \pm 1.5 \text{ \AA}$, where R_A and R_B are the corresponding WR according to Bondi, were taken into account. The broad range ensured that the sample thus obtained would not lead to results expected in advance.

Distribution histograms of nonbonded distances for various atom pairs were constructed²² with a bin size of 0.1 Å. Different types of histograms were obtained. Some of them showed a monotonic dependence of the number of atom pairs (n) on the distance ($H \cdots H$). Other histograms had a well-defined peak ($Cl \cdots Cl$). In some cases, a maximum was poorly defined ($H \cdots F$) or absent [histograms had only a shoulder ($C \cdots N$)] (Fig. 1).

Histograms of the first type were not analysed because they gave no numerical characteristics of the distribution.[†] Rowland

[†] These histogram patterns are due to the fact that all intermolecular distances (in particular, $H \cdots H$) are taken into consideration, among them distances that do not correspond to the real van der Waals ('reference'⁷) contacts in crystals. However, the last-mentioned contacts serve as a basis for the determination of WR of atoms in crystals. Consequently, an approach used by the authors of the work²² is of limited utility and cannot be used for estimating values of typical van der Waals $H \cdots H$ contacts.

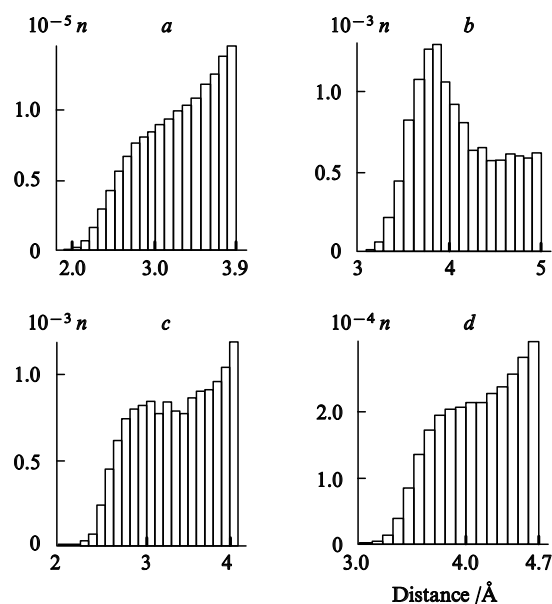


Figure 1. Distribution histograms of nonbonded intermolecular distances for selected atomic pairs:²² $H \cdots H$ (a); $Cl \cdots Cl$ (b); $H \cdots F$ (c); $C \cdots N$ (d).

and Taylor²² suggested the use of the parameter d (the distance corresponding to the histogram half peak or shoulder height; Fig. 2) as a characteristic of histograms of all the other types. The stability of this parameter is the major argument in favour of its application as a numerical characteristic. Other possible (and most commonly used) characteristics, such as the shortest contacts[‡] or the position of the distribution maximum, appeared to depend strongly on the choice of the bin size and the boundaries of the distribution. Because of this, the value of d can be estimated much more reliably than the position of the maximum of the histogram or the shortest contacts.

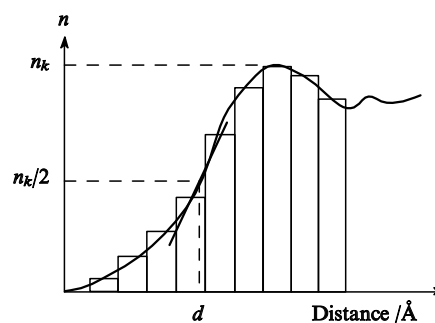


Figure 2. Scheme for the determination of the parameter d ;²² n_k is the height of the maximum of the histogram.

The distributions of the lengths of $O \cdots O$, $N \cdots O$ and $N \cdots N$ nonbonded distances have a pronounced peak at short distances corresponding to typical lengths of hydrogen bonds (Fig. 3). Since only van der Waals contacts were considered in the work cited,²² all contacts of the NH and OH groups were also excluded. This restriction resulted in the removal of maxima corresponding to H bonds from all three distributions.

[‡] It is self-evident that the expression 'interatomic contacts' makes sense only for the left portion of the histogram where the distances are close to the sum of WR.

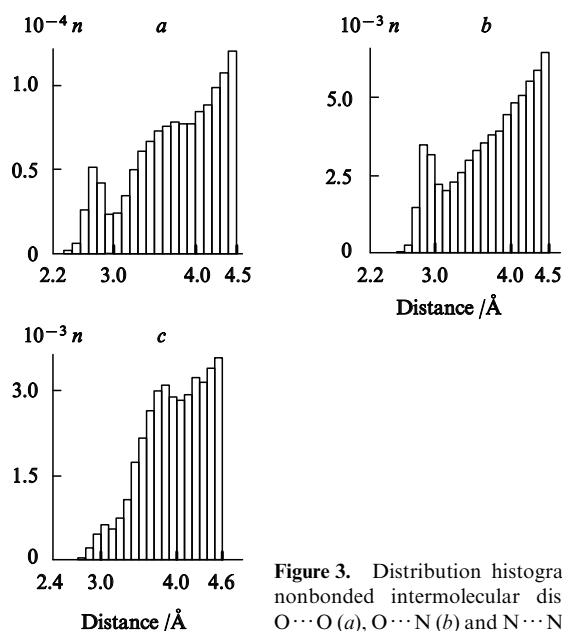


Figure 3. Distribution histograms of nonbonded intermolecular distances O...O (a), O...N (b) and N...N (c).²²

As expected, the values of d (Table 1) for the (O,N)H...N(O) distances are markedly smaller than those for the (C)H...O(N) distances (Fig. 4). On the contrary, the values of d for (O,N)H...Cl(Br) are larger than those for (C)H...Cl(Br). This can be explained by the fact that the OH and NH groups are almost always involved in strong hydrogen bonds with oxygen or nitrogen atoms, while bonds with halogen atoms appear to be 'secondary' and hence, are substantially weaker. If this assumption is true, the concept of WR for the oxygen and nitrogen atoms (at least, for the OH and NH groups) in organic crystal structures containing hydrogen bonds is meaningless. Taking into account the aforesaid, Rowland and Taylor²² estimated the values of d for the H...O, H...N and H...S distributions considering only hydrogen atoms at carbon atoms.

Table 1. Observed values of d (Å).²²

Atom	H	C	N	O	F	S	Cl	Br	I
H		3.02	2.59		2.54	2.91	2.88	2.99	3.14
C	3.02	3.59	3.31	3.24		3.61			
N	2.59	3.31	3.43	3.28	3.13	3.42	3.41		
O		3.24	3.28		3.00	3.45	3.33	3.48	
F	2.54		3.13	3.00	2.90				
S	2.91	3.61	3.42	3.45		3.60	3.55		
Cl	2.88		3.41	3.33		3.55	3.50		
Br	2.99			3.48				3.70	
I	3.14							4.05	

The authors calculated the values (r_i) that characterise WR of the atom of the i th type using the values for all kinds of pairs of atom-atomic contacts (see Table 1) by minimising the following function:

$$f = \sum_i \sum_{j < i} w_{ij} [d_{ij} - (r_i + r_j)]^2,$$

where d_{ij} is the value of d for the pair of atoms i and j , w_{ij} is the weighting coefficient, which is equal to 1 and 0.25 for bin sizes of 0.1 and 0.2 Å, respectively. The summation was made over all types of atoms.

We recall that Rowland and Taylor²² proposed to use d as a characteristic of the distribution of intermolecular distances based on the numerical constancy of this value regardless of the choice of

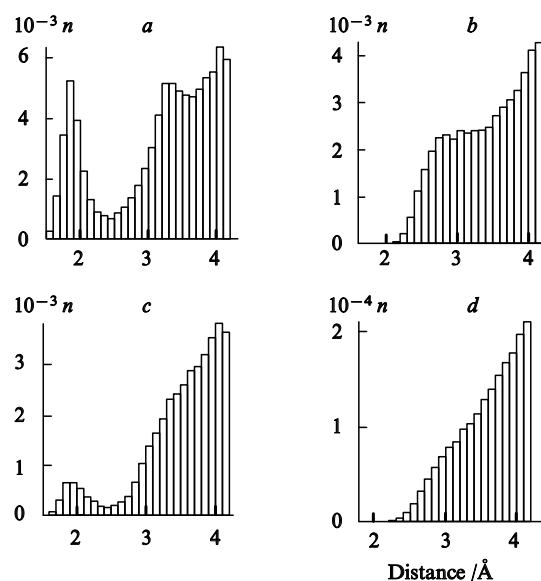


Figure 4. Distribution histograms of nonbonded distances (O,N)H...O (a), (C)H...O (b), (O,N)H...N (c) and (C)H...N (d).²²

the bin size and boundaries of the distribution rather than on the expectation that d can be equal to the sum of WR of the corresponding atom pair. The authors only assumed that the values of r_i thus determined would correlate with the values of WR (R_w): $r_i = cR_{wi}$, where c is the correlation coefficient. The coefficient c appeared to be close to unity.

The values of r_i determined as described above as well as the values of WR determined independently are given in Table 2. It can be seen that the values of r_i agree most closely with Bondi's system of radii. The authors²² believed that this is most likely a random coincidence. It was noted that, on the whole, the radii which were determined in the work cited from a large number of interatomic distances in crystals agree well with WR determined by Bondi, yet some exceptions were observed. In particular, WR of hydrogen atoms in Bondi's system are 0.1 Å larger. The calculation taking account of the distribution of the H...H contacts determined only by the neutron diffraction method gave a radius of 1.19 Å. This value is close to that determined by Bondi. When H...O and H...N contacts were included in the consideration, the value of the radius under consideration decreased. The values of WR in Bondi's system were determined primarily from the H...H contacts in adamantane. It is known that covalently bound hydrogen atoms are partially positively charged in the majority of organic compounds. Therefore, H...H distances would be expected to be somewhat elongated due to

Table 2. Van der Waals radii of selected atoms (Å).

Atom	I	II	III	IV	V	VI	VII
H	1.2	1.17	1.16	—	1.2	1.2	1.10
C	—	1.72	1.71	—	1.7	1.7	1.77
N	1.5	1.57	1.50	1.60	1.6	1.55	1.64
O	1.40	1.36	1.29	1.54	1.5	1.52	1.58
F	1.35	—	—	1.38	1.4	1.47	1.46
S	1.85	2.02	1.84	2.03	1.85	1.80	1.81
Cl	1.80	1.78	1.90	1.78	1.8	1.75	1.76
Br	1.95	—	—	1.84	1.9	1.85	1.87
I	2.12	—	—	2.13	2.1	1.98	2.03

Note. The values of R_w were determined by: I, Pauling;⁵ II, Kitaigorodskii;⁷ III, Zefirov and Zorky;⁷⁴ IV, Nyburg and Faerman;⁷⁵ V, Batsanov;⁷⁶ VI, Bondi;⁶ VII, values of r_i calculated by Rowland and Taylor.²²

electrostatic repulsions. On the contrary, the H $\cdots$ O distances can be somewhat shortened due to electrostatic attractions. Therefore, the radii which were determined²² with the use of all types of H $\cdots$ X contacts based on a large body of statistical data are presumably more accurate than those determined by Bondi. Yet another noticeable difference in the values of WR was observed for the nitrogen atoms. A larger (compared to Bondi's radius) value of r_N was obtained due to the unexpectedly large value of d for the N $\cdots$ N distance distribution. The authors²² believe that the value of WR for the nitrogen atom suggested by them is more appropriate for interpreting N $\cdots$ N contacts in crystals.

It should be noted that with only a few exceptions, the dispersion of the values of WR for atoms determined by different authors is small (~ 0.1 Å). It is with this (or even narrower) accuracy that WR are generally determined in experiments.⁷⁶ Therefore, the results discussed in this section can be considered as the demonstration of a new statistical approach to the estimation of these values rather than as yet another attempt to refine WR of atoms. In our opinion, a possible line of further investigation in this field with the use of the CSD can involve analysis of typical intermolecular distances in crystals at different temperatures. It is known that cooling of molecular crystals results in contraction of intermolecular contacts, which is more substantial (up to 0.2 Å) than those of other contacts. Therefore, systematic analysis of these changes in crystals with a decrease in temperature (generally, from room temperature to -100 °C and below) is of special interest.

IV. Principle of close packing in crystals and distribution of molecular centres in crystallographic unit cells

The major principle of organic crystal structures, namely, the principle of close packing, was stated by Kitaigorodskii in 1955.⁷ In recent years, several researchers concerned with computational modelling of crystal packings noted that if calculations were based on the molecular geometry of compounds, several close-packed structures were generally observed, all with packing energies within 5 kJ mol^{-1} of the global minimum.⁷¹ The observed crystal structure is often the one found to coincide with the global minimum, but not always.^{1–4}

Some researchers believe that the principle of close packing contradicts the tendency of molecules to form stable associates in crystals through hydrogen bonds or other specific intermolecular interactions, at least in the case of polyfunctional or bulky and branched molecules.³⁵ On the whole, the problem of *a priori* calculations of a crystal structure of a particular compound is far from an unambiguous solution. However, considerable progress has been observed in this field in recent years. In the recent review,⁴ Gavezzotti noted that nowadays the answer to the question 'Are crystal structures predictable?' would have to be 'Yes, sometimes'. This question was also discussed in detail in another paper.⁶³

The major aim of *a priori* calculations of crystal structures is to search for optimum packings of molecules and/or their associates. In this case, the principle of close packing can provide a basis for these calculations. Therefore, the examination of its applicability with the use of abundant statistical data in the CSD is an urgent problem.

Motherwell³⁴ attempted to find regularities of molecular arrangements in crystalline compounds. He expected to reveal preferred molecular arrangements for the purpose of using the rules found in computational modelling of crystal structures.

First, the most common space groups were revealed. In the 1996 version of the CSD (160 000 structures), 82% of all organic structures encompassed by seven space groups. These are: $P\bar{1}$ (19%), P_2 (6%), P_2/c (35%), $C2/c$ (7%), $P_212_12_1$ (9%), $Pbca$ (4%) and $Pnma$ (2%). Crystal structures belonging to the above-listed groups were retrieved from the CSD with the use of the

QUEST search programme. The selection was restricted to structures with one molecule per asymmetric unit ($Z' = 1$). Disordered and polymeric structures were rejected. An exception was made for the space group $Pnma$, where all molecules have an inherent mirror plane coinciding with the crystallographic plane m . For this study, a selection was made with $Z' = 1/2$.

It was decided to use the coordinates of the molecular geometrical centre as the characteristics of the molecular position. These coordinates were calculated as the average of all atomic coordinates (including hydrogen atoms if present). The molecular centre coordinates were transformed as to place the molecule into the first quarter of the unit cell. The calculations were performed with the use of a modification of the standard programme PLUTO CSD. Then the data obtained were used as input parameters to the statistical display programme VISTA.

The distribution patterns of the molecular centres were displayed as three-dimensional maps, which readily illustrate the cluster character of the distributions. The maps were presented as planar projections onto the coordinate planes and distribution histograms along the coordinate axes.

1. Group $P\bar{1}$

For the group $P\bar{1}$, 967 structures that satisfy the above-mentioned requirements were selected. The results of calculations of the molecular geometrical centres are shown in Fig. 5. In the normalised distribution (*i.e.*, with the coordinates brought into the first quarter of the unit cell; Fig. 5b), the points corresponding to clusters form a distinct cross with the following coordinates of the centre: $x = 0.25$, $y = 0.25$, $z = 0.25$. As expected, in this space group the patterns are very similar for all three projections. The regions of the increased density of the distribution have the coordinates $(x,y) = (0.25, 0.25)$. The regions of the decreased density of the distribution have the coordinates $(x,y) = (x,z) = (y,z) = (0, 0)$, $(0, 0.5)$, $(0.5, 0)$, $(0.5, 0.5)$. The

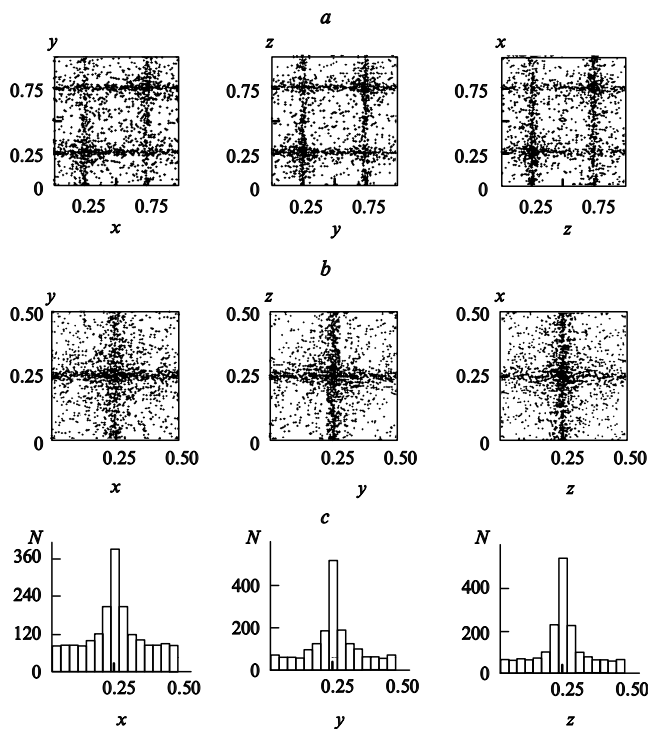


Figure 5. Distributions of geometrical molecular centres in the group $P\bar{1}$:³⁴ scattergrams for the total unit cell (a); scattergrams adjusted to bring the reference molecule to the first quarter of the unit cell (b); distribution histograms of positions of the geometrical molecular centres along the axes of coordinates of the unit cell (c). Hereinafter N is the number of points.

areas of low population correspond to the positions of the symmetry elements in this space group, *i.e.*, to the centres of symmetry.

Motherwell³⁴ suggested that this distribution pattern of the molecular centres is a graphical illustration of the principle of close packing. Clearly, the molecules cannot occupy inversion centres since asymmetrical molecules, which have no inherent centre of symmetry, were chosen. The reasons why the molecules will tend to 'avoid' regions about the inversion centres are obvious if one considers the location of this molecule between two centres of symmetry at a distance d from each of them. Evidently, the best location of a 'spherical' molecule is halfway between these centres. However, the shapes of real molecules are far from spherical ones and, in addition, the molecules have functional groups which can be involved in specific directional interactions (for example, hydrogen bonds). Nevertheless, judging from the results obtained, a general tendency exists according to which the molecules prefer to occupy the midpoints between centres of symmetry at a distance equal to one-quarter along each coordinate axis.

2. Group $P2_1$

For the group $P2_1$, 1000 structures were selected. To simplify consideration, the projection along the y axis was used as an informative projection. It was established that the molecular centres cluster predominantly halfway between the screw axes $(x,z) = (0.25, 0.25)$ (Fig. 6). In the regions $(x,z) = (0, 0)$, $(1.0, 0.5)$, $(0.5, 0)$, $(0.5, 0.5)$, *i.e.*, on the screw axes, areas of the minimum density of the distribution are observed. This confirms the above-mentioned tendency of molecules to occupy the midpoints between symmetry elements (in this case, between screw axes).

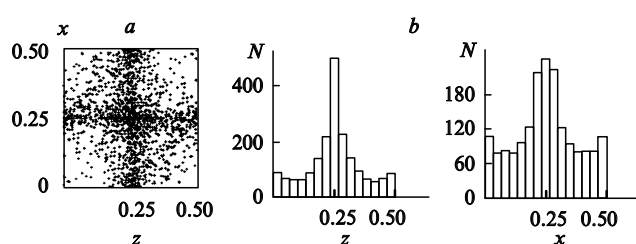


Figure 6. Scattergram (a) and distribution histograms (b) of molecular centres in the group $P2_1$.³⁴

3. Group $P2_1/c$

The group $P2_1/c$ contained 994 structures after elimination of structures with $Z' > 1$. The distribution histogram (Fig. 7) shows

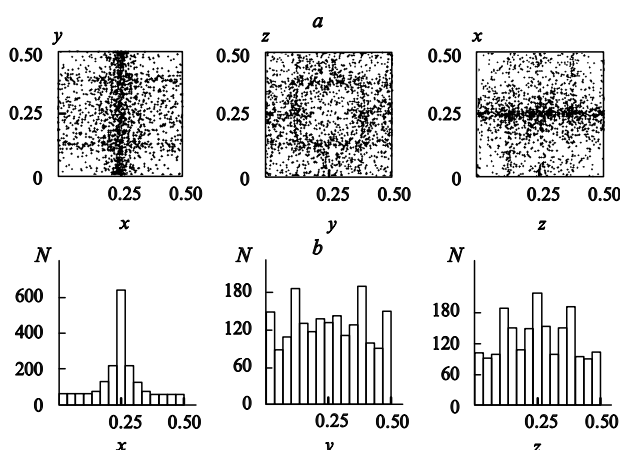


Figure 7. Scattergrams (a) and distribution histograms (b) of molecular centres in the group $P2_1/c$.³⁴

one narrow peak on the axis x . The histograms along the axes y and z have substantially less pronounced peaks with the coordinates $(0.125, 0.375, 0.5)$ and $(0.125, 0.25, 0.375)$. The characteristic feature of the distribution pattern in this group is a broad band of points in the plane defined by $x = 0.25$, which corresponds to positions of molecules along the glide plane. The areas of low population in the plane (x,z) are located at the positions corresponding to the centres of symmetry: $(0, 0)$, $(0, 0.5)$, $(0.5, 0)$, $(0.5, 0.5)$.

4. Group $C2/c$

The sample for the group $C2/c$ consisted of 984 structures. The distribution histograms show pronounced narrow peaks at $x = 0.125$ and 0.375 (Fig. 8). The distribution pattern along the axis y is less distinct but the histogram has a narrow peak at $y = 0.25$. The distribution histogram along the direction z , as well as the histogram along x , have distinct peaks at 0.125 and 0.375 . The distribution patterns consist of narrow bands in the plane xy ($x = 0.125$ and 0.375). It may be noted that there is an obvious increase in the density extending in the direction of the glide plane c and large voids in the regions $(x,z) = (0, 0.25)$ and $(0.5, 0.25)$, which correspond to the positions of rotation twofold axes. This is an expected result because it is obvious that molecules related by rotation axes cannot be closely packed.

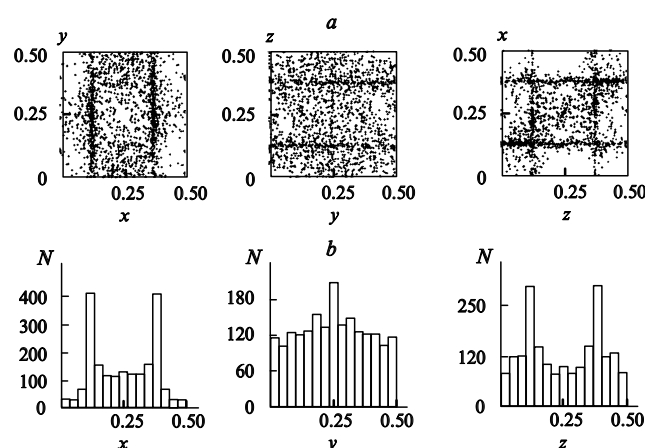


Figure 8. Scattergrams (a) and distribution histograms (b) of molecular centres in the group $C2/c$.³⁴

The regions of low population are also observed at the inversion centres, like in other space groups.

5. Group $P2_12_12_1$

The sample for the group $P2_12_12_1$ consisted of 999 structures. The histograms and the distribution densities of molecular centres in the crystal unit cell appeared to be most uniform. The only characteristic feature is the low density along the screw axis parallel to the axis z .

6. Group $Pbca$

The distribution of molecular centres for the group $Pbca$ (999 structures) shows clear maxima on each axis at the positions 0.125 and 0.375 . The points are distributed as distinct bands in all three planes with the coordinates $(0.125, 0.375)$ along each crystal axis. The regions of low population correspond to the positions of centres of symmetry and positions of screw axes. As in the groups $P\bar{1}$ and $P2_12_12_1$, all three directions are equivalent.

7. Group $Pnma$

The distributions of molecular centres for the group $Pnma$ were constructed based on the data on 731 compounds. Since all molecules in this group have a mirror plane, the only informative

distribution histogram is the projection (x, z). This projection has clusters of points in the regions about (0.25, 0) and (0.25, 0.5). However, these clusters are very diffuse. Regions of low population at (0, 0), (0.5, 0) and (0.5, 0.5), which correspond to the centres of symmetry, are better defined.

Let us emphasise again that all the structures considered above were selected regardless of chemical atom types. The distributions of molecular centres were obtained without taking into account hydrogen bonds, electrostatic interactions and the fact that approximately 45% of all the structures under consideration belonged to complex organometallic molecules whose shapes are far from spherical. To exclude possible objections, the distribution patterns of molecular centres were considered for a subset of the $P2_1/c$ sample consisting of hydrocarbons only (126 structures) and no significant difference could be seen in the distribution of molecular centres.

With the aim of analysing the molecular environment in crystals in more detail, an extension was written for the programme PLUTO to display the molecular coordination sphere about the reference molecule according to the approaches of Kitaigorodskii⁷ and Gavezzotti.⁷⁹ The coordination sphere was determined based on calculations of the energy of intermolecular interactions. Only molecules whose energy of interactions with the reference molecule is not lower than 4.18 kJ mol⁻¹ were included in the calculations. The typical coordination numbers of molecules in the CSD were found to be 12–14, which confirmed the suggestion of Kitaigorodskii.⁷ The potential energy was calculated by summing energies of pairwise atom-atomic interactions using Gavezzotti's empirical potential.⁷⁹ The electrostatic term was ignored. Analysis of several hundreds of coordination spheres determined as described above demonstrated that, almost without exception, a close-packed layer of six adjacent molecules can be observed in this coordination sphere. Needless to say that the real situation is far from simple. Many examples can be presented where the molecules form strongly bound dimers or chains. However, in these cases the molecules also tend to form a coordination sphere, which is the nearest to the closest packing of spheres.

Therefore, the distribution histograms of molecular centres in the symmetry groups under consideration show peaks or clusters corresponding to the preferred positions of molecular centres in unit cells. These centres are located halfway between the inversion centres or screw axes in unit cells. The calculations of the energy of intermolecular interactions with the adjacent molecules in the coordination sphere confirmed that these assumptions are energetically justified. It is useful to approximate molecules by spheres to visualise the preferential formation of close-packed layers of molecules and tendencies to close packings of spheres.

V. Relative frequencies of occurrence of space groups

Analysis of relative frequencies of space-group occurrence for the known crystal structures is one of the most evident areas of application of the CSD in studies of general regularities of crystal structures. This analysis is of interest not only from the theoretical, but also from the practical standpoint, because crystal symmetry determines a number of important properties manifested by many crystals. Evidently, the problem of the choice of a particular space group by a molecule is thus currently the most studied.

Kitaigorodskii⁷ was the first to demonstrate that only a few of 230 theoretically plausible groups are of rather frequent occurrence. Examples of crystal structures belonging to other groups are few in number, while certain space groups are 'prohibited'. Among the most populated groups, centrosymmetrical space groups are by far 'favourites'. Kitaigorodskii ascribed this selectivity to the difference in the packing energy of symmetric arrangements of molecules in crystals. On the whole, it was concluded that organic molecules crystallise preferentially in

space groups (SG) that can ensure the close packing of spheres or tri-axial ellipsoids (which are most commonly used as approximations for organic molecules). In this respect, the groups $P2_1/c$ and $P\bar{1}$ were assigned to most convenient.

More recently, Belsky and Zorky^{40, 51, 52, 80} published a series of papers in which the most populated space groups were established based on a rather large body of data.^{9, 10} It appeared that there are only 9 such groups, viz., $P2_1/c$, $P\bar{1}$, $P1$, $P2_1$, $P2_12_12_1$, $Pbca$, $C2/c$, $Pna2_1$ and $Pnma$. They account for 79.2% of all the structures known at that time. The results obtained demonstrated that organic molecules actually crystallise preferentially in centrosymmetrical SG. Over 50% of all known organic structures belong to only two space groups, viz., $P2_1/c$ and $P\bar{1}$. In addition, it was noted that the inherent molecular symmetry and the number of crystallographic orbits occupied by molecules must be taken into account.

More than a dozen of recent publications were devoted to studies of the relative frequencies of occurrence of SG for both organic (Wilson,^{36–39} Padmaja *et al.*,⁴¹ Belsky *et al.*,^{42, 81} Mighell *et al.*,^{44, 82} and Brock and Dunitz⁴⁵) and inorganic (Mackay,⁴³ Mighell *et al.*,^{44, 82} and Baur and Kassner⁸³) crystals based on statistically reliable data using computer databases.

All authors noted the prevailing occurrence of centrosymmetrical SG. However, the frequency of occurrence of these groups for organic compounds reported in different works varies from 66% to 75%. Among inorganic compounds (Inorganic Crystal Structure Database, 1992), this frequency is, on the average, even higher (78%). Proteins and other natural polymers consisting of pure enantiomeric molecules are the exceptions, where chiral SG prevail.⁴¹

Note that the preference of a particular SG (centrosymmetrical or noncentrosymmetrical) for a molecule is of exceptional importance from the practical standpoint to researchers involved in the design of new organic materials. In particular, compounds that can possess nonlinear-optical properties and are potentially able to generate the second harmonic of laser radiation crystallise most often in centrosymmetrical SG excluding the manifestation of the above-mentioned properties in crystals. Below we dwell on works aimed at establishing the reasons why the majority of organic molecules tend to crystallise in centrosymmetrical SG.

The preferential occurrence of centrosymmetrical SG may be only indicative of the fact that organic compounds can exist as racemic mixtures of enantiomers rather than reflects the fact that these SG are energetically more favourable. Strictly speaking, to determine correctly the actual frequency of occurrence of SG it is necessary to know whether the crystals were obtained from a solution of a pure enantiomer, from a mixture of enantiomers or from a solution of an achiral compound. The great majority of crystals were grown from mixtures of enantiomers. Therefore, it is not surprising that they belong to centrosymmetrical SG. If this is the case, the problem of the preparation of noncentrosymmetrical materials can be reduced to the problem of spontaneous resolution of enantiomers or to the development of procedures for their forced resolution. It was noted⁵² that in recent years the number of noncentrosymmetrical groups in the CSD increased somewhat, which may be indicative of an increase in the number of the natural compounds and products of the stereoselective synthesis studied.⁸

For the crystalline compounds studied to date, virtually all 230 possible space groups are observed, except for 7 groups for inorganic compounds and 28 groups for organic and organometallic compounds.⁸³ This fact can be considered as the experimental corroboration of the Kitaigorodskii theory. However, as for their frequency of occurrence, only certain of space groups are

§ This example provides further evidence that care is required in the data rejection and sample creation. Even a very large body of structural data does not necessarily assure that the statistical characteristics or property is reliable.

Table 3. Distribution of organic crystals among space groups.⁴²

Number	SG	<i>m</i>	<i>n</i> (%)
1	<i>P2₁/c</i>	7634	37.97
2	<i>P2₁2₁2₁</i>	3052	15.18
3	<i>P1</i>	2658	13.22
4	<i>P2₁</i>	1684	8.38
5	<i>C2/c</i>	1149	5.71
6	<i>Pbca</i>	998	4.96
7	<i>Pna2₁</i>	414	2.06
8	<i>Pnma</i>	257	1.28
9	<i>Pca2₁</i>	199	1.00

Note. The following notations are used: SG is the space group; *m* is the number of structures belonging to a particular SG; *n* is the ratio between structures belonging to a particular SG and the total number of the structures under consideration.

rather populated.^{7,80} Only a few examples of the remaining groups are available.

Thus only 18 most 'popular' (according to Baur and Kassner⁸³) space groups account for 92.71% of all known structures of organic compounds. Belsky⁴² has distinguished 9 most frequently occurring groups, which account for 89.8% of all compounds. The nine groups mentioned by Belsky (Tables 3 and 4) enter into 18 groups of Baur (Fig. 9).

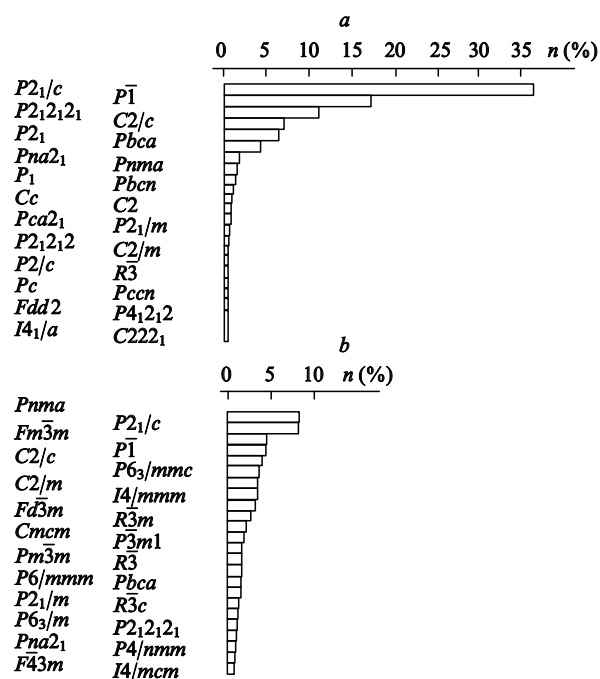
Table 4. Distribution of organic crystals among crystal systems.⁴²

System	<i>m</i>	<i>n</i> (%)
Triclinic	2823	14.04
Monoclinic	11061	55.01
Orthorhombic	5563	27.67
Tetragonal	360	1.79
Hexagonal	268	1.33
Cubic	32	0.16

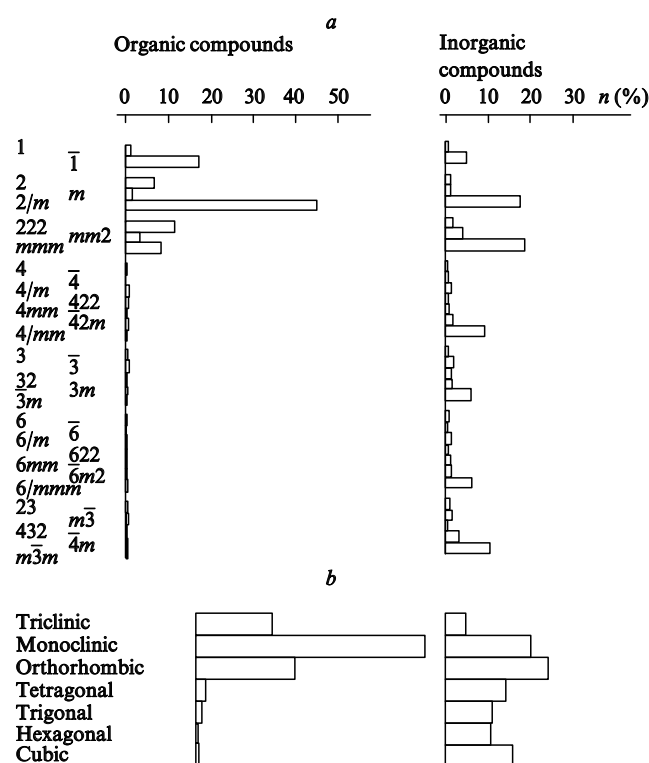
Note. The following notations are used: *m* is the number of structures belonging to a particular crystal system; *n* is the ratio between structures belonging to a particular system and the total number of structures under consideration.

For inorganic compounds, Baur has also distinguished 18 most frequently occurring groups. However, these groups account for only 56.86% of all structures. The distribution histogram of space groups for inorganic compounds is more shallow than that observed for organic compounds (see Fig. 9). In the case of inorganic compounds, it is more difficult to reveal 'leading' group. The dominant space groups for organic and inorganic compounds are also substantially different in spite of the above-mentioned common predominance of centrosymmetrical SG. The most substantial difference is that inorganic compounds crystallise in higher-symmetry space groups, namely, in trigonal, tetragonal, hexagonal and cubic systems. Thus 31.58% of the total number of inorganic compounds crystallise in groups belonging to the symmetry classes *3m*, *4/mmm*, *6/mmm* and *m3m*. Only 0.63% of organic compounds belong to the above-listed groups.

According to the data reported by Brock and Dunitz,⁴⁵ in the case of protein and polymeric structures, the tetragonal and trigonal systems are also more abundant (13% and 16%, respectively) than in chiral crystals of organic compounds (3% and 2%, respectively). The groups *C2* and *C222₁* in the Protein Data Bank account for 13% and 5% of structures, respectively, while these groups in the CSD (for chiral crystals) account for only 4% and 1% of structures, respectively. The populated SG of

**Figure 9.** Most populated space groups for organic (a) and inorganic (b) crystal structures (in percent of the total number of structures).⁸³

organic compounds belong exclusively (95.38%) to triclinic, monoclinic and orthorhombic systems (Fig. 10). These crystal systems account for only 48.92% of inorganic compounds. Thus the distribution of inorganic compounds is more diversified.

**Figure 10.** Distributions of frequencies of abundance of crystals of organic and inorganic compounds over classes of point symmetry (a) and crystal systems (b).⁸³

Among the above-listed 18 most frequently occurring SG of inorganic compounds, all crystal systems are present (see Fig. 10).

The majority of organic molecules crystallise in low-symmetry space groups, while the majority of elements, intermetallic compounds and inorganic salts crystallise in high-symmetry groups. However, this does not imply that the packing rules for these compounds are different. The difference in structure is most likely determined by the shape of the initial structural unit as well as by the presence or absence of strong long-range electrostatic interactions. For inorganic compounds, the structural units are most often nearly spherical atoms or ions as well as octahedral or tetrahedral fragments. That is the reason that a large number of inorganic compounds crystallise in high-symmetry groups. The vast majority of organic compounds archived in the CSD consist of low-symmetry electroneutral molecules. Therefore, it is not surprising that organic compounds crystallise predominantly in low-symmetry groups.

Presently, it is generally agreed that the molecular shape affects the symmetry of the crystal structure formed.^{38,39,45,84} When estimating the frequency of occurrence of SG, this fact must be taken into account. Brock and Dunitz,⁴⁵ like Kitaigorodskii,⁷ exemplified this fact by crystals of molecules possessing inherent symmetry elements, namely, a twofold rotation axis (2) and a mirror plane (*m*). In spite of the obvious fact that these elements are unfavourable,⁷ space groups containing the plane *m* are rather frequent, which is exclusively due to molecules possessing the inherent symmetry *m*. The plane *m* in the corresponding SG is virtually always 'occupied'. If molecules possessing the inherent mirror symmetry are excluded from consideration, the distribution pattern of space groups is changed (the above-mentioned group *Pnma* no longer belongs to abundant groups). In a half of the cases, a twofold rotation axis is occupied and in the remaining cases, it is free. In the latter case (for chiral molecules), this axis plays the same role as an inversion centre in the case of a racemic pair, namely, stable dimers are formed due to a twofold axis. Concave-shaped protein molecules often consist of such dimers, which allows them to be closely packed. Apparently, for this reason space groups containing a twofold axis occur more frequently in the Protein Data Bank than in the CSD.⁴¹

From the analysis of the frequency of occurrence of space groups for organic crystals in the CSD, Brock and Dunitz⁴⁵ found what symmetry elements are relatively more favourable. Thus it appeared that the screw axis 2₁ is much more favourable than the simple translation or the screw axes of higher orders. It is generally believed⁷ that the axis 2₁ is favoured over the glide plane, which, in turn, is favoured over the translation. However, Brock and Dunitz believe that glide planes play the same role as translations in organisation of crystal structures. This conclusion is not quite without doubt, because the translation is a symmetry element of the first kind under the action of which the chirality of the molecule is retained, while the glide plane is a symmetry element of the second kind, which inverts the chirality. Therefore, it may be that comparisons were carried out based on different classes of compounds, which is not quite correct.

The number of formula units per asymmetric unit (*Z'*) (the number of occupied orbits) is yet another important characteristics necessary for analysing the frequency of occurrence of space groups. Belsky and Zorky, who developed the concept of structural classes,^{51,80} were the first to note the importance of the consideration of *Z'*. Recently, other authors also pointed to the importance of account of this parameter. Padmaja *et al.*⁴¹ found that structures with *Z'* > 1 belong predominantly to low-symmetry crystal systems (particularly often, to the group *P1*). Analysis of the results obtained by Brock and Dunitz with the use of the 1991 version of the CSD⁴⁵ confirmed the above conclusions. It appeared that the overall number of structures with *Z'* > 1 in the most populated chiral groups is larger than in the corresponding centrosymmetrical groups:

<i>n_{Z'}</i> > 1, %	45.0	14.0	11.2	4.5	11.3	5.7	3.0	3.0

Brock and Dunitz suggested that many acentric crystals with *Z'* > 1 are actually pseudosymmetrical structures. First sampling tests demonstrated that of 55 of a total of 256 structures with *Z'* > 2 belonging to the group *P2*₁ can be described by the pseudogroup *P2*₁/*c*. The pseudosymmetry elements $\bar{1}$, 2, 2₁ and *t* are most often observed in the above structural type. The phenomenon of pseudosymmetry and problems associated with this effect are discussed below in more detail.

VI. Why do organic crystals prefer centrosymmetrical groups?

1. The effect of molecular dipoles on the crystal-packing organisation

Whitsell and coworkers⁴⁹ were among the first to perform studies aimed at elucidating the reasons for the preferential occurrence of centrosymmetrical packings with the use of the CSD. The authors attempted to verify the thesis that molecules with large dipole moments crystallise preferentially in centrosymmetrical space groups. This concept is commonly accepted by researchers involved in studies of nonlinear optics of molecular crystals.^{46,47} It is based on simple inferences that the role of the electrostatic component in stabilisation of the crystal structure increases in the case of the antiparallel arrangement of molecular dipoles, which ultimately leads to the formation of centrosymmetrical crystals.

As early as 1955, Kitaigorodskii⁷ noted that electrostatic interactions (in the dipole–dipole approximation) must be taken into account for crystals of strongly polar molecules. However, recent calculations performed by Gavezzotti and Filippini^{85,86} for small molecules containing C=O and N≡C groups demonstrated that dipole-dipole interactions make only an insignificant contribution to the total energy of crystal stabilisation.

In the estimation of the role of the molecular dipole moment in the crystal symmetry, it was suggested⁴⁹ that if the antiparallel orientation of molecules with large dipole moments is preferable, the number of crystals containing such molecules should be substantially larger among centrosymmetrical crystal structures than among noncentrosymmetrical structures.

This suggestion was verified when crystal structures belonging to three space groups (*P* $\bar{1}$, *P1* and *P2*₁) were retrieved from the CSD (1994 version). Typical schemes of the molecular arrangements in these groups are shown in Fig. 11. In the group *P1*, all molecular dipoles are parallel to each other due to the absence of symmetry operations other than translations *t*. Therefore, the average dipole moment of the crystal is determined by the sum of all molecular dipole moments. In the group *P* $\bar{1}$, an antiparallel neighbour corresponds to each molecular dipole and the total dipole moment is equal to zero. In the group *P2*₁, pairs of molecules are related by a combination of rotation and translation operations and the value of the structural dipole should depend on the orientation of the molecular dipole relative to the screw axis (angle θ). Since the experimental data on molecular dipole moments (μ) are scarce, these values for a large series of

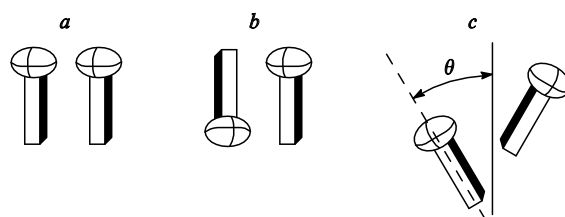


Figure 11. Mutual arrangement of molecular dipole moments in crystals belonging to the space groups *P1* (a), *P* $\bar{1}$ (b) and *P2*₁ (c).

Group	<i>P1</i>	<i>P2</i> ₁	<i>C2</i>	<i>P2</i> ₁ 2 ₁	<i>P</i> $\bar{1}$	<i>P2</i> ₁ / <i>c</i>	<i>C2</i> / <i>c</i>	<i>Pbca</i>

compounds were calculated using the AMPAC programme with the AM1 parameterisation.⁸⁷

Crystal structures in the CSD were chosen so that the values of μ could be correctly calculated within the framework of the above-mentioned approximation. Therefore, when statistical samples for the three above-listed space groups were created, the following objects were rejected: (1) compounds in which d -orbital interactions can occur; (2) organometallic ionic and polymeric structures; (3) structures containing molecules of solvation; (4) structures in which molecules occupy several systems of equivalent positions and (5) structures in which molecules form strong hydrogen bonds (*i.e.*, compounds containing OH or NH groups). As a result, a

Table 5. Values of the average dipole moments of organic molecules.⁴⁹

Space group	<i>n</i>	$\mu/\mu\text{B}$	σ	$\bar{\mu}/\mu\text{B}$
<i>P</i> 1	28	3.41	0.37	3.36
$\bar{P}$ 1	161	3.33	0.15	3.22
<i>P</i> 2 ₁	179	3.14	0.15	3.04

Note. The following notations are used: *n* is the number of structures under consideration; σ is the error of calculation of μ ; $\bar{\mu}$ is the value of the dipole moment for the midpoint of the distribution.

total of 28, 161 (out of 1229) and 179 (out of 722) examples were selected in the groups *P*1, $\bar{P}$ 1 and *P*2₁, respectively.

The results obtained in the work⁴⁹ are presented in Table 5 and in the histograms (Fig. 12). It can be seen that the average molecular dipole moments in centrosymmetrical and noncentrosymmetrical SG are virtually identical within the rather small dispersion. No statistically reliable correlation was observed between the dipole moments of molecules and their orientations relative to the polar direction in the group *P*2₁. Hence, the molecular dipole moment is not the governing factor in choosing the space group and does not account for the observed predominance of racemic space groups over chiral groups. However, some effects, such as hydrogen bonds, specific interactions of polar groups and the shape of the molecule, can affect the crystal packing. Apparently, interactions of molecular dipoles play an important role at large distances. In crystals, adjacent molecules are located at distances comparable with their dimensions. Moreover, dimensions of the majority of molecules are substantially larger than the shortest distances between them. Therefore, it is hardly probable that attempts to construct the molecular packing

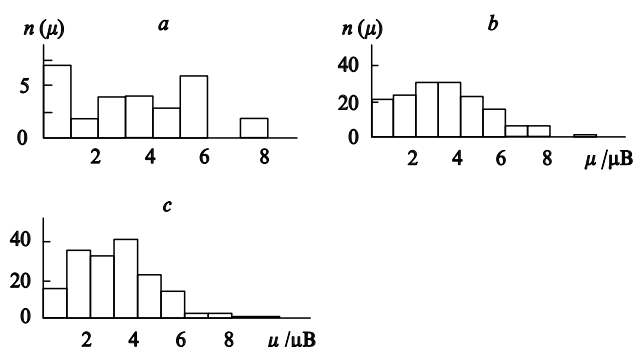


Figure 12. Distribution histograms for molecular dipole moments in the space groups *P*1 (a), $\bar{P}$ 1 (b), and *P*2₁ (c).⁴⁹

based primarily on the consideration of total molecular dipole moments will succeed.

2. Density and stability of racemic crystals and their chiral counterparts

The commonly accepted postulate that explains the preference of centrosymmetrical crystals is known as Wallach's rule.⁸⁸ According to this rule, racemic crystals tend to be denser than their chiral counterparts.

The question of whether molecules in racemic crystals are packed more closely than in the corresponding chiral crystals has been a subject of speculations since 1895.⁸⁸ This question has in essence two aspects:⁸⁹ are racemic crystals generally more stable than their chiral counterparts and is this greater stability reflected in a larger density of racemic crystals?

Wallach has deduced his rule by considering 8 chiral–racemic pairs, and only one of these pairs was an exception. More recently, Jacques, Collet and Wilen⁸⁹ considered 12 corresponding pairs and found 4 exceptions to Wallach's rule. The improved accuracy of determination of X-ray densities ($\sim 0.15\%$) made it possible more correctly to verify the validity of Wallach's rule. Mason⁹⁰ was the first to perform this verification. He analysed 14 pairs of compounds and found 9 exceptions to Wallach's rule. Apparently, only statistical analysis of a large sample can provide a reliable answer to the above question.

For this purpose, Brock and coworkers⁵⁰ used the CSD (1989 version). The authors created two files. The first file contained data on only noncentrosymmetrical groups ($\sim 25\%$ instances). The second file contained data on only racemic groups ($\sim 75\%$ instances). The data of the files were sorted according to chemical compositions of compounds and compared. The sets of structures having the same chemical composition were considered as potential objects of investigation. In several instances, compounds filed in the CSD under the same code turned out to be diastereomers. In this case, they were excluded from consideration. Particular attention was given to the problem of ambiguities of space-group determination. The space groups differing only by the presence or absence of an inversion centre were subjected to special scrutiny. For each pair, the relative differences between the densities of racemic (D_r) and chiral (D_c) crystals were calculated as follows:

$$\Delta D = \frac{100(D_r - D_c)}{0.5(D_r + D_c)}.$$

The final list contained 129 pairs. This number of examples was insufficient to obtain the smooth distribution (the shape of the histogram depends on the choice of the bin size and boundaries). Thus, the authors presented two variants of distributions of the values of ΔD , which differ by the choice of the initial boundaries (Fig. 13). In spite of the differences, both distributions exhibit a pronounced bimodal character. The average value of ΔD for 129

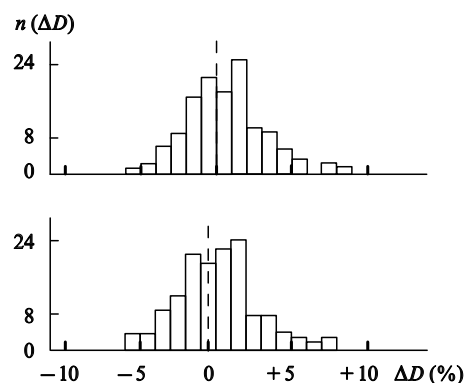


Figure 13. Distribution histogram for the values ΔD for 129 chiral–racemic pairs of the structures under study (two variants of the choice of the initial bin size are given).⁵⁰

pairs was 0.56%. However, this value is too small to confirm the rule, but it is too large to demolish it.

Taking into account the bimodality of the ΔD distribution, the authors attempted to divide the selected objects into two groups. One way of dividing objects is to separate pairs which are polymorphic modifications. An alternative way is to separate pairs which are not polymorphs. This separation was carried out according to the definition of polymorphs suggested by McCrone.⁹¹ According to McCrone, polymorphs are different solids that give the same liquid upon melting or dissolution. Therefore, crystal pairs of the first group (polymorphic modifications) contain either achiral molecules or chiral molecules that can rapidly undergo racemisation in solutions. Crystal pairs of the second group consist of enantiomers that can be readily resolved

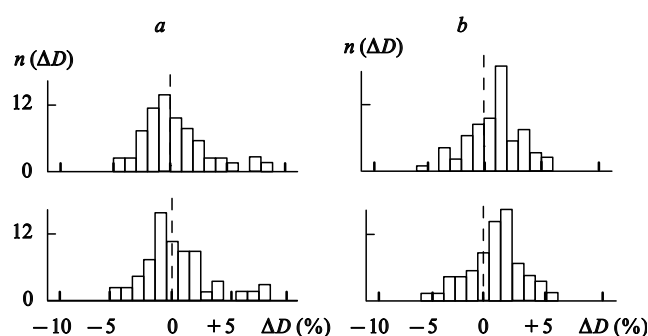


Figure 14. Distribution histograms for the values ΔD for 64 pairs of structures of the first group (enantiomers that can be rapidly interconverted, achiral compounds) (a) and for 65 pairs of the structures of the second group (enantiomers that can be resolved) (b).⁵⁰

(consequently, they are difficultly interconvertible).

For 64 pairs of the objects of the first group, the average value of ΔD was *ca.* +0.20% (Fig. 14a). Consequently, a comparison of polymorphic pairs showed no noticeable difference between the packing densities of racemic and chiral crystals.

The average ΔD value for the second group of objects consisting of 65 pairs was +0.92% (Fig. 14b). The packing densities of racemic crystals of the second group are, on the average, $\sim 1\%$ higher than those of their chiral counterparts. Therefore, it was concluded that Wallach's rule is apparently valid only for enantiomers that can be resolved.⁵⁰

It is not inconceivable that the difference in the average values of ΔD for the groups of crystals under consideration is due to different initial conditions of crystallisation. Compounds of the first group are always crystallised from solutions of achiral compounds or mixtures of enantiomers, while compounds of the second group are crystallised from solutions of both enantiomeric mixtures and pure enantiomers.

Crystallisation of compounds of the first group from solutions depends on the relative stability of possible solid phases and sometimes affords several crystal forms. Evidently, the stabilities of these forms should be approximately equal. Enthalpies of polymorphic modifications rarely differ by more than 1 kcal mol⁻¹. Therefore, it is hardly probable that less stable modifications of compounds of the first group will be obtained.

For compounds of the second group, the situation is quite different. Racemic solutions may yield racemic crystals, racemic conglomerates of chiral crystals or mixtures of both types depending on their relative stability. In contrast, crystals obtained from enantiomerically pure solutions must be chiral. Therefore, chiral crystals can be obtained even if they are thermodynamically much less stable than the racemic crystals. This implies that the second group of compounds is statistically biased. Thus, pairs in which racemic crystals are energetically more favourable can be more

frequent in the second group than in the first one. This is reflected in different distributions of ΔD .

Jacques and coworkers⁸⁹ compared thermodynamic characteristics of the melting process for 36 pairs of chiral and racemic crystals belonging to the second group. The average values of such characteristics as ΔH , ΔS and ΔT are 7.54 kcal mol⁻¹, 18.5 kcal mol⁻¹ K⁻¹ and 405 K for racemic crystals and 6.28 kcal mol⁻¹, 15.7 kcal mol⁻¹ K⁻¹ and 395 K for chiral crystals. Based on these data, the authors concluded that racemic crystals are thermodynamically more stable than chiral crystals.

However, it is hardly reasonable to consider this conclusion to be the general rule because the statistical data (in particular, the thermodynamic characteristics) are still scarce. It is quite probable that racemic crystals appear to be more stable because pairs in which they are less stable are absent only among compounds that have already been studied rather than among naturally occurring compounds.

Therefore, statistically reliable evidence for the higher density and thermodynamic stability of racemic crystals compared to their chiral counterparts has not yet been found.

3. Comparison of thermodynamic characteristics of polymorphic modification of organic crystals

The phenomenon of polymorphism in organic crystal structures has long been known. Such aspects as thermodynamic stability, pharmaceutical properties of polymorphs, conformational polymorphism, *etc.* have been studied in considerable detail.^{4, 92–98} Unfortunately, the data available in the literature are primarily descriptive and each instance of polymorphism was considered by itself. Accumulation of a large body of structural data on polymorphic modifications (PM) in the CSD brought systematic statistical studies in this field to reality. The existence of polymorphs is still a headache problem for scientists involved in computational modelling of molecular packings. However, it is evident that due to the constancy of the chemical composition in polymorphic pairs (triads, *etc.*) these systems can serve as a potential source of detailed information on the structure–property relationship in organic solids because in this case the difference in the physical properties can be explained by the difference in their structural organisations.

The first investigation devoted to this problem was performed by Gavezzotti and Filippini.³ The authors compared the thermodynamic and structural characteristics of the polymorphs available in the 1993 version of the CSD. They selected only objects which were studied at room temperature, had more than one polymorphic modification and consisted of C, H, N, O, Cl and S atoms. A total of 163 compounds which satisfy these requirements were found, 147 of them with two, 13 with three and three with four polymorphic modifications. A total of 345 crystal structures were found.

For these polymorphic modifications, thermodynamic characteristics of crystals were calculated according to procedures reported in the Refs 3, 86, 99 and 100. The parameters for the 6-exp potential function for intermolecular interactions were chosen^{98, 100} so as to reproduce the values of thermodynamic characteristics at room temperature. Generally, the calculated values of thermodynamic characteristics agree, at best, only qualitatively with the experimental values (due to an inaccuracy of both calculated and experimental values). Nevertheless, the regularities found by the authors can be considered as justified because possible inaccuracies affect in the same manner the results of calculations for both forms, while the differences between the calculated values used by the authors are free from errors.

The polymorphic pairs of compounds were placed in order of decreasing density. Therefore, the differences between the densities ΔD for polymorphic modifications are positive by definition. The differences (%) in the other properties (*P*) were determined as follows:

$$\Delta P = \frac{100(P_i - P_j)}{P_j}, \quad j > i.$$

The total number of points was 204. The following parameters P were calculated: D , the crystal density; V , the molecular volume; K , Kitaigorodskii's packing coefficient; E , the packing energy; S , the lattice-vibrational entropy; G , the lattice free energy, and Z' , the number of molecules per asymmetric unit.

The ΔD , ΔE , ΔS and $\Delta Z'$ distribution histograms are shown in Fig. 15. It appeared that the difference in the density between polymorphs is small and seldom exceeds a few percent. Thus 93%

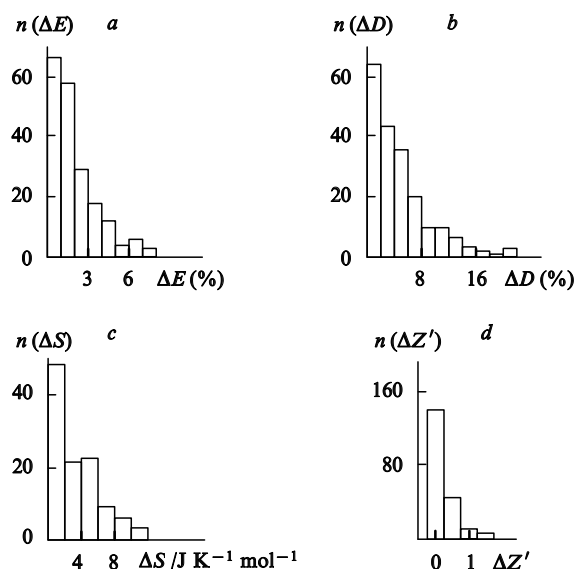


Figure 15. Distribution histograms for the packing energy ΔE (a), ΔD (b), ΔS (c), and $\Delta Z'$ (d).³

of the values of ΔD are smaller than 5%, which confirms the results reported in the work.⁵⁰ This implies that molecules can be packed in different fashions, but, apparently, not at the expense of a decrease in compactness. Cases with $\Delta D > 7\%$ occur either due to inaccuracy in determination of atomic coordinates or to large conformational differences in the molecules.

Similar conclusions are drawn by examination of the ΔE histograms: the packing energies of PM are generally close. A few exceptions can be attributed to the structural disorder or to inaccurate positioning of some key atoms of the system. The differences in the lattice entropies ΔS between polymorphs in pairs are also very small (see Fig. 15).

Thus the density, packing energy and lattice entropy for a polymorphic pair have close values. The results on the number of molecules per asymmetric unit (Z') are unexpected: 62 structures (18% of the pairs selected) have $Z' > 1$ [this value is substantially higher than the overall percentage in the CSD (8.3%)] and 46 compounds (28%) of 163 compounds selected have modifications with different values of Z' .

The authors considered also possible relationships between the calculated values (bivariate statistics). The dependence of ΔD on ΔE (Fig. 16a) demonstrates that in most cases higher packing energy is accompanied by higher density. The existence of crystal structures with high energies and low packing densities can be attributed to the presence of exceptionally strong and directional hydrogen bonds in a crystal. In all cases under consideration, the differences in the free energies ΔG between polymorphs in pairs have the same sign as the differences in the packing energies ΔE (Fig. 16b). As expected, the higher the density the lower the entropy (Fig. 16c). These results demonstrate that higher crystal

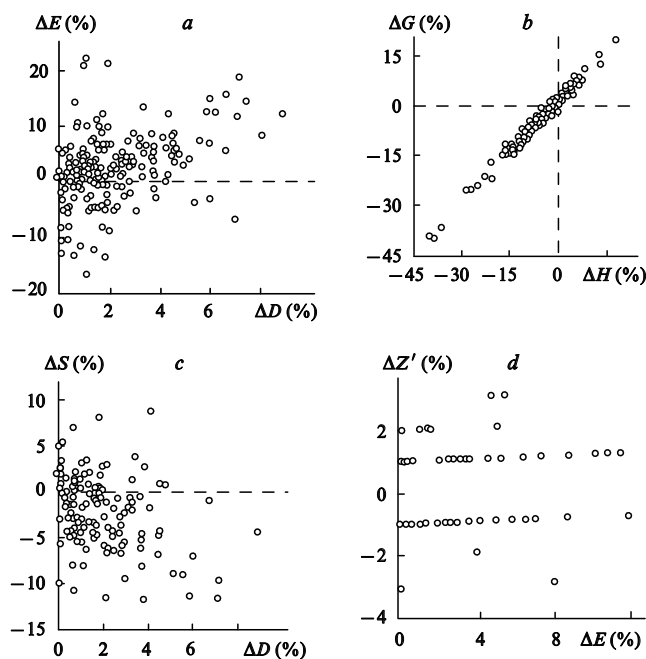


Figure 16. Relationships between ΔE and densities ΔD (a), ΔG and enthalpies ΔH (b), ΔS and ΔD (c), and $\Delta Z'$ and ΔE (d).³

density corresponds to higher packing energy and lower vibrational entropy.

The dependence of $\Delta Z'$ on ΔE is shown in Fig. 16c. The structures with $Z' > 1$ are more stable in ~ 50% of the occurrences. Hence, the presence of more than one molecule per asymmetric unit does not lead to a decrease in the stability of a crystal.

Therefore, the knowledge of thermodynamic characteristics of polymorphs existing at room temperature is insufficient for explanation of their relative stability because the differences in these characteristics are generally small. Thus, it is useful to analyse molecular-packing symmetry to gain insight into the ways of formation of crystal structures in different polymorphic modifications.

The space group remains the same for 28% of the polymorphic pairs under consideration; 82% of all structures belong to the group $P2_1/c$ and the remaining 18% of the structures are distributed among the groups $P\bar{1}$, $Pbca$, $C2/c$ and $P2_12_12_1$. The greatest number of plausible arrangements of the same molecule was observed for organic crystals belonging to the group $P2_1/c$.

As mentioned above, one of polymorphic forms often has $Z' > 1$. Although a detailed analysis of such cases has not been performed, preliminary consideration of the data revealed instances in which molecules in the asymmetric unit are related by pseudosymmetry operations. A detailed examination of pseudosymmetry relations in crystals will allow one to 'visualise' possible ways of formation of crystal structures, which have not been realised.

The authors also noted that in 20 polymorphic pairs (24%) the molecules decide between centrosymmetrical and noncentrosymmetrical space groups. Ten pairs $P2_1/c - P2_12_12_1$, six pairs $P2_1/c - P2_1$, four pairs $P2_1/c - Pc$ and four pairs $P2_1/c - Pna2_1$ were found.

Comparison of thermodynamic characteristics of the polymorphs did not allow the authors of the works cited (Refs 3, 49 and 50) to reach definite conclusions about regularities of organisation of crystal structures. However, although the analysis of structural regularities in polymorphic modifications did not provide answers to the problems under considerations, it doubtlessly made it possible to mark the route and develop a strategy of further investigations in this field.

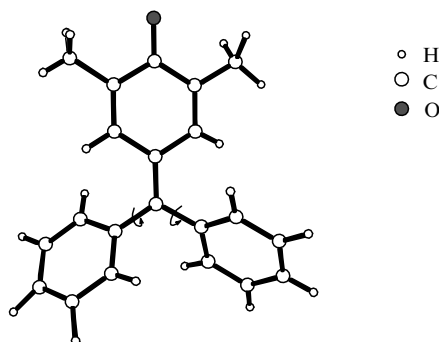


Figure 17. Molecular structure of 2,6-dimethyl-4-(diphenylmethylene)cyclohexa-2,5-dienone (DMFUSC).^{101, 102}

We attempted to search for PM containing chiral–racemic partners in the 1996 version of the CSD. A total of 102 such pairs were found. The same distribution pattern of chiral and racemic modifications was observed: 45 pairs (44.1%) $P2_1/c - P2_12_12_1$, 17 pairs (16.7%) $P2_1/c - P2_1$, 14 pairs (13.6%) $P2_1/c - Pna2_1$, 10 pairs (9.8%) $P2_1/c - Pc$, 3 pairs (2.9%) $P2_1/c - P\bar{1}$, 7 pairs (6.9%) $P\bar{1} - P2_12_12_1$, 2 pairs (2.0%) $P\bar{1} - P2_1$, 2 pairs (2.0%) $P\bar{1} - Pc$ and 2 pairs (2.0%) $P\bar{1} - Pna2_1$. We hope to reveal reasons for the preferential occurrence of these chiral–racemic pairs from a detailed analysis of structures of these polymorphic modifications.

Let us offer an example of a typical situation for the $P2_1/c - P2_12_12_1$ pair. In the case of 2,6-dimethyl-4-(diphenylmethylene)cyclohexa-2,5-dienone^{101, 102} (DMFUSC),[†] the molecules adopt identical conformations in both polymorphic modifications. The chirality in the molecule (Fig. 17) is determined by the difference in the rotation of the phenyl rings. In solutions, both enantiomeric forms are present due to rotation of the rings. In both crystals, molecules of one enantiomeric form are packed in identical layers (Fig. 18). The adjacent layers in the β form ($P2_12_12_1$) are stacked in a congruent fashion, while in the α form ($P2_1/c$) the adjacent layers are related by centres of symmetry. The $\alpha - \beta$ phase transition was observed at 383 K. Therefore, in this case two polymorphic modifications exist due to different modes of packing of layers and the enantiomeric forms readily undergo interconversion with a small consumption of energy. Analogous

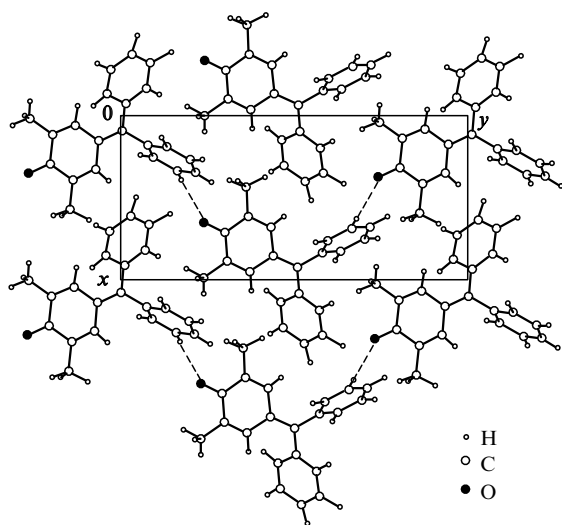


Figure 18. Structure of the layer in the orthorhombic modification of DMFUSC (projection onto the $xy0$ plane). The layer in the monoclinic modification has an analogous structure.

situations were observed in di(1-piperidyl) disulfide¹⁰³ (DPIPDS),[‡] *o*-chlorobenzamide¹⁰⁴ (CLBZAM),[‡] *m*-nitrophenol^{105, 106} (MNPOL),[‡] and bis(trimethylbenzylammonium) tetrachlorocuprate(II)¹⁰⁷ (MBAMCC).[‡] These compounds can be assigned to the first group, *i.e.*, they are enantiomers that interconvert rapidly.

VII. Number of molecules per asymmetric unit and pseudosymmetry

As mentioned above in the section devoted to the relative frequency of occurrence of space groups, the increasing attention is paid to crystal-chemical analysis of structures with $Z' > 1$. Several computer programmes have already been developed for revealing pseudosymmetry in such crystal structures.^{108, 109} These programmes were devised originally for revealing improper symmetry in structural studies and therefore they treat pseudosymmetry as a ‘negative factor’. The main purpose of these programmes is to determine deviations of atoms from certain ideal symmetry positions, which imply that some symmetry operations were missing in the course of determination of crystal symmetry.

Initially, when only a few instances of crystals containing two independent molecules per asymmetric unit were known, researchers pinned hopes on comparison of their conformations and molecular geometry. This approach seemed to be very promising for studying the effect of crystal environment on molecular structure. However, expectations were not realised completely because such structures remained for long few in number.

Studies of noncrystallographic (pseudosymmetrical) symmetry operations that related independent molecules in crystals have attracted growing interest as the corresponding structural data has been accumulated.^{45, 53, 54} Analysis of the data in the 1991 version of the CSD demonstrated that in 27% of structures with $Z' > 1$, the molecules are related by approximate pseudosymmetry elements $\bar{1}$, 2, 2_1 and t (translation), *i.e.*, by elements which are also present most often in space groups of crystals.[†] Undoubtedly, a pseudocentre of symmetry is the most frequently occurring element.

In the next stage, relationships between space groups describing the crystal symmetry and pseudosymmetry transformations were searched for. The symmetry of real crystals often appeared to be a symmetry subgroup of a certain ‘hypothetical’ crystal. It is derived by ‘eliminating’ the corresponding symmetry element (which becomes a pseudoelement) from the symmetry group of the hypothetical crystal. Thus, Brock and Dunitz⁴⁵ found 256 crystals belonging to the group $P2_1$ with $Z' = 2$ in the 1989 version of the CSD of which 55 crystal structures contain an inversion pseudocentre and are described by the symmetry pseudogroup $P2_1/c$. It was suggested that the great majority of structures with $Z' > 1$ belonging to the group $P1$ are actually pseudosymmetrical structures.

The application of the CSD made it possible to reveal also some other statistical regularities. Padmaja *et al.*⁴¹ noted that structures with $Z' > 1$ are substantially more frequent in low-symmetry crystal systems (especially in the group $P1$). These results were confirmed.⁴⁵ It was demonstrated that structures with $Z' > 1$ are, on the whole, more abundant in chiral groups than in the corresponding centrosymmetrical groups (see Section IV). Certain preliminary conclusions were made about classes of chemical compounds for which structures with $Z' > 1$ are most often realised. In particular, ~40% of crystals of aliphatic alcohols in the CSD have $Z' > 1$. Craven¹¹⁰ noted that in ~50% of crystals of cholesterol derivatives, $Z' > 1$.

We performed sampling of structures of 3- and 4-hydroxy derivatives of hydropyridine in the 1996 version of the CSD. A total of 320 structures were found of which 21% instances have

[†] The reference code of the compound in the CSD.

[‡] R Davies and A Willer (private communication; see Ref. 45).

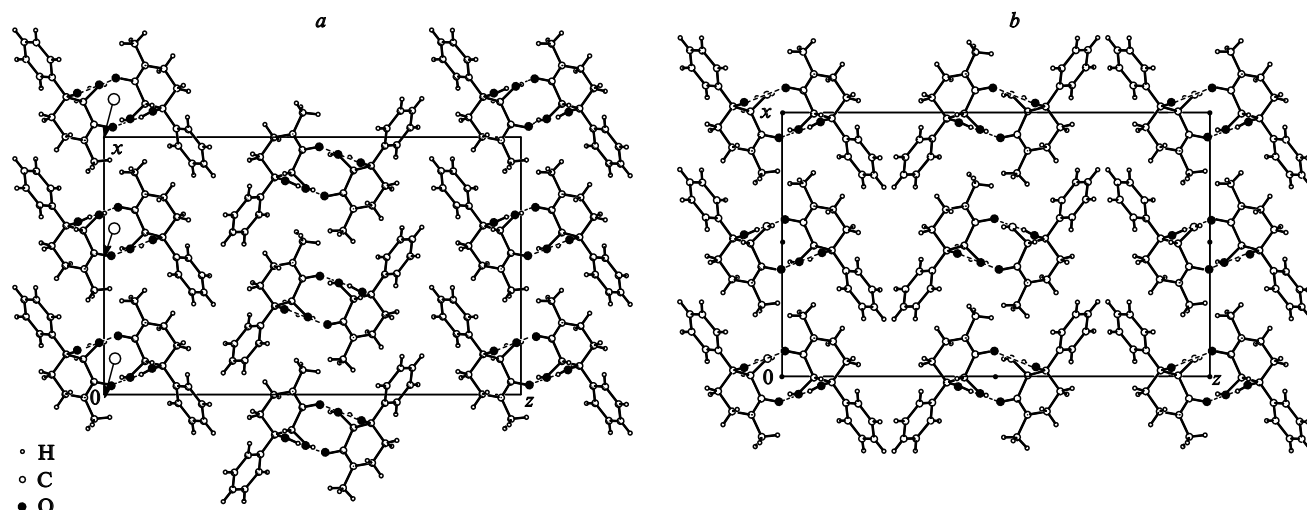


Figure 19. Projection of the crystal structure of 3,4-dihydroxy-1-methyl-2-oxo-4-phenylpiperidine onto the $x0z$ plane (a) and the hypothetical crystal structure obtained by shifting pseudosymmetrical chains in the crystal (b).¹¹¹

$Z' > 1$. Apparently, for all classes of compounds containing hydroxy groups there is a high probability of formation of crystals with $Z' > 1$. It is known that compounds containing hydroxy groups form stable associates in crystals through hydrogen bonds. It can be assumed that these associates are present even in the initial mother liquor from which crystals are grown. Thus single crystals can be formed from associates rather than from isolated molecules. The packing of associates does not necessarily lead to the optimum symmetry due to insignificant shifts required for closer packing.

Let us exemplify the aforesaid by the crystal structure of 3,4-dihydroxy-1-methyl-2-oxo-4-phenylpiperidine,¹¹¹ which crystallised in the space group $Pca2_1$, $Z' = 2$. Two independent molecules are linked in a pseudocentrosymmetrical dimer through hydrogen bonds. These dimers are linked in infinite chains through hydrogen bonds, and the crystal structure as a whole is formed from these layers (Fig. 19a). This noncentrosymmetrical structure can be transformed into the centrosymmetrical one (symmetry $Pbcn$) by slightly shifting the chains with respect to each other. The shift is equal to ~ 1.5 Å. The pseudocentrosymmetrical dimers can be seen in Fig. 19a. Chains formed in the structure through hydrogen bonds are located perpendicular to the plane of the paper. The hypothetical crystal structure and the molecular arrangement are shown in Fig. 19b. It can be seen that the shift of chains in the real crystal with respect to each other leads to a closer packing.

The probability of the detection of $Z' > 1$ and consequently, of the presence of pseudosymmetry is also very high for crystals of mesogenic compounds, which are solid-crystalline precursors of liquid crystals (among them are cholesterol derivatives).¹¹⁰ It is known that mesogenic compounds are prone to aggregation in the liquid state, which does not necessarily occur through hydrogen bonding. For example, in four of eight crystal structures of cholesteryl benzoate derivatives, which do not form intermolecular hydrogen bonds,⁵⁸ $Z' > 1$. Calculations of the energy of intermolecular interactions demonstrated that molecules are packed in crystals in a layered-stacked fashion and the strongest interactions occur between molecules related either by screw axes or by translations along the stack axis. The existence of this energy-distinguishable direction is very important because weaker interactions between layers and stacks are primarily weakened when passing to the mesophase. In this case, shifts of stacks with respect to each other as well as slight mutual rotations of adjacent molecules in stacks about stack axes become possible. Rotations result in the appearance of a supramolecular structure twisted about the stack direction. This structural feature emphasises the

role of screw axes in cholesterogenic crystals. The results reported in the work⁵⁸ suggested that a genetic relationship exists between crystalline and liquid-crystalline structures and can provide the basis for further systematic studies with the use of the CSD data aimed at the design of new compounds potentially exhibiting liquid-crystalline properties.

Interestingly, at least one polymorphic form often has $Z' > 1$. The overall percentage of structures with $Z' > 1$ in the CSD is 8.3%, while twice as many such structures are observed among polymorphic modifications (16%).³ Thus, the presence of more than one independent molecule per asymmetric unit may indicate that several different crystal packings can exist.

The existence of pseudosymmetry in a particular crystal structure is an indication that a distorted higher-symmetry structure can exist. Based on this fact, Abrahams^{53, 54} suggested that if this distortion is rather small, the crystal structure would be expected to become more symmetrical at higher temperature as a result of phase transition. Recall that in the cases of phase transitions of the first and second kinds, the crystal symmetry changes abruptly at the transition point. In the case of phase transitions of the first kind, a correlation between the structures of the initial and newly formed phases can be either present or absent. The characteristic feature of phase transitions of the second kind is that the symmetry group of the low-symmetry phase is a subgroup of the symmetry group of the other phase, because only some symmetry elements disappear as a result of displacements of atoms, while other elements persist. It is the latter that form a subgroup. A higher-symmetry phase corresponds, as a rule, to the high-temperature modification. These reasonings provided the basis for a procedure proposed by Abrahams for a search for new crystals possessing ferroelectric properties in the crystallographic databases. This method is based on the analysis of the available structural data. The ferroelectric phase transition is accompanied by loss of an inversion centre, a mirror plane m or a rotation axis 2. If H is a polar space group of the structure under study, the minimum supergroup G of the paraelectric phase can be written as follows:

$$G = H + \left(\frac{g}{t} \right) H,$$

where the operator $g(\bar{1}, m, 2)$ represents the rotational component. In the general case, the orientation of a plane m or an axis 2 is limited by the space group H , but the translation term (t) of the equation can take any value within limits determined by the group G . To put it differently, an inversion centre, a mirror plane or a

rotation axis that are lost can be located in any position with respect to the original one chosen for the description of the group H . Abrahams restricted the consideration to pseudocentres and mirror pseudoplanes. Polar crystal structures in which deviations (shifts) of atoms Δr with respect to hypothetical nonpolar configurations lie in the range between 0.1 and 1 Å were considered as materials that will, most probably, exhibit ferroelectric–paraelectric phase transitions. It was suggested that the maximum deviation of atoms Δr along the polar axis from the totally symmetrical position be considered as a quantitative parameter for estimating the degree of pseudosymmetry of the structure. On the basis of this parameter, the following empirical equation was derived for predicting the transition temperature:

$$T_c = C(\Delta r)^2,$$

where $C \approx 2.0 \times 10^4 \text{ K } \text{Å}^{-2}$. Abrahams has cast doubt on space groups determined for structures with $\Delta r < 0.1 \text{ Å}$. Compounds satisfying the above conditions⁵⁴ were selected in the Inorganic Crystal Structure Database (1987). For these compounds, more than 50 new ferroelectric crystals were predicted.

Based on the approach developed by Abrahams, Igartua and coworkers⁵⁵ suggested a procedure for systematic studies of materials exhibiting both kinds of high-temperature phase transitions. The authors suggested that compounds possessing pseudosymmetry under ordinary conditions would possess structural phase transitions at elevated temperatures. This was exemplified with the space group $P2_12_12_1$. A total of 442 structures were retrieved from the Inorganic Crystal Structure Database and for 407 of them the values Δr were calculated. It appeared that in all 14 compounds, for which high-temperature phase transitions and pseudosymmetry were reported, $\Delta r < 1.5 \text{ Å}$. About 20 structures with pseudosymmetry and $\Delta r < 1 \text{ Å}$ were additionally found for which phase transitions are highly probable.

Therefore, it is evident that systematic studies of pseudosymmetrical crystals are promising for establishing structural regularities and for design of materials possessing desired physical properties.

An analogous search for organic crystals in the CSD was not carried out. However, it is possible to trace the route to a search for compounds with the desired physical properties in the database based on certain crystal-structural ‘indications’ (for example, values of $Z' > 1$). In particular, systematic analysis of structures of long-chain molecules with $Z' > 1$ will apparently allow one to reveal crystals of new mesogenic compounds. A successful search for new nonlinear-optical noncentrosymmetrical crystals in the CSD was carried out based on a search for molecules similar in geometry to dicyanovinylanisole (a known nonlinear-optical material).¹¹² It appeared that the CSD already contained data on the crystal structure of *p*-chlorodicyanovinylbenzene,¹¹³ which possesses high ability to generate the second harmonic of laser radiation in the crystal.

VIII. Supramolecular synthons and the possibility of prediction of crystal structures

A governing role of intermolecular interactions, in particular of hydrogen bonds, in crystal structures of organic molecules became apparent about 40 years back.^{114,115} At that time, it was already noticed that hydrogen bonds favour the formation of stable molecular associates in crystals. A series of works by Leiserowitz and coworkers in 1969–1978^{116–118} can be considered as the first systematic study in this field. In these works, the authors attempted to derive possible molecular associates that are realised in some classes of chemical compounds, namely, in carboxylic acids and in primary and secondary amides. The geometrical characteristics of hydrogen bonds in crystals were determined for the first time¹¹⁹ based on statistical data on the published crystal structures and the theory of graphs was applied for deducing theoretically possible fragments formed through hydrogen bonds in crystals. In addition, typical and anomalous modes of forma-

tion of such molecular associates were determined based on the analysis of more than 2000 structures.¹²⁰

The determination of the geometrical parameters of different types of hydrogen bonds based on more detailed statistical data became possible as the CSD data have become available. Taylor and Kennard²³ were the first to determine the geometrical parameters of $\text{CH} \cdots \text{O}$ interactions. These interactions are commonly assigned to weak hydrogen bonds. Berkovitch-Yellin and Leiserowitz¹²¹ noted that these weak $\text{CH} \cdots \text{O}$ interactions in crystals along with hydrogen bonds can lead to the formation of stable molecular associates. The works devoted to the consideration of the role of $\text{CH} \cdots \text{O}$ hydrogen bonds in the formation of crystal structures were most completely surveyed in the review.²⁹

More recently, it was shown that the majority of functional groups form a limited number of graph-sets of associates, which are found repeatedly in different structures. Moreover, even chemically different functional groups often form associates described by the same graph-sets.¹²² Each type of interaction is characterised by an inherent ideal geometry of the contact. Therefore, the knowledge of functional groups of a molecule makes it possible to predict, with a high probability, associates that will be present in crystals.

Etter¹²² derived rules for formation of hydrogen bonds in crystals. She has supplemented Donohue’s principle, according to which all ‘acid’ hydrogen atoms in solids participate in hydrogen bonds, by the addition of the following concepts: (1) the hydrogen-bond acceptors are used to the maximum extent if H-bond donors are available and (2) in crystals containing several potential donors and acceptors, H bonds are preferentially formed between the best donor and the best acceptor. The latter principle is very helpful in the analysis of crystal structures of polyfunctional molecules because it makes it possible to reveal a ‘hierarchy’ of formation of hydrogen bonds. Based on this principle in the case of branched systems of H bonds in crystals, Bernstein *et al.*⁶¹ suggested that systems of H bonds be divided into separate subfragments with account of intermolecular distances and symmetry operations of space groups. This approach allows one to unify a procedure for revealing molecular associates formed through H bonds in all crystals listed in the CSD. Etter and Bernstein were the first to perform studies in the field of crystal engineering.^{61,122}

Presently, investigations in this field follow two paths. The first aim is to reveal principles of molecular aggregations in crystals based on studies of the diversity of the available crystal structures. The second line of investigation is aimed at the development of calculation procedures for crystal structures design on the basis of only the molecular geometry.^{1–3} These two lines are ‘two sides of a coin’ and are aimed at solving the direct and inverse problems of crystal engineering.

In studies devoted to the first problem, the nature of forces owing to which molecules in crystal structures are linked in associates (hydrogen bonds, other weaker specific interactions or even usual van der Waals interactions) is first established and then one tries to reveal structural fragments consisting of most strongly bound molecules (supramolecular synthons). Works devoted to the second line of investigation are based on the molecular geometry. One tries to calculate the most favourable mutual arrangement of two molecules (dimers), of chains or planes formed by molecules and finally of a three-dimensional structure.¹ Alternative calculation algorithms are also available (see Ref. 31).

Note that chemists involved in computation of crystal structures address themselves more and more often to structural databases (most often to the CSD) primarily for choosing potential-function parameters and also for testing calculation procedures with the use of a large number of the published crystal structures. The algorithm (FlexCryst) which was developed¹ for predicting organic crystal structures was used for calculating 131 crystal structures belonging to the space group $P1$ and 95 crystal structures belonging to the space group $P\bar{1}$ retrieved from the

CSD. The agreement between the calculated and the real structures was 98% and 85% for the groups $P1$ and $P\bar{1}$, respectively. Needless to say that these results are very promising. However, this algorithm does not presently allow calculations for other space groups. The algorithm MOLPAK² allows one to treat also the space groups $P2_1$, $P2_1/c$ and $P2_12_12_1$. A total of 242 crystal structures were calculated with the use of this program. The programme PROMET allows one to make rather reliable predictions about realisation of a particular space group. This programme made it possible to calculate polymorphic modifications of sulfathiazole, probucol and aspirin.³

IX. Conclusion

Investigations with the use of the CSD as a tool in studying general regularities of organic crystal structures demonstrated that this approach produces good results. Thus the principle of close packing of organic and organometallic compounds in crystals was confirmed by statistical analysis of positions of molecular geometrical centres in crystal unit cells. The statistical values of the van der Waals radii of nonmetals were determined based on the analysis of a large sample of nonbonded interatomic distances in the published structures. The preferential types of molecular packings of organic molecules were revealed and an overwhelming predominance of centrosymmetrical space groups was noted. However, statistical analysis demonstrated no evidence that centrosymmetrical packings are energetically preferable to non-centrosymmetrical structures. Neither gain in density nor noticeable differences in the thermodynamic characteristics were revealed.

Conceivably, a predominance of centrosymmetrical space groups reflects the fact that compounds can exist as racemic mixtures of enantiomers rather than the fact that they are energetically more favourable. If this is the case, then crystals belonging to noncentrosymmetrical space groups can be obtained if one establishes the reasons for spontaneous resolution of enantiomers upon crystallisation or finds a procedure for their forced resolution. It is also probable that noncentrosymmetrical crystals just have received lesser attention and, in spite of a large body of data in the CSD, a sample of compounds in this case is not yet representative. Statistical studies confirmed that molecular association in crystals through hydrogen bonds plays a governing role in the formation of crystal packings. Some structural features of crystals whose packings contain stable synthons (dimers, chains or layers) were revealed. These are, first of all, a high probability of occurrence of polymorphic modifications, structures with $Z' > 1$ and with pseudosymmetry and cases of spontaneous resolution of isomers. These structures often possess (or can possess) useful physical properties. A procedure was developed for the search for new ferroelectrics and other materials exhibiting phase transitions.

Analysis of the results of the first systematic statistical studies of organic crystal structures with the use of the CSD allows one to draw up a plan of further investigations in this field. Thus the first stage of studies of the reasons for spontaneous resolution of enantiomers upon crystallisation should apparently involve the establishment of types and forms of molecules that can undergo spontaneous resolution and analysis of the role of molecular association in crystals (apparently, from the initial solution). In this respect, it is very advantageous to compare crystal packings of compounds having centro- and noncentrosymmetrical polymorphic modifications. A search for compounds exhibiting polymorphic transformations and compounds potentially possessing liquid-crystalline and nonlinear-optical properties in the CSD can be rather simple. These are only some applications of the CSD.

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^c — *J. Struct. Chem. (Engl. Transl.)*

^d — *Russ. J. Inorg. Chem. (Engl. Transl.)*

Donor – acceptor complexes and radical ionic salts based on fullerenes

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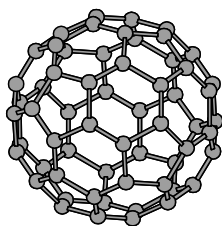
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Abstract. The review generalises for the first time the published data on the synthesis and properties of donor-acceptor type of compounds based on fullerenes, various solvates and clathrates, inclusion compounds, molecular complexes and charge-transfer complexes both with inorganic donors and with organoelement donors of the tetrathiafulvalene, amine, metallocene and metalloporphyrin series. Radical ionic salts of fullerenes with bulky cations and alkali metals obtained by intercalation or by direct synthesis in solution are discussed. Results of studies of fullerene compounds by IR, optical, ESR, X-ray photoelectron and ^{13}C NMR spectroscopy, as well as their conducting (including superconducting), magnetic and optical properties are discussed. The bibliography includes 208 references.

I. Introduction

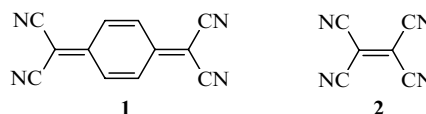
The discovery of fullerenes, a new allotropic modification of carbon, in the mid-80's¹ confirmed the prediction of theorists^{2,3} on the possible existence of polyhedral carbon molecules with icosahedral symmetry.



In the early 90's, a simple method to obtain fullerene C_{60} in gram amounts was found; this gave an impetus to more detailed studies of physical and chemical properties of the C_{60} clusters and compounds based on them.⁴ The number of works in this area grows steadily, and they cover an ever wider range of fundamental and applied branches of science and technology. In 1996, Kroto, Smalley and Curl were awarded the Nobel Prize in chemistry for

the discovery of fullerene and for their great contribution to the development of this area.

Generally, fullerenes display acceptor properties^{5–7} and can be regarded as π -acceptors. They can form various donor–acceptor (D–A) non-covalent compounds, similar to the well-known planar π -acceptors, *e.g.*, tetracyanoquinodimethane **1** (TCNQ), tetracyanoethylene **2** (TCNE), *p*-quinone, *etc.*^{5,8}



These D–A compounds are formed due to rather weak (in comparison with the standard covalent chemical bonds) van der Waals interactions and due to charge transfer from the donor to the acceptor.⁹ Charge transfer plays a very important role and results in qualitatively new physicochemical properties of these compounds. D–A compounds can be divided into several groups according to the degree of charge transfer (δ), although there is no distinct boundary between these groups. The compounds with δ close to zero can be attributed to molecular complexes. In the case of partial charge transfer from the donor to the acceptor ($0 < \delta < 1$), charge-transfer complexes (CTC) $\text{D}^{\delta+}\text{A}^{\delta-}$ are formed. For example, in the TTF–TCNQ complex, where TTF is tetrathiafulvalene, different estimates give $\delta = 0.48–0.67$.⁸ A characteristic feature of CTC is the appearance of a new band in the absorption spectrum of the complex in the visible and near IR regions due to the transfer of an electron from the donor to the acceptor when absorption of a light quantum occurs.⁹ In the extreme case, *i.e.*, in the complete charge transfer from the donor to the acceptor or in the formation of a compound from oppositely charged ions, radical ionic salts $\text{D}^{n+}\text{A}^{n-}$ are formed (in the case of radical ionic salts of fullerenes, n is an integer).

The charge-transfer complexes and radical ionic salts based on planar polyconjugated heterocyclic π -donors and acceptors are being intensely studied lately. Many of them, the so-called organic metals, have unique conduction and magnetic properties.^{10,11}

Radical cationic salts of tetrathiafulvalene derivatives draw special attention. The majority of organic metals and superconductors obtained to date correspond to this class of compounds.^{10,11}

The discovery of fullerene has given the researchers a new π -acceptor with a number of essential features that distinguish it from other acceptor molecules: larger size, spherical shape, unique electronic structure, high symmetry and polarisability. The resulting specific features of donor-acceptor interactions in compounds of the C_{60} fullerene enabled the design of materials with

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unusual physical properties. For example, it was found that intercalation of C_{60} by alkali metals results in superconductors with composition M_3C_{60} ($M = K, Rb, Cs$) with rather high superconductivity transition temperatures (T_c) ($18 \leq T_c \leq 40$ K).^{12–14} The salt of C_{60} with an organic donor, tetrakis(dimethylamino)ethylene (TDAE), is a ferromagnetic with $T_c = 16.1$ K,¹⁵ and apparently has superconducting properties.¹⁶ Combination of conducting polymers with fullerene enables efficient phototransfer and separation of charges with long lifetime, which increases considerably the photoconductivity of polymers and can be utilised in xerography and energy phototransducers.¹⁷

By now, a considerable number of various D–A compounds of fullerenes have been obtained, including molecular complexes, CTC and radical ionic salts with different states of oxidation or reduction. The C_{60} fullerene molecule can accept up to 12 electrons^{13, 14, 18} and release one electron,⁷ *i.e.*, the charge of the C_{60} molecule can vary from +1 to –12. As a result, C_{60} compounds manifest a broad spectrum of properties.

The considerable interest of experts from different areas in fullerenes and compounds based on them is reflected in a number of books and reviews.^{19–28} In particular, the reviews are devoted to chemistry,²¹ spectroscopy^{22–26} and magnetic properties²⁷ of fullerenes and compounds based on them, as well as to intercalation of fullerenes with alkali and alkaline-earth metals.^{13, 14, 28}

The present review generalises for the first time the published data on the synthesis of D–A compounds based on fullerenes that are formed both through van der Waals interaction and charge transfer. These include solvate and clathrate compounds, inclusion compounds, molecular complexes, CTC and radical ionic salts of fullerenes with organic and organometallic donors and various metals. Data on IR, electronic, ESR, X-ray, photoelectron and ¹³C NMR spectroscopy are considered. The features of D–A complexes and radical ionic salts of fullerenes, including superconducting, magnetic and optical properties, are discussed.

II. Fullerenes

1. Features of fullerene structure

It is known that the molecule of the C_{60} fullerene has icosahedral symmetry (group I_h), and its surface consists of 20 six- and 12 five-membered rings.¹

The molecule of the C_{70} fullerene consists of 25 six-membered and 12 five-membered rings. It has an elongated shape and lower symmetry (D_{5h}). Higher fullerenes also represent polyhedral molecules and contain a larger number of hexagonal facets.²⁵

All 60 carbon atoms in the C_{60} molecule are equivalent, which is confirmed by the presence of a single signal in the ¹³C NMR spectrum.²⁹ The mean C–C distance in C_{60} (1.44 Å) is close to the C–C distance in graphite (1.42 Å). Each carbon atom in the C_{60} molecule is linked to three other carbon atoms by two longer 6–5 bonds in five-membered rings and by one shortened 6–6 bond, which is common to two fused six-membered rings. Thus, the carbon atoms in C_{60} have a near- sp^2 hybridisation.^{25, 30}

Usually, the symmetry axis of the π -orbital is orthogonal ($\theta_{\sigma\pi} = 90^\circ$) to the plane of the three σ -bonds in the sp^2 hybridisation. Because of the spherical shape of the C_{60} fullerene molecule, the four mutually linked carbon atoms do not lie in the same plane and the angle $\theta_{\sigma\pi}$ is 101.64° rather than 90° .³⁰ Thus, pyramidalisation of carbon atoms occurs in fullerenes, which results in significant strain in the fullerene molecule and changes the character of the π -orbitals; thus, there is certain contribution by a σ -orbital to the π -orbitals of all fullerenes. Pyramidalisation affects strongly the electronic properties of fullerenes and pre-determines their high electron affinity, as the strain in the molecule is partially eliminated upon reduction of fullerenes.³⁰

2. Donor – acceptor properties and polarisability of fullerenes

The ionisation potentials (IP),²⁵ electron affinities (EA)⁶ and the corresponding redox potentials (E_{Ox} , E_{Red})³¹ of the C_{60} , C_{70} and C_{76} fullerenes are listed in Table 1.

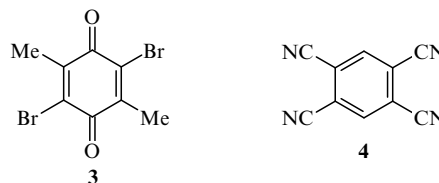
Table 1. Vertical electron affinity (EA),⁶ first and second reduction potentials of fullerenes (E_{Red}^1 and E_{Red}^2),³¹ ionisation potentials (IP)²⁵ and oxidation potentials of fullerenes (E_{Ox}).⁷

Fullerene	EA/eV	E_{Red}^1 /V ^a	E_{Red}^2 /V ^a	IP/eV	E_{Ox} /V ^b
C_{60}	2.67	–0.44	–0.82	7.58	+1.26
C_{70}	2.68	–0.41	–0.80		+1.20
C_{76}	2.86	–			+0.81

^a CH_2Cl_2 , SCE, 0.05 M $Bu_4^+NBF_4^-$; ^b relative to Fc/Fc^+ (Fc is ferrocene).

The first redox potentials of the C_{60} and C_{70} fullerenes in the polar solvents are close to each other. The redox potential of the C_{60}/C_{60}^- pair is –0.44 V in dichloromethane and acetonitrile^{5, 31} and –0.33 V in tetrahydrofuran³² relative to the saturated calomel electrode (SCE). These values are 0.6–0.7 V smaller than the corresponding redox potentials of TCNQ (+0.22 V) and TCNE (+0.28 V).⁵ Changing the polarity of the solvent shifts the redox potential of C_{60} insignificantly. For example, the redox potential in nonpolar benzene is –0.36 V relative to SCE.³²

The C_{60} fullerene is rather a weak acceptor. The EA of C_{60} in the gas phase is 2.67 eV.⁶ The adiabatic EA of C_{60} in solution (estimated from the energy of charge transfer and redox potentials) is much lower and equals 2.10–2.20 eV.⁵ These values are comparable with the EA of such weak acceptors as 3,6-dibromo-2,5-dimethylquinone (**3**) or 1,2,4,5-tetracyanobenzene (**4**) (2.1 eV) but are much lower than those of TCNQ (2.82 eV) and TCNE (2.90 eV).⁵



One possible way to increase the EA is the introduction of strong acceptor substituents in fullerenes. It has been shown^{33, 34} that halogenated fullerenes have stronger acceptor properties than C_{60} . For example, the theoretically calculated EA for $C_{60}Br_8$ is ~ 4.0 eV.³³ Fluorinated fullerenes, *viz.*, $C_{60}F_{36}$, $C_{60}F_{48}$ and $C_{70}F_{54}$, have considerably more positive first redox potentials than the corresponding fullerenes (–0.05, +0.51 and +0.76 V, respectively, relative to an Ag/Ag^+ reference electrode in dichloromethane).³⁴ The electron affinities of $C_{60}F_{36}$ and $C_{60}F_{48}$ are also higher than that of C_{60} (3.48 and 4.06 eV, respectively).³⁴ Functionalisation results in significant changes in the symmetry and electron structure of the C_{60} fullerene.³³

Fullerenes, especially C_{60} , have high oxidation potentials. The ESR method detected the formation of the C_{60} radical cation in solutions containing strong oxidants,³⁵ but individual compounds in which C_{60} is charged positively have not been isolated yet.

Higher fullerenes possess higher electron affinities, and thus they are stronger acceptors. The C_{76} fullerene and other higher fullerenes undergo oxidation a little more readily than C_{60} .⁷ For example, C_{76} is oxidised with hexabromocboranyltris(2,4-dibromophenyl)ammonium ($E_{Red} = +1.16$ V) to give a radical cationic salt with positive charge on the fullerene.⁷

The polarisability of the C_{60} fullerene molecule is high ($\alpha \sim 85$ Å)³⁶ and is several times higher than that of other π -acceptors. Therefore, polarisation van der Waals forces are essential in the formation of D–A complexes and radical ionic salts of fullerenes.

3. Features of the crystal structure of C₆₀ fullerene

At room temperature, C₆₀ has a face-centred cubic (FCC) lattice.³⁷ The shortest distance between the centres of the C₆₀ molecules in a crystal is 10.02 Å, which is smaller than the van der Waals diameter of the C₆₀ molecule, considering the size of its π -electron cloud (10.18 Å, Ref. 25), hence the π -orbitals of the C₆₀ molecules in a crystal overlap little. The weakness of interactions between the fullerene molecules in the solid state is the reason for the fast isotropic rotation of the C₆₀ molecules in the crystal. Below 255 K, C₆₀ crystals undergo a phase transition from the face-centred cubic lattice to a simple cubic lattice.³⁷ The rotation of the fullerene molecules in these crystals becomes anisotropic, it slows down, gets synchronised and occurs ratchet. In the case of such rotation, adjacent C₆₀ molecules can be present in two different orientations relative to each other, which have different energies. In the first orientation, the shortened 'double' bond of one C₆₀ molecule is located above the electron-deficient pentagonal facet, whereas in the second orientation, it is above the hexagonal facet of the C₆₀ molecule. As the temperature is decreased, the number of pairs of molecules in the first orientation increases and reaches 83% at 90 K. Below 90 K, the ratio of molecules in the first and second orientations remains constant, but ratchet rotation of the C₆₀ molecules occurs in such a manner that each of two orientations is transformed only to the equivalent one.²⁵ This results in ordering, in which the rotation of the C₆₀ molecules in a crystal is synchronised completely. This kind of ordering can also occur in D–A complexes and radical ionic salts of fullerenes provided that the distances between the C₆₀ molecules are short.^{38–40}

4. Conducting and magnetic properties of fullerenes

The upper unoccupied and lower occupied levels of the C₆₀ molecule are presented in Fig. 1. The highest occupied h_u level is five times degenerate and is completely filled with ten electrons. The lowest free t_{1u} and t_{1g} levels are three times degenerate.^{25, 36}

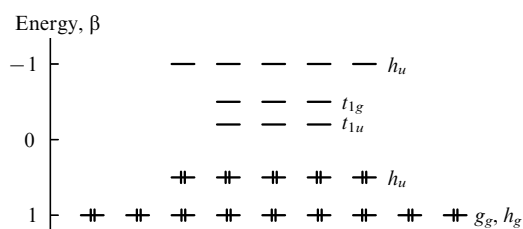


Figure 1. Highest occupied and lowest unoccupied molecular π -orbitals of the C₆₀ fullerene calculated by the Hückel method;³⁶ β is resonance integral.

Overlapping of π -orbitals of the adjacent C₆₀ molecules in a crystal results in the formation of a valence band and a conduction band. The energy gap between the valence band and the conduction band in C₆₀ is estimated as 1.5–1.8 eV,^{25, 36} hence crystalline fullerene is a semiconductor. The highest-energy edge of the valence band consists of the h_u levels, while the lowest-energy edge of the conduction band consists of the t_{1u} levels (see Fig. 1).

Magnetic measurements carried out with pure C₆₀ and C₇₀ fullerene specimens have shown that magnetic transitions are observed at 60 K.⁴⁰ This is due to the fact that the currents of π -electrons in the six- and five-membered fullerene rings are different and create a very small but distinct magnetic moment in the fullerene molecule [for C₆₀, $\mu = -0.35 \times 10^{-9}$ A m² (see Ref. 27)]. Cooling of specimens of pure C₆₀ below 90 K results in the transition to ratchet synchronised rotation of the fullerene molecules. In this transition, the positions of 83% of the magnetic moments of the C₆₀ molecules are frozen in an ordered fashion, but 17% of the magnetic moments are frozen in disorder. This results in a glassy magnetic state.⁴⁰

When C₆₀ specimens are placed in a magnetic field, the magnetic moments of the C₆₀ fullerene molecules are oriented along the external magnetic field. Therefore, cooling of C₆₀ specimens in a magnetic field below the temperature of transition to synchronised rotation of fullerene molecules results in freezing of the ordered positions of the magnetic moments of the C₆₀ molecules and formation of the frozen glassy magnetic state. Heating of the specimens above the temperature of this transition results in violation of the synchronised rotation of fullerene molecules, and ordering of the magnetic moments of the C₆₀ molecules disappears.⁴⁰

III. Donor – acceptor complexes and radical ionic salts of fullerenes

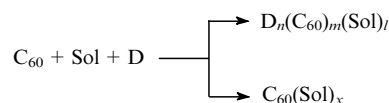
1. Methods of preparation

Fullerene compounds are prepared using various methods: slow concentration of solutions,^{41–43} diffusion methods,^{44–52} cooling of saturated solutions,^{53, 54} precipitation with a solvent^{48–50, 55} and an electrochemical method.^{56–61}

Concentration of solutions containing a fullerene and a donor is the basic method for the preparation of molecular fullerene complexes. The concentration is carried out in an inert atmosphere, as molecular oxygen can be absorbed on the surface of the fullerene molecule, which blocks the approach of the donor to the fullerene.⁶²

As a rule, those solvents are used in which fullerenes are well soluble: carbon disulfide (7.9 mg ml^{−1}), benzene (1.5 mg ml^{−1}), toluene (2.9 mg ml^{−1}) and chlorobenzene (5.7 mg ml^{−1}).^{63, 64} Fullerene forms solvates of the type C₆₀(Sol)_x with many of these solvents.^{65–74}

Two competing reactions occur upon concentration in a reaction system 'donor–C₆₀–solvent':



Sol is a solvent, D is a donor;

$n = 1–6$, $m = 1–3$, $l = 0–4$; $x = 0.4–4$.

Shifting of the reaction equilibrium towards the formation of a complex (as the solvent is present in a considerable excess in comparison with the donor) sometimes requires a great molar excess of the donor relative to the fullerene (up to 100 : 1).^{75–77} As the temperature is increased, the rate of displacement of the solvent by the donor from the solvent shell increases, thus the time of heating or refluxing of the reaction mixture is an essential factor. An increase in the temperature of concentration of fullerene solutions in benzene results in a decrease in the content of benzene in the crystal solvate [C₆₀–C₆H₆], and above 40 °C the solvate is decomposed completely and virtually pure fullerene is formed.⁴²

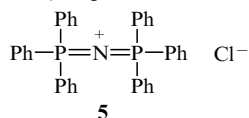
To avoid losses on the walls of the reaction vessel in the preparation of microquantities of complexes, special techniques for the concentration of the solvent in closed volume using a temperature gradient have been developed.^{41, 42}

Fullerene compounds can be isolated from solutions by precipitation or cooling of saturated solutions. For example, radical anionic salts of fullerenes are isolated from solutions in pyridine and benzonitrile by precipitation with non-polar solvents (pentane or hexane). However, this results in polycrystalline specimens.^{48–50, 55} Single crystals of the K₃C₆₀(THF)₁₄ salt can be prepared by slow gradient cooling of a solution obtained by treatment of the C₆₀ fullerene with potassium in tetramethylethylenediamine in the presence of tetrahydrofuran and diethyl ether.⁵³

The diffusion method (in which the vessels with solutions of a fullerene and an appropriate donor are connected by a tube filled with a solvent) is most suitable for the preparation of single crystals of poorly soluble C₆₀ compounds. Single crystals of the

complexes (DAN)C₆₀(C₆H₆)₃ (DAN is dianthracene),⁴⁴ the salt (TDAE)C₆₀ [TDAE is tetrakis(dimethylamino)ethylene]^{45,46} and others have been obtained using this procedure.⁴⁷

The diffusion method is also used in the synthesis of fullerene radical anionic salts by cationic metathesis. The reaction is carried out in two stages. In the first stage, C₆₀ is reduced with an excess of sodium in THF in the presence of dibenzo-18-crown-6^{48–50} or other crown ethers.⁵¹ The degree of reduction of the fullerene to the C₆₀^{n−} anion is controlled by the exact molar ratio of the fullerene and the crown ether (1 : *n*). The salt [Na⁺(18-crown-6)]C₆₀[−](THF)₃ is isolated from THF by precipitation with hexane.⁴⁹ Similar C₆₀^{2−}, C₆₀^{3−} and C₆₀^{4−} salts are poorly soluble in THF and spontaneously precipitate from solutions.^{49,51} In the second stage, the resulting sodium salts of C₆₀ are dissolved in acetonitrile and placed in a vessel. A compound with a bulky cation, for example, bis(triphenylphosphoranylidene)ammonium chloride **5** (PPNCl), is placed in the other vessel.^{50,51}



The vessels are connected by a tube containing the pure solvent. Single crystals of (PPN)₂C₆₀ have been obtained by this method.⁵⁰ Cationic metathesis of Rb₃C₆₀ with the salts Me₄NCl, Et₄NBr and Me₄PCl in liquid ammonia can also be used; the specimens were isolated as powders.⁵²

In the electrochemical method, the radical anions C₆₀^{−•} and C₇₀^{−•} were obtained by reduction of neutral fullerenes in an H-shaped cell on a platinum cathode. Compounds Ph₄PCl or PPNCl with bulky cations were used as the supporting electrolytes.^{56–60} 1,2-Dichlorobenzene or mixtures of dichloromethane with toluene and chlorobenzene with tetrahydrofuran served as the solvents. The fullerene salts crystallised on the cathode.^{56–60}

The salts M_xC₆₀(THF)_y with alkali metals (M = Li, Na, K, *x* ~ 0.4, *y* ~ 2.2) were obtained by electrochemical reduction of C₆₀ in the presence of a supporting electrolyte, *viz.*, the corresponding tetraphenylborate. A mixture of chlorobenzene with THF served as the solvent.⁶¹

2. Solvate and clathrate compounds. Inclusion compounds

Dissolution of C₆₀ in various solvents results in formation of donor–acceptor compounds.^{65,66} The interaction of the solvent with C₆₀ occurs basically through polarisation van der Waals forces. In fact, the solubility of fullerenes in solvents with high polarisability, especially in benzene (*α* ~ 10 Å³) and naphthalene derivatives (*α* ~ 20 Å³) is the highest.^{63,64} Most of the complexes with solvents are unstable, but in some cases C₆₀ solvates can be isolated as crystals by slow concentration of the solutions.^{67–74}

The interaction with the solvent molecules results in the orientational ordering of molecules compared to crystalline C₆₀; in certain cases, this allows one to perform X-ray diffraction studies of these compounds. Solvate compounds have diverse crystal structures: C₆₀(C₆H₆)CH₂I₂ has lamellar packing,⁶⁷ C₆₀(C₆H₆)₄ forms a cage with hexagonal channels,^{68,69} while C₆₀(C₆H₁₂)₂⁷⁰ and C₆₀(1,2-Me₂C₆H₄)₂⁷¹ have hexagonal layered packing. The crystal cells of the solvates have lower symmetry than that of pure C₆₀. However, the crystal structure could not be determined for many solvates, such as C₆₀(Cl₂C=CHCl),⁷² C₆₀(CS₂)⁷³ and C₆₀(CCl₄)₁₀,⁷⁴ because of significant orientational and structural disorder.

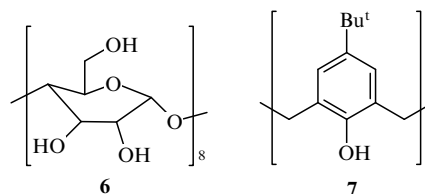
The solvent molecules in clathrate compounds are located in the cavities between the bulky fullerene molecules. Clathrate compounds of C₆₀ are obtained by precipitation of the fullerene from toluene with a large excess of the other solvent, *viz.*, *n*-pentane, 1,3-dibromopropane, butanone, diethyl ether, acetone,⁷⁸ *n*-heptane,⁷⁹ *etc.*^{80,81} The composition of the clathrates is C₆₀(Sol)_{*x*}. For solvents with small molecules, *x* = 1. As the size of solvent molecules increases, *x* decreases. Precipitation of fullerene with isobutane results in pure C₆₀.⁷⁸ Clathrate compounds have

been obtained basically with the solvents in which the solubility of fullerene is very small; this suggests that the interaction between the molecules of the solvent and fullerene is weak.^{78–81}

Solvate and clathrate compounds are characterised by phase transitions related to orientational ordering of the fullerene molecule. For instance, phase transitions for C₆₀(Me₂CO) occur at 240 K,⁷⁸ for C₆₀(CS₂)_{*x*} at 230 K,⁷⁸ for (TSeT)_{*x*}C₆₀(CS₂)_{*y*} (TSeT is tetraselenatetracene) at 203–240 K,⁸² for C₆₀(C₅H₁₂) at 190 K,⁷⁸ for C₆₀[Br(CH₂)₃Br] at 190 K⁷⁸ and for C₆₀(Cl₂C=CHCl), at 167 K.⁷² All these transitions are similar to the phase transition in pure C₆₀ at 255 K.³⁷

Compound (TSeT)_{*x*}C₆₀(CS₂)_{*y*} contains up to 26% of carbon disulfide and only traces of the donor.⁸² The high content of the solvent probably results in orientational disorder and separates the C₆₀ molecules from each other to such an extent that upon complete removal of carbon disulfide the fullerene is completely sublimed at ~ 520 °C, whereas the maximum sublimation rate of pure C₆₀ is reached only at 700 °C.⁸²

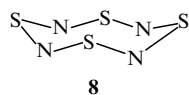
Inclusion compounds of fullerenes are obtained by refluxing aqueous solutions of γ-cyclodextrin (**6** (γ-CD)) with finely dispersed fullerene.^{83–85} There are two types of complexes of γ-CD with C₆₀: one C₆₀ molecule forms van der Waals contacts with two γ-CD molecules, or a van der Waals aggregate of several C₆₀ molecules forms short contacts with several γ-CD molecules.^{83–85} The unique property of these compounds is their solubility in water, therefore such complexes can be utilised in reactions that occur in the presence of water. In particular, complexes of fullerene with γ-CD can be used for medical purposes.⁹⁵ Similar compounds are formed upon dissolution of a mixture of fullerenes with *p*-tert-butylcalix[8]arene (**7**) in toluene.⁸⁶ Complexation with calixarenes has been proposed for efficient separation of fullerene mixtures.^{86,87} It is possible to isolate C₆₀ of 99.5% purity by multiple recrystallisation of a mixture containing 85% C₆₀ and 15% C₇₀.⁸⁶ It was shown that fullerene molecules are separated from each other in crystal structures of compounds C₆₀–*p*-iodocalix[4]arene⁸⁸ and C₆₀–*p*-iodocalix[5]arene.⁸⁹



3. Complexes with inorganic compounds

Complexes of fullerenes with S₈,^{41,90–92} P₄,⁹³ I₂,⁹⁴ S₄N₄,^{75,95} and a number of other small molecules have the composition C₆₀X₂ or C₆₀X(Sol). The crown-shaped S₈ molecule is very flexible, and molecular sulfur readily forms complexes with fullerenes. The structures of compounds C₆₀(S₈)₂ and C₆₀S₈(CS₂) are cage lattices of the fullerene molecules with channels filled with the sulfur molecules.^{90,91} In compounds C₇₀(S₈)₆ and C₇₆(S₈)₆, the fullerene molecules form loose corrugated hexagonal layers with distances between the fullerene molecules 10.2–10.5 Å.^{41,92} All S₈–fullerene compounds contain shortened S–C contacts [3.13–3.52 Å, which is shorter than the sum of the van der Waals radii of sulfur and carbon (3.7 Å)]. As a result of this strong interaction, the rotation of fullerene molecules ceases almost completely. This made it possible to establish the structure of the fullerenes C₇₀ (see Ref. 92) and C₇₆ (see Ref. 36) more precisely. The complex C₆₀(P₄)₂ has a laminar structure.⁹³ In compound C₆₀I₂(C₆H₅Me), iodine can act as an acceptor with respect to C₆₀, as its EA (3.06 eV) is higher than that of fullerene (2.65 eV). This compound has a donor–acceptor sandwich structure, in which the iodine molecules are located between the fullerene and toluene molecules.⁹⁴

Tetrasulfur tetranitride S₄N₄ (**8**), like S₈, has a crown shape and forms a number of molecular complexes with the C₆₀ fullerene.



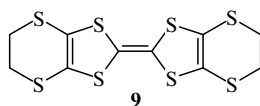
The following compounds were isolated from toluene: $C_{60} \cdot S_4N_4$ and $C_{60}(S_4N_4)_2$.⁷⁵ The similarity of the sizes of the S_4N_4 and benzene molecules results in their mutual replacements in the crystal lattice of the complex. For this reason, compounds of the series $C_{60}(S_4N_4)_{2-x}(C_6H_6)_x$ were isolated from benzene, where $x < 2$.^{75,95} This replacement has a random character, and the use of an excess of the donor yields compounds with a higher content of S_4N_4 . In the crystal structure of the complex $C_{60}(S_4N_4)_{1.33}(C_6H_6)_{0.67}$, the densely packed layers of fullerene molecules alternate with layers of tetrasulfur tetranitride and benzene molecules.⁹⁵

The Pd_6Cl_{12} cluster and C_{60} form a complex $C_{60}(Pd_6Cl_{12})_2(C_6H_6)_3$ with cage structure, in which each fullerene molecule is surrounded by eight Pd_6Cl_{12} molecules.⁹⁶

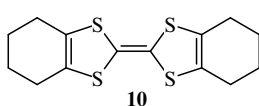
4. Complexes with organic donors

The interest in complexes of fullerenes with donors of the tetrachalcogenafulvalene class (**9–17**) is primarily related to the fact that both tetrathiafulvalene and its derivatives are the main components in the production of organic metals and superconductors.¹⁰

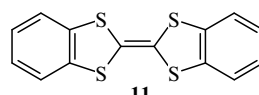
It is known⁹⁷ that tetrachalcogenafulvalenes are strong donors with IPs ranging from 6.3 to 7.4 eV. The molecular polarisability of these donors is 15–38 Å.⁹⁷ Tetrathiafulvalenes have planar structures, sometimes with a small deviation of the terminal groups from the conjugation plane.¹⁰ This structure allows arrangement of their salts in regular stacks or layers. A partial charge transfer ($0.25 \leq \delta \leq 1$) from the donor to the acceptor is a prerequisite for the appearance of conductivity.⁸ Tetrathia(selenium,tellura)fulvalenes **9–17** are widely used as donors for the preparation of complexes with fullerenes.



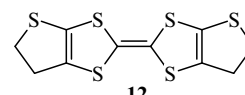
(BEDT – TTF)



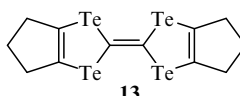
(OM – TTF)



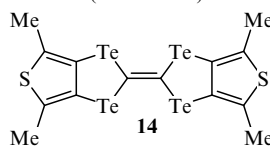
(DB – TTF)



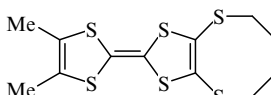
(BET – TTF)



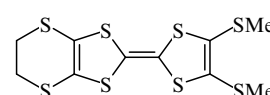
(HM – TTeF)



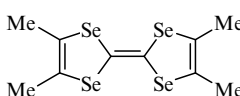
(BDMT – TTeF)



(TMDTDM – TTF)



(C₁TET – TTF)



(TM – TSeF)

The (BEDT-TTF)₂C₆₀ complex was the first to be obtained.⁹⁸ Subsequently, about a dozen compounds of fullerenes with tetrachalcogenafulvalene derivatives have been synthesised (Table 2). It was found that the degree of charge transfer in these compounds is insignificant.^{5,98,103–106} This is due both to the weak acceptor properties of fullerene and the steric factors unfavourable for charge transfer from the π -orbitals of the initially flat donors to the spherical t_{1u} orbital of C₆₀.¹⁰⁶ The formation of complexes with spherical fullerene molecules results in strong distortion of the flat tetrachalcogenafulvalene molecules, which assume boat conformations: the dihedral angles between the flat central fragment E₄C₂ and the terminal groups of tetrachalcogenafulvalene derivatives are 20–30°,^{98,101,103,105,107} which results in some violation of π -conjugation in these molecules.¹⁰⁸

The packing of fullerene molecules in the crystals of these complexes can be diverse: dense^{5,89,100} or rather loose^{107,108} layers of C₆₀ molecules,^{98,100} double chains of C₆₀ molecules^{98,102,110} as well as island motifs with isolated C₆₀ mole-

Table 2. Fullerene complexes with tetrachalcogenafulvalenes.

Donor	Abbreviation	Solvent	Donor : fullerene : solvent ratio	Structural type	Ref.
Bis(ethylenedithio)tetrathiafulvalene	BEDT – TTF (9)	without solvent	2 : 1	chain	98, 99
Octamethylenetetrafulvalene	OM – TTF (10)	C ₆ H ₆	1 : 1 : 1	layered	5
Dibenzotetrathiafulvalene	DB – TTF (11)	C ₆ H ₆	1 : 1 : 1	island	100
		C ₅ H ₅ N	1 : 1 : 1	—	100
		C ₆ H ₆	1 : 1 : 1 ^a	—	100
Bis(ethylenethio)tetrathiafulvalene	BET – TTF (12)	C ₆ H ₅ Me	1 : 1 : 1	layered	101
		C ₆ H ₅ Cl	1 : 1 : 1	"	101
Hexamethylenetetrafulvalene	HM – TTeF (13)	without solvent	1 : 1	"	102
Bis(dimethylthio)tetrafulvalene	BDM – TTeF (14)	CS ₂	1 : 1 : 1	island	103
Tetramethylenedithiodimethyltetrafulvalene	TMDTDM – TTF (15)	CS ₂	2 : 1 : 3	layered	104, 105
Bis(methylthio)ethylenedithiotetrathiafulvalene	C ₁ TET – TTF (16)	without solvent	2 : 1	double chains	106
Tetramethyltetraselenafulvalene	TM – TSeF (17)	CS ₂	1 : 1 : 2	layered	107
		C ₆ H ₆	1 : 1 : 0.5	"	102

^a For the C₇₀ fullerene.

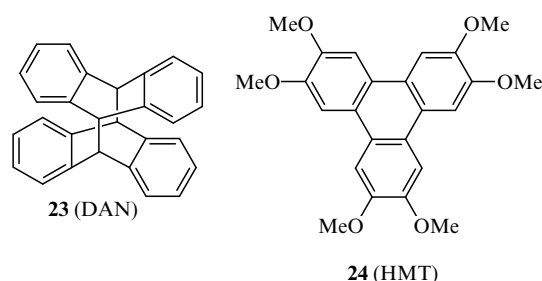
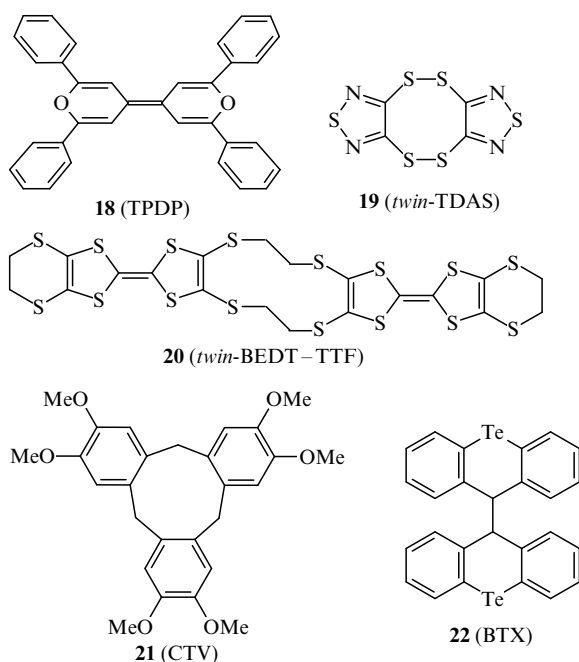
Table 3. Complexes of C₆₀ with organic donors.

Donor	Abbreviation	Solvent	Donor : fullerene : solvent ratio	Structural type	Ref.
2,2',6,6'-Tetraphenyldipyranilidene	TPDP (18)	CS ₂	1 : 2 : 4	layered	43, 109
3,3',4,4'-Tetrathiabis(1,2,5-thiadiazole)	<i>twin</i> -TDAS (19)	without solvent	4 : 3	cage	113
Bis(ethylenedithiotetrathiafulvaleno)[<i>b,h</i>]-1,4,7,10-tetrathiacyclododeca-2,8-diene	<i>twin</i> -BEDT – TTF (20)	CS ₂	1 : 1 : 1	chain	110
Cyclotrivenatrylene	CTV (21)	C ₆ H ₅ Me	1 : 3 : 1	island	114
9,9'- <i>trans</i> -Bi(telluraxanthenyl)	BTX (22)	CS ₂	1 : 1 : 1	"	54, 111
(9,10,9',10')-Bi(9,10-dihydroanthrylene) (dianthracene)	DAN (23)	C ₆ H ₆	1 : 1 : 3	layered	44
2,3,6,7,10,11-Hexamethoxytriphenylene	HMT (24)	without solvent	2 : 1	island	115
SbPh ₃		the same	6 : 1	"	116
Au(PPh ₃)Cl		"	2 : 1	"	117
Hydroquinone		"	3 : 1	"	118

cules.^{101, 105, 111} The donor-acceptor interaction of tetrathiafulvalene molecules with C₆₀ occurs both by the $n-\pi$ type (the n -orbitals of the sulfur atom of the central E₄C₂ donor fragment are directed to the centre of the six-membered ring of one C₆₀ molecule) and by the $\pi-\pi$ type (the central E₄C₂ donor fragment is almost parallel to the six-membered ring of the other C₆₀ molecule).^{98, 105} The distance between heteroatoms of the donor and atoms of the C₆₀ molecule is somewhat shorter than the sum of the van der Waals radii of the corresponding heteroatoms and carbon atoms.^{98–107}

Syntheses of tetrathiafulvalene complexes with halogenated fullerenes have been described. As halogenated fullerenes are stronger acceptors than the C₆₀ fullerene, the oxidation of tetrathiafulvalenes with the formation of radical cationic salts is possible.^{33, 119}

In addition to compounds of fullerenes with tetrachalcogenafulvalene derivatives, compounds with donor molecules of other classes (Table 3) have also been obtained.



The molecules of compounds **21** (CTV),¹¹⁴ **22** (BTX)^{54, 111} and **23** (DAN)⁴⁴ have three-dimensional shapes (BTX and DAN, of the 'double butterfly' type, and CTV, of the hemisphere type). The structures of these molecules match well the spherical surface of the C₆₀ molecule, which forms molecular complexes with them owing to numerous van der Waals contacts. DAN has a unique ability to undergo cocrystallisation with C₆₀ almost quantitatively even from dilute solutions in benzene; this can be utilised for the isolation of C₆₀ from various mixtures.⁴⁴ The C₇₀ fullerene matches less the spatial shape of such molecules as CTV and DAN and does not form complexes with these donors.^{44, 114} However, it forms complexes with composition 1 : 1 : 0.5 with BTX and CS₂.¹¹⁹ Isolated packing of C₆₀ molecules is characteristic of complexes with other donors, such as HMT,¹¹⁵ SbPh₃,¹¹⁶ Au(PPh₃)Cl¹¹⁷ and hydroquinone¹¹⁸ (see Table 3).

All of the complexes described above are dielectrics with a conductivity of $\sim 10^{-6}$ S cm⁻¹ and less.^{5, 100, 103, 104}

5. Composites of conducting polymers with the C₆₀ fullerene

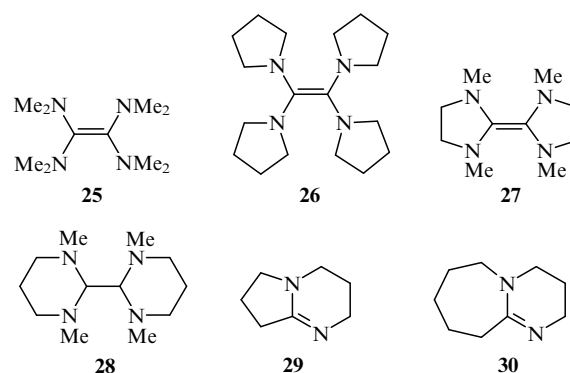
The discovery of the photoinduced charge transfer in polyvinylcarbazole–C₆₀ composites¹⁷ stimulated the intense development of studies in this field. Composites with a dozen of different polymers have been studied by now.¹²⁰ Films of polymer–C₆₀ composites are prepared by concentration of solutions of a polymer and a small amount of a fullerene (from 1% to 3% of the polymer weight) in aromatic hydrocarbons on a substrate.^{17, 120–122}

Only weak charge transfer from the polymer to the fullerene is observed in these composites in the ground state.^{121, 122} For example, an ESR signal corresponding to an insignificant concentration of C₆₀^{•-} (2.3×10^{18} spins g⁻¹) was detected in a composite polyvinylpyrrolidone–C₆₀.¹²²

The polymer photoexcitation occurs at energies higher than the difference between the HOMO and LUMO levels of the polymer. This is accompanied by fast transfer of an electron

The possibility of using these composites in xerography, in solar energy phototransducers and in other devices is being studied.^{120, 121}

Saturated amines, such as *N,N,N',N'*-tetramethyl-*p*-phenylenediamine (TMPD) or triphenylamine (TPA) (see Table 4), possess weaker donor properties than the amine **25**, and form only weak charge-transfer complexes.^{76, 77, 129} These compounds are obtained by concentrating solutions of fullerenes in chlorobenzene with a large excess of the donor (100 : 1). The existence of charge transfer in compounds of C₆₀ with TMPD is confirmed by the presence of an absorption band of C₆₀^{•+} at 1070 nm in the optical spectrum and a shift of the absorption band of the T_{1u}(4) vibration of C₆₀, which is sensitive to charge transfer onto the fullerene molecule, in the IR spectrum.⁷⁶


$$\text{Am} + [\text{C}_{60}] \xrightarrow{k_1} [\text{Am}^+][\text{C}_{60}^-] \xrightarrow{k_2} [\text{Am}^+\text{C}_{60}^-]$$

salt zwitter-ion

If the first reaction step is sufficiently fast (k_1 is high) and the resulting salt is poorly soluble in the solvent (as in the case of TDAE), the reaction stops in the first step, and the salts $[\text{Am}^+][\text{C}_{60}^-]$ can be isolated. If k_1 is small and the formation of salts occurs slowly (as in the case of amines **29**, and, especially, **27** and **30**), and the resulting salts are rather soluble in the solvent, the amine adds to C_{60} in this stage to give diamagnetic zwitterions.^{123, 127, 128} These reactions are accompanied by recombination of radicals, which results in a gradual decrease in the signal of the radical anion C_{60}^- . The addition products that are precipitated from the solution contain a small amount of the radical anion C_{60}^- [4% and 2% for (DBU) C_{60} and (TMBI) C_{60} , respectively^{123, 128}]. Fullerene mixed addition and reduction products are perhaps formed in the reaction. If the salt is rapidly precipitated from benzene, the addition cannot go to completion. In this case, the reaction product, *viz.*, (DBN) C_{60} , contains a large percentage of reduced C_{60}^- (14%) and manifests strong magnetic fluctuations down to 80 K.¹²⁷ The addition of amines to C_{60} complicates the study of these compounds and results in significant differences in the estimation of their magnetic properties.

The compound (TDAE)C₆₀ has been studied by IR,¹³³ Raman,¹³⁴ ESR,¹³⁵⁻¹³⁷ NMR¹³⁸ and X-ray photoelectron¹³⁹ spectroscopies. The temperature of ferromagnetic transition in (TDAE)C₆₀ is 16.1 K. It has been shown^{39,43,135} that the onset of

Table 4. Donor-acceptor complexes and radical ionic salts of C₆₀ with amines.

Donor	Abbreviation	D : C ₆₀ ratio	Compound type	S ^a	Magnetic properties	Ref.
Tetrakis(dimethylamino)ethylene	TDAE (25)	1 : 1	salt	1	ferromagnetic ($T_c = 16.1$ K)	15
Tetrakis(pyrrolidino)ethylene	TPYE (26)		—		superposition of paramagnetic and ferromagnetic phases	125
2,2-Bi(1,3-dimethylimidazolidin-2-ylidene)	TMBI (27)	1 : 1	CTC	0.02	weak paramagnetic	123
			see note ^b		ferromagnetic ($T_c < 140$ K)	124
2,2'-Bi(1,3-dimethylhexahydropyrimidin-2-yl)	TMBH (28)	—	—		antiferromagnetic	126
1,5-Diazabicyclo[4.3.0]non-5-ene	DBN (29)	2 : 1	CTC ^b	0.14	weak antiferromagnetic	127
1,8-Diazabicyclo[5.4.0]undec-7-ene	DBU (30)	2 : 1	CTC ^b	0.04	only near magnetic order observed	128
<i>N,N,N',N'</i> -Tetramethyl- <i>p</i> -phenylenediamine	TMPD	1 : 1	CTC		—	76, 129
Triphenylamine	TPA	1 : 1	molecular complex		—	77
1,5-Diaminopentane	DAP	3 : 1	—		—	130, 131

^a Number of spins per formula unit determined by ESR; ^b addition of amine to fullerene is possible.

the ferromagnetic state in (TDAE)C₆₀ specimens requires that they were kept for several days at 20–100 °C (constant temperature). Without this procedure, the (TDAE)C₆₀ specimens manifest only antiferromagnetic properties.^{39, 43, 135}

Several mechanisms for the origin of the ferromagnetic state in (TDAE)C₆₀ have been discussed.^{38, 140, 141} It has been shown by ESR^{137, 142} that in (TDAE)C₆₀ complete charge transfer from the donor to the fullerene occurs. It was assumed that ferromagnetism is due to the presence of the radical anion C₆₀^{•−}. However, other salts with the radical anion C₆₀^{•−} do not manifest any ferromagnetism.^{38, 141}

It was suggested^{38, 39} that ferromagnetism in (TDAE)C₆₀ is also determined by the presence of the radical cation TDAE^{•+}. The ESR spectrum of (TDAE)C₆₀ contains only one line with $g = 2.0008$, which is an average value between those for TDAE^{•+} ($g = 2.0035$) and C₆₀^{•−} ($g = 1.9960$).^{38, 142} This is probably due to the strong exchange interaction between TDAE^{•+} and C₆₀^{•−}. The C₆₀ molecules in crystalline (TDAE)C₆₀ are packed in one-dimensional chains along the crystallographic axis $\bar{c}$ with shortened distances between the centres (9.98 Å)^{15, 45} (Fig. 2). The presence of shortened contacts between the C₆₀ molecules allows the slowing down of the rotation of these molecules on cooling, with transition to synchronised ratchet rotation, as in crystals of pure C₆₀ cooled below 90 K. In fact, the rotation of the C₆₀ fullerene molecules in (TDAE)C₆₀ slows down at temperatures below 150 K, as confirmed by broadening of the ¹³C NMR signal.^{38, 138} According to theoretical calculations, the negative charge of the radical anion C₆₀^{•−} is mostly concentrated in the equatorial area of the fullerene sphere. Because of this, long-range magnetic order can be formed in this salt upon transition to synchronised rotation of C₆₀ molecules.^{38, 39} In this case, the spins of C₆₀^{•−} in the fullerene chain along the crystallographic axis $\bar{c}$ are ordered antiferromagnetically. The antiferromagnetic interaction can be transferred between the fullerene chains through the radical cation TDAE^{•+} (see Refs 38 and 39).

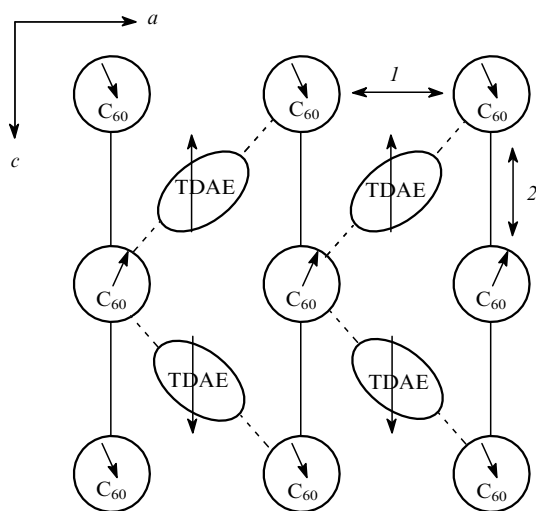


Figure 2. Scheme for formation of ferromagnetic order in the salt (TDAE)C₆₀ by the spin polarisation mechanism;^{38, 39} (1) is ferromagnetic interaction; (2) is antiferromagnetic interaction.

According to theory,³⁹ distortion of the radical cation TDAE^{•+} may result in inhomogeneous spin density distribution on TDAE^{•+} (Fig. 2). In fact, after keeping of the salt (TDAE)C₆₀ at constant temperature,³⁹ the ¹H NMR spectrum displays two sets of lines (A and B) from the methyl groups of TDAE^{•+} (see Ref. 138). This implies an asymmetrical spin density distribution in the radical cation TDAE^{•+}. Asymmetrical spin density distribution results in violation of the antiferromagnetic order of the C₆₀^{•−} spins (Fig. 2) and the onset of ferromagnetic transition

below 16.1 K. Ferromagnetic ordering of the C₆₀^{•−} spins is observed in the plane ab normal to the crystallographic axis $\bar{c}$ (Fig. 2).

Compound (TDAE)C₆₀ manifests only antiferromagnetic properties without preliminary keeping at constant temperature. In this case, the spin density is uniformly distributed on TDAE^{•+}, and the intensity ratio of lines A and B in the ¹H NMR spectrum of (TDAE)C₆₀ differs from that of the specimens kept at constant temperature.^{39, 138}

No ferromagnetic properties have been found for compounds of TDAE with higher fullerenes (C₇₀–C₉₆). This is apparently due to differences in the electronic structures of C₆₀^{•−} and radical anions of higher fullerenes, as the negative charge in the mono-anions of higher fullerenes was found to be delocalised over the entire anion surface rather than in the equatorial area of the sphere, as is the case in C₆₀^{•−} (see Ref. 143).

The conducting properties of some compounds of fullerenes with amines have been studied.^{45, 46, 123} The antiferromagnetic phase of the salt (TDAE)C₆₀ displays semiconductor properties with a conductivity of about 10^{−5} S cm^{−1} and an activation energy (E_a) of 0.4–0.8 eV.⁴⁶ The conductivity of the ferromagnetic phase of (TDAE)C₆₀ at room temperature is of the same order of magnitude (5 × 10^{−5} S cm^{−1}). It is also of activated character and is due to tunnelling of electrons between the fullerene molecules. Electron transfer is largely affected by the rotation of fullerene molecules; for this reason, the decrease in the activation energy at 150 K from 0.3 to 0.14 eV is explained by slowing down of the rotation of C₆₀ molecules in this salt.⁴⁵ It was shown¹²³ that the conductivity of (TMBI)C₆₀ is 5 × 10^{−4} S cm^{−1}.

Measurements on a SQUID magnetometer have shown that a superconducting phase with $T_c = 17.4$ K may be present in (TDAE)C₆₀.¹⁶ The volume of the superconducting phase increases if the sample is cooled very slowly at ~150 K, which temperature corresponds to the transition to hindered and synchronised rotation of the C₆₀ molecules.

7. Complexes and radical ionic salts of C₆₀ with metallocenes

Table 5 lists the compounds of C₆₀ with metallocenes. The donor properties of metallocenes vary over a wide range, and they can form compounds with different degrees of charge transfer with fullerenes (from molecular complexes to radical ionic salts containing C₆₀^{3−•}).^{50, 151} The cyclopentadienyl rings of metallocenes coordinated with fullerenes are parallel to the five-membered fullerene rings. For example, the deviation from this plane in the structure [(C₅Me₅)₂Ni]C₆₀(CS₂) is only 0.3° (see Ref. 149). Such a coordination ensures the maximum overlapping of the metallocene and fullerene π -orbitals and efficient charge transfer.

Two types of structures are characteristic of compounds of metallocenes with fullerenes. In compounds of C₆₀ with ferrocene and cobaltocene, dense layers of fullerene molecules alternate with layers of the metallocene molecules.^{47, 145} The layers of the fullerene molecules in compounds with substituted metallocenes are looser and also alternate with the layers of the donor.¹⁴⁹ The physical properties of these compounds are little studied. It is known that the ESR spectra of compounds of C₆₀ with nickelocene and decamethylferrocene contain a signal corresponding to C₆₀^{•−} (see Ref. 147). The complexes [(C₅H₅)₂Ni]C₆₀ and [(C₅H₅)₂Co]C₆₀ display magnetic properties with an S-shaped magnetisation curve which has a hysteresis. However, these properties disappear on exposure of the specimens to air,¹⁴⁰ which indicates that the radical anions C₆₀^{•−} in these complexes are sensitive to oxygen. It has been shown that the conductivity of [(C₅Me₅)₂Ni]C₆₀(CS₂) is rather high (10^{−2} S cm^{−1}).¹⁴⁹

8. Fullerene salts with bulky cations

Radical anionic salts of C₆₀^{•−} and C₇₀^{•−} with bulky cations, such as Ph₄P⁺, PPN⁺ and others,^{56–58, 152–154} are stable in air (Table 6). Each radical anion of C₆₀ in these ionic compounds is located in a highly symmetrical cationic environment. The phenyl substituents

Table 5. Compounds of C₆₀ fullerene with metallocenes.

Donor	Solvent	D : C ₆₀ : Sol ratio	Compound type	Magnetic properties	Ref.
(C ₅ H ₅) ₄ Fe ₄ (CO) ₄	C ₆ H ₆	1 : 1 : 0.3	molecular complex	—	144
(C ₅ H ₅) ₂ Fe	without solvent	2 : 1	the same	—	145
(C ₅ Me ₅) ₂ Fe	the same	2 : 1	CTC ^{a, b}		146
Biferrocenyl	MeCN	0.8 : 1 : 0.7	CTC	superposition of paramagnetic and ferromagnetic phases	147
(C ₅ H ₅) ₂ Ni	without solvent	1 : 1	CTC ^{a, b}	displays magnetic properties ^b	146
(C ₅ Me ₅) ₂ Mn	the same	1 : 2	CTC		148
(C ₅ Me ₅) ₂ Ni	CS ₂	1 : 1 : 1	CTC ^a	$\sigma = 10^{-2} \text{ S cm}^{-1}$	149
(C ₅ H ₅) ₂ Co	PhCN	1 : 1 : 1		displays magnetic properties ^b	48
	CS ₂	1 : 1 : 1	CTC ^{a, b}	the same	47
(C ₆ H ₆) ₂ Cr	without solvent	1 : 1	CTC		150
(C ₅ Me ₅) ₂ Co	PhCN	1 : 1 : 1	salt C ₆₀ ⁿ⁻ ($n = 1, 2, 3$)		50
(C ₅ H ₅)(C ₆ Me ₆)Fe			salt C ₆₀ ⁿ⁻ ($n = 1, 2, 3$)		151

^a The compound gives a signal corresponding to C₆₀[•] in ESR spectra; ^b the compound gives an S-shaped magnetisation curve with hysteresis.¹⁴⁷

Table 6. Salts of fullerenes with bulky cations.

Cation	Composition	Charge on the fullerene	Method of synthesis	Ref.
Ph ₄ P ⁺	(Ph ₄ P)C ₆₀ (Ph ₄ PCl)	−1	electrocrystallisation	57
	(Ph ₄ P)C ₆₀ (Ph ₄ PCl) ₂	−1	"	56
	(Ph ₄ P) ₂ C ₆₀ (Ph ₄ PBr)	−1	"	152
	(Ph ₄ P) ₂ C ₆₀ I _x ($0 < x < 1$)	−1	"	153
	(Ph ₄ P)C ₇₀ (Ph ₄ PI)	−1	"	154
Ph ₄ As ⁺	(Ph ₄ As)C ₆₀ (Ph ₄ AsCl)	−1	"	152
PPN ⁺ (5)	(PPN)C ₆₀ (C ₆ H ₅ Cl)	−1	"	48
	(PPN) ₂ C ₆₀	−2	diffusion	50, 155
	(PPN) ₂ C ₆₀ (PPNCl)MeCN	−2	cationic metathesis	49
	(PPN) ₃ C ₆₀ (MeCN) ₂	−3	the same	49
Ru(bipy) ₃ ²⁺	[Ru(bipy) ₃](C ₆₀) ₂	−1	electrocrystallisation	59

of the cations are drawn together to the six-membered rings of the fullerene in such a manner that the phenyl groups surround completely the C₆₀[•] radical anion. In the salt C₆₀(PPN)₂,¹⁵⁵ one fullerene molecule is surrounded by 22 phenyl groups of the cations, which efficiently shield the charge of the C₆₀²⁻ anion. According to X-ray diffraction data, there are no shortened distances between the fullerene anions in the crystal; the shortest distance between the centres of fullerene molecules is $\sim 12.5 \text{ \AA}$.^{152, 153, 155}

A study of the magnetic susceptibility of these salts⁴⁹ showed that they are paramagnetic.^{49, 50} Apparently, the bulky cations surrounding the C₆₀ fullerene radical anions interfere with their magnetic interaction. The magnetic susceptibility is determined by the spin ground state of fullerene radical anions. The magnetic moment of salts containing the C₆₀[•] and C₆₀³⁻ anions is $1.8 \mu_B$ at room temperature, which corresponds to the singlet ground state with $S = 1/2$. At low temperatures, the magnetic susceptibility in C₆₀[•] salts decreases because of the weak antiferromagnetic interaction between the neighbouring fullerene molecules. The magnetic moment of C₆₀²⁻ salts at room temperature was found to be $2.5 \mu_B$.^{49, 50}

A study of the conductivity of these salts showed that all of them are semiconductors. The conductivity of the salt [Ru(bipy)₃](C₆₀)₂ (Table 6) is $10^{-2} \text{ S cm}^{-1}$, and this salt is a semiconductor with an activation energy of 0.15 eV .⁵⁹ It has been shown^{56, 153} that the conductivity of the salts of C₆₀[•] with the Ph₄P⁺ cation is from 10^{-7} to $10^{-4} \text{ S cm}^{-1}$. The low conductivity is apparently due to the large distances between the fullerene anions in these compounds.

9. Salts of the C₆₀ fullerene with metalloporphyrins

The redox properties of metalloporphyrins also make it possible to use them for the reduction of fullerenes. For example, compound Cr(II)(TPP), where TPP is tetraphenylporphyrin, has strong donor properties ($E_{Ox} = -0.86 \text{ V}$)¹⁵⁶ and reduces fullerene in tetrahydrofuran to C₆₀[•] to give the [Cr(TPP)]C₆₀(THF)₃ salt.¹⁵⁶ The reaction is reversible; the addition of toluene shifts the equilibrium towards the formation of neutral C₆₀. In pure toluene, the reduction of C₆₀ does not occur. The [Cr(TPP)]C₆₀(THF)₃ salt is a paramagnetic with $S = 1/2$.¹⁵⁶

The Sn(II)(TpTP) complex, where TpTP is tetra-*p*-tolylporphyrin ($E_{Ox} = -1.17 \text{ V}$), in the presence of *N*-methylimidazole (*N*-MeIm) forms a salt with C₆₀ with composition [Sn(TpTP)](*N*-MeIm)₂(C₆₀)₂. *N*-Methylimidazole stabilises the Sn(TpTP)²⁺ cation and hence facilitates the formation of the complex.⁴⁸

10. Metal salts of fullerenes

a. Conducting properties of fullerene salts. Superconductivity

Reduction of fullerene results in the population of the t_{1u} energy levels, which can be populated with up to six electrons.^{25, 36} Therefore, the compounds obtained can display conducting and superconducting properties if the degree of reduction x of the C₆₀ fullerene ranges from 0 to 6.^{13, 14, 25}

The character of conductivity in the salts M_{*x*}·C₆₀ varies strongly depending on the degree of the fullerene reduction. At the degree of reduction $x = 1$, the salts M·C₆₀ can display metallic conductivity.^{61, 157–159}

The compounds M₃C₆₀ have higher conductivity (*e.g.*, the conductivity of K₃C₆₀ at room temperature was shown to be

$2.5 \times 10^{-3} \text{ S cm}^{-1}$) than the compounds M_xC_{60} with different stoichiometry. At low temperatures, the salts M_3C_{60} display metallic conductivity and can pass into the superconducting state.

The density of energy states at the Fermi level $N(E_F)$ (number of states eV^{-1}) is an important parameter determining the superconductivity transition temperature (T_c). Because of the small overlapping of the π -molecular orbitals of the neighbouring C_{60} molecules in the compounds M_3C_{60} , the conduction band is half occupied and has a width of 0.2–0.3 eV. At a small band width, the density of states at the Fermi level is rather high (25 states eV^{-1} for K_3C_{60} and 35 states eV^{-1} for Rb_3C_{60} , see Ref. 25). It is this fact that explains higher T_c values in fullerene salts with alkali metals in comparison with other known organic superconductors.¹⁰

In the compounds M_3C_{60} with face-centred cubic (FCC) lattice, an increase in the size of the alkali metal atom results in an increase in the distance (d) between the fullerene molecules in the crystal cell and a linear increase in T_c . The explanation for the latter phenomenon is that the increase in $d(\text{C}_{60}-\text{C}_{60})$ in M_3C_{60} decreases the overlapping of the π -molecular orbitals of the neighbouring fullerene molecules and, accordingly, the width of the conduction band. The narrowing of the conduction band increases the density of states at the Fermi level (as the number of states at the Fermi level does not depend on the band width and is constant) and increases the temperature of superconductivity transition (T_c).^{13, 14, 28} However, if the distance between the centres of fullerene molecules in the crystal cell is more than 10.3 Å, the compound becomes a Mott dielectric.¹⁶¹

It was found that the M_2C_{60} and M_4C_{60} salts, in which the C_{60} molecule accepts two or four electrons, display only semiconductor properties with an activation energy of about 0.5 eV.¹⁶⁰ The significant difference of these phases from the M_3C_{60} phase may be due to a decrease in the symmetry of the fullerene molecule in these compounds. Partial removal of the degeneracy of the t_{1u} orbital and splitting of the conduction band into two bands (completely filled and vacant) with an energy difference between them of ~ 0.5 eV occurs in M_2C_{60} and M_4C_{60} .¹⁶⁰

At $x = 6$, the conduction band is filled completely, and M_6C_{60} compounds are dielectrics.¹³

If more than six electrons are introduced in a C_{60} molecule, filling of the t_{1g} level starts; this level can accept six electrons. Therefore, metallic conductivity is displayed again and transition to the superconducting condition is possible at a degree of reduction of fullerenes, x , in C_{60} compounds from 6 to 12.^{13, 18}

The conductivity of C_{70} fullerene salts is little studied. Calculations show that M_xC_{70} phases, where M is an alkali metal and $x = 4$, can have metallic conductivity, while at $x = 1.8$ they can be semiconductors. For example, the K_4C_{70} phase actually has metallic conductivity but is not a superconductor down to 1.35 K.¹³

b. Intercalation of fullerenes

The crystals of the C_{60} fullerene have a densely packed FCC lattice³⁷ with relatively weak intermolecular bonds between separate molecules. This lattice contains two tetrahedral and one octahedral cavities per molecule with radii 1.10 Å and 2.06 Å, respectively, hence fullerene is a convenient object for intercalation. If the cavities are completely filled with the metal atoms, the composition of the compounds obtained has the formula M_3C_{60} . As the dopant size or the number of its atoms are increased (to $n = 6$), the densely packed FCC-lattice is transformed to a less dense volume-centred cubic (VCC) lattice with six equivalent tetrahedral cavities per C_{60} molecule.^{13, 14, 28}

Diverse methods for the intercalation of fullerenes have been developed. In the most popular procedure for the synthesis of M_xC_{60} compounds, a fullerene and x equivalents of an alkali metal are placed in a quartz tube evacuated to 10^{-2} – 10^{-5} Torr, which is then sealed and heated at 200–500 °C.¹⁶² The intercalation of the C_{60} fullerene with alkali metal hydrides, borohydrides and azides and other reagents has also been described.^{13, 14}

The gas-phase intercalation of the C_{60} fullerene suffers certain drawbacks. In this case, it is difficult to control the degree of reduction of the fullerene; the formation of a mixture of M_xC_{60} phases with different content of the metal is possible (for example, M_3C_{60} contains the M_6C_{60} phase, which is a dielectric). An inevitable heterogeneity of the specimens formed complicates the study of the crystal and electronic structure of these materials.

Single crystals of these compounds are obtained by syntheses with $\text{C}_{60}^{\cdot-}$ and $\text{C}_{60}^{3-\cdot}$ radical anions in solutions.^{153, 154}

Refluxing a fullerene solution with a 90-fold excess of K or Rb in toluene results in a precipitate containing 1% of a superconducting K_3C_{60} phase and 7% of a superconducting Rb_3C_{60} phase.¹⁶³ The addition of 5%–30% of benzonitrile to toluene favours the electron transfer from the alkali metal to the fullerene and interferes with the precipitation of intermediate compounds with the $\text{C}_{60}^{\cdot-}$ and $\text{C}_{60}^{2-\cdot}$ anions, which allows one to obtain specimens with high content (up to $\sim 50\%$) of the superconducting M_3C_{60} phase. Reduction of fullerene with an alkali metal in pure benzonitrile results in M_xC_{60} compounds, where $x = 4, 5$ and 6.¹⁶² A drawback of the method is the presence of an unconsumed alkali metal among the reaction products.

Heating and stirring of a suspension of fullerene in *N*-methylimidazole with a high excess of a metal (Li, Na, Ba, Fe, Cu, Zn) resulted in the corresponding salts of $\text{C}_{60}^{\cdot-}$ and $\text{C}_{60}^{2-\cdot}$. The compounds have the formulas: $[\text{M}(\text{N-MeIm})_x]\text{C}_{60}$ and $[\text{M}(\text{N-MeIm})_x]_2\text{C}_{60}$, where $x = 4$ –6.¹⁴⁸

A series of compounds $\text{M}_x\text{C}_{60}(\text{THF})_y$, where $x = 0.4$ –3 and $y = 1$ –14, have been obtained by the reaction of C_{60} with alkali metals in THF in the presence of 1-methylnaphthalene,⁵⁵ by cooling a C_{60} solution reduced with potassium in tetramethylethylenediamine⁵⁵ or by the reaction of C_{60} with $\text{K}[\text{Mn}(\text{C}_5\text{Me}_5)_2]$ in THF.¹⁶⁴ Salts with small x (~ 0.4) and y (~ 2.2) values have been obtained by electrochemical reduction of fullerene in the presence of an alkali metal tetraphenylborate.⁶¹

The anions $\text{C}_{60}^{3-\cdot}$ in the structure of $\text{K}_3\text{C}_{60}(\text{THF})_{14}$ are packed in linear chains;⁵³ one of the K^+ ions is coordinated with a five-membered ring of C_{60} and serves as a bridge between two fullerene radical anions. The other two K^+ cations are located above and below the $\text{C}_{60}^{3-\cdot}$ anion, forming contacts with six-membered rings of C_{60} . The K^+ cations are also coordinated with THF molecules. Judging by the arrangement pattern of the $\text{C}_{60}^{3-\cdot}$ anions, the structure of $\text{K}_3\text{C}_{60}(\text{THF})_{14}$ is similar to that of M_3C_{60} superconductors with an FCC lattice. However, the distance between the $\text{C}_{60}^{3-\cdot}$ ions is large, and this compound does not display metallic properties.⁵³ A compound with a different stoichiometry, *viz.*, $\text{M}_x\text{C}_{60}(\text{THF})_y$, where $x \sim 0.4$ and $y \sim 2.2$, has a conductivity of 50 S cm^{-1} at room temperature, which increases with a decrease in temperature and is about 1000 S cm^{-1} at 100 K. This is probably due to incomplete charge transfer to the fullerene ($\delta = 0.4$) and the presence of small distances between C_{60} molecule centres along the crystallographic axis c (9.93 Å) in the crystal.⁶¹

After removal of tetrahydrofuran from the salt $\text{K}_3\text{C}_{60}(\text{THF})_7$ by evacuation, keeping at constant temperature at 300 °C for 12 h and subsequent cooling to 103 °C, heat evolution in the sample is observed, which is explained by a transition to a more stable phase with an FCC lattice. As a result, the sample becomes a superconductor containing 31% of the superconducting K_3C_{60} phase.¹⁶⁴

c. Fullerene polymerisation in MC_{60} and M_3C_{60} salts

The intercalation of C_{60} fullerene with alkali metals in stoichiometric ratio (1 : 1) gave the radical anionic salts KC_{60} , RbC_{60} and CsC_{60} .^{157–159} On slow cooling of the intercalation products, [2+2]-cycloaddition of the neighbouring fullerene molecules occurs, which results in the polymerisation of $\text{C}_{60}^{\cdot-}$ into linear chains. The distance between the centres of fullerene molecules decreases to 9.11–9.13 Å.¹⁵⁷ Polymeric compounds are stable in air,¹⁵⁷ insoluble in tetrahydrofuran and depolymerise only on heating above 320 °C. A study of the conductivity of the resulting

polymeric specimens showed that $[\text{KC}_{60}]_n$ is a three-dimensional metal the conductivity of which slowly increases on decreasing the temperature to 4 K.¹⁵⁸ Magnetic measurements also show¹⁵⁹ that $[\text{KC}_{60}]_n$ behaves as a three-dimensional metal down to liquid-helium temperatures. Unlike $[\text{KC}_{60}]_n$, the $[\text{RbC}_{60}]_n$ and $[\text{CsC}_{60}]_n$ polymers are one-dimensional metals and pass to the dielectric state at 50 K and 40 K, respectively. At 25 K, the $[\text{RbC}_{60}]_n$ and $[\text{CsC}_{60}]_n$ polymers undergo magnetic transition with antiferromagnetic ordering of spins in the polymeric chain. The interaction between antiferromagnetic polymeric chains occurs through alkali metal atoms, which results in three-dimensional magnetic ordering of spins.¹⁵⁹

The nature of conductivity in these compounds is not clear yet. It is possible that polymerisation of fullerenes results in π -conjugated bonds between the molecules and the conduction electrons can move through them along the fullerene chain. Another possible mechanism assumes that the carbon atoms that are not bound directly and correspond to the neighbouring fullerene skeletons approach each other with overlapping of the t_{1u} orbitals of these skeletons, and the conduction electrons move through these orbitals.¹³ The second variant is more likely, as it has been shown¹⁵⁸ that the decrease in the ionic radius of the metal on going from rubidium to potassium results in overlapping of the t_{1u} orbitals of fullerenes belonging to different polymeric chains and to a change from one-dimensional to three-dimensional conductivity.

If C_{60} doped by alkali metals is rapidly cooled by liquid nitrogen, polymerisation cannot occur and monomeric radical anionic salts are obtained, such as KC_{60} , RbC_{60} and CsC_{60} .¹⁵⁷ Heating of monomeric KC_{60} above 77 K, or RbC_{60} and CsC_{60} above 160 K, results in dimerisation; the dimeric phase $\text{K}_2(\text{C}_{60})_2$ is a dielectric.¹⁵⁷

It has been shown that the radical anion $\text{C}_{60}^{3-\cdot}$ in compounds M_3C_{60} can polymerise as well.¹⁶⁵ $\text{Na}_2\text{CsC}_{60}$ polymerises with transition to an orthorhombic phase at a pressure of 3 kbar; the resulting polymer maintains superconducting properties.¹⁶⁵

d. Superconducting compounds of C_{60}

To date, about thirty superconductors have been obtained based on C_{60} . Their superconducting transition temperatures range within 2–40 K (Fig. 3).

Compounds with composition M_3C_{60} , where $\text{M} = \text{K}, \text{Rb}$ or a combination of K, Rb and Cs , with an FCC lattice (Fig. 3, 1) have been studied in most detail.^{12–14, 28} It was found for this series of compounds that T_c increases linearly with the size of the alkali metal atom and the distance between the centres of fullerene molecules, $d(\text{C}_{60}-\text{C}_{60})$, in the crystal cell.^{13, 14, 28, 166} An increase in T_c is also observed in the reaction of the M_3C_{60} salts with ammonia. For example, the intercalation of $\text{Na}_2\text{CsC}_{60}$ with

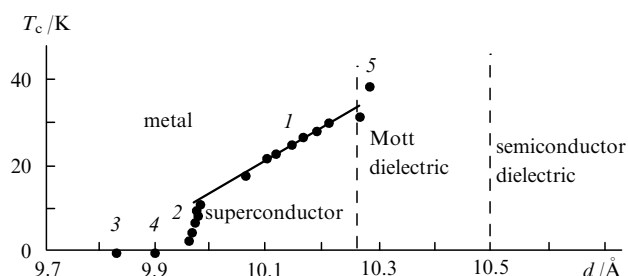


Figure 3. Phase diagram for the salts M_3C_{60} . Dependence of T_c on the closest distance (d) between the centres of C_{60} molecules in crystalline state at room temperature:¹⁴ (1), experimental data for M_3C_{60} (K_3C_{60} , $\text{K}_2\text{RbC}_{60}$, $\text{K}_2\text{CsC}_{60}$, $\text{KRb}_2\text{C}_{60}$, Rb_3C_{60} , $\text{Rb}_2\text{CsC}_{60}$ and $\text{RbCs}_2\text{C}_{60}$) with FCC lattice; (2), experimental data for the series $\text{Na}_2(\text{Rb}_x\text{Cs}_{1-x})\text{C}_{60}$ with simple cubic lattice; (3), $\text{Li}_2\text{RbC}_{60}$; (4), $\text{Li}_2\text{CsC}_{60}$; (5), Cs_3C_{60} with A15 structure, which has superconductor properties under 15 kbar.

ammonia results in $(\text{NH}_3)_4\text{Na}_2\text{CsC}_{60}$ with a similar crystal lattice, while the distance between the $\text{C}_{60}^{3-\cdot}$ radical anions increases from 9.99 Å to 10.23 Å. This is accompanied by an increase in T_c from 10.5 K in $\text{Na}_2\text{CsC}_{60}$ to 29.6 K in $(\text{NH}_3)_4\text{Na}_2\text{CsC}_{60}$.¹⁶⁶ However, it was found¹⁶⁰ that the compound Cs_3C_{60} with the A15-type structure and distances between the fullerenes molecule ~ 10.35 Å is the Mott dielectric and becomes a superconductor with $T_c = 40$ K only at a pressure of 15 kbar.¹⁶⁰

The salts M_xC_{60} have the highest temperature of superconductivity transition for $x = 3$.²⁸ If the stoichiometry deviates from this value in either direction, T_c starts to decrease, and at $x \leq 2$ and $x \geq 4$ the compounds no longer pass into the superconducting state.

On transition from one crystal lattice type to the other, the character of interaction between the neighbouring fullerene molecules changes. Therefore, the compounds $\text{Na}_2\text{MC}_{60}$, where $\text{M} = \text{K}, \text{Rb}$ and Cs , with simple cubic lattice have a different dependence of T_c on the distance between the fullerene molecules than the compounds M_3C_{60} with FCC lattice. A minor increase in this distance in compounds with a simple cubic lattice strongly increases the T_c (Fig. 3, 2).¹⁴

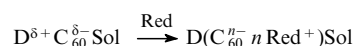
A weak covalent interaction $\text{Li}-\text{C}$ in compounds $\text{Li}_2\text{MC}_{60}$ (Fig. 3, 3, 4) changes their electronic structure, and these compounds do not display superconducting properties.¹⁴

A group of superconductors A_xC_{60} obtained by intercalation of C_{60} with alkaline-earth metals, *i.e.*, Ca, Sr and Ba , is of interest.^{13, 18} Unlike M_3C_{60} ($\text{M} = \text{K}, \text{Rb}, \text{Cs}$), in which the population of the t_{1u} orbital occurs, the superconductivity in these compounds is due to the population of the t_{1g} orbital. The T_c of compounds A_xC_{60} ranges within 4–8.5 K and depends little on the distance between the fullerene ions.¹³ The superconducting state is observed at different populations of the conduction band, but it is rather difficult to determine the exact extent of charge transfer (δ) to the fullerene. In the series of compounds Ca_xC_{60} with $x = 3-6$, Ca_5C_{60} has the maximum conductivity (the degree of charge transfer to C_{60} δ equals 10) and passes in the superconducting state at 8.4 K.^{13, 18} The compounds Ca_3C_{60} ($\delta = 6$) and Ca_6C_{60} ($\delta = 12$) (the conduction band is completely populated) do not display metallic properties.^{13, 18} As opposed to Ca_3C_{60} and Ca_6C_{60} , a weak covalent interaction of Ba and Sr with fullerene in Ba_3C_{60} , Ba_6C_{60} , Sr_3C_{60} and Sr_6C_{60} is possible because of the larger ionic radii of these metals. This results in a decrease in the actual charge transfer to the fullerene and in only partial population of the conduction band at $x = 3$ and $x = 6$.¹⁸ Therefore, Ba_3C_{60} and Sr_3C_{60} display metallic properties, and Ba_4C_{60} , Sr_6C_{60} and Ba_6C_{60} have superconducting properties at $T_c = 4, 7$ and 4 K, respectively.^{13, 18}

It has been shown¹⁶⁶ that C_{60} fullerene intercalated with lanthanides can also be a superconductor (for example, $\text{Yb}_{2.75}\text{C}_{60}$ has $T_c = 6$ K).

e. Intercalation of molecular complexes of C_{60} with alkali metals

Structural diversity of organic molecules allows one to create C_{60} compounds with different packing of the C_{60} molecules in the crystal, *viz.*, one-dimensional chains, two-dimensional layers or three-dimensional arrangement of the C_{60} molecules. Fullerene compounds with one-dimensional and two-dimensional packing of the C_{60} molecules are of special interest for the study of conducting and superconducting properties. In addition, by using different donor molecules, it is possible to control the distance between the fullerene molecules in the crystal lattice in order to obtain materials with high T_c . This stimulated studies of the intercalation of C_{60} complexes with alkali metals. The intercalation of molecular complexes of C_{60} is accompanied by reduction of the fullerene according to the scheme:



Red is reducing agent.

The intercalation of C_{60} complexes with octamethylenetetra-thiafulvalene (**10**) $(OM-TTF)C_{60}(C_6H_6)$ or bis(ethylenedioxy)-tetrathiafulvalene $[(BEDO-TTF) \sim C_{60}]$ with potassium and rubidium is carried out at 10^{-4} – 10^{-5} Torr and 55 and 67 °C, respectively, as in the case of pure C_{60} .^{168, 169} The intercalation of $(OM-TTF)C_{60}(C_6H_6)$ gave compounds with composition $K_x(OM-TTF)C_{60}(C_6H_6)$, where $x \leq 1.8$. Apparently, the solvent is retained in the compound.¹⁶⁸ Because of their small radii, the alkali metal atoms occupy the cavities in the structure of the starting molecular complex; this increases somewhat the parameters of its crystal cell.¹⁶⁹ The intercalation of $(OM-TTF)C_{60}(C_6H_6)$ with potassium gives a superconducting phase with a transition temperature of 17–18.8 K, and that with rubidium gives a superconducting phase with $T_c = 23$ –26 K. The intercalation of $[(BEDO-TTF) \sim C_{60}]$ with potassium yields a superconducting phase with $T_c = 15$ K.^{168, 169}

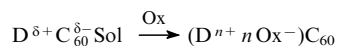
f. Intercalation of fullerenes and their complexes with halogens

The intercalation of fullerenes with molecular iodine (I_2) and interhalides, *viz.*, IBr and ICl , gives the complexes $(Hal_2)_x C_{60}$. The reaction is carried out at 100–250 °C in evacuated tubes.^{40, 170, 171} The content (x) of the halogen in the sample can vary from 0.2 to 2,^{170–172} depending on the conditions and duration of intercalation. A study of the structure of the $(I_2)_2 C_{60}$ complex has shown that it has a layered structure; the C–I distances (3.6–4.0 Å) are smaller than the sum of the van der Waals radii of carbon and iodine.¹⁷⁰ There is no charge transfer from the fullerene to iodine in these compounds. Iodine is weakly bound to the fullerene and is removed from the compound at 200 °C.¹⁷⁰ $(I_2)_2 C_{60}$ is a dielectric the conductivity of which is less than 10^{-9} S cm⁻¹ (Ref. 170).

A study of the magnetic properties of C_{60} complexes obtained by intercalation of fullerene with I_2 , ICl and IBr revealed magnetic transitions^{40, 171} at 60 K, 30 K and 30 K, respectively. For pure C_{60} and C_{70} fullerenes, these are also observed at 60 K.³⁸ Apparently, these magnetic transitions, like those in the case of pure fullerenes, are due to transition of the specimens to the frozen glassy magnetic state,³⁸ because synchronisation of rotation of the C_{60} molecules is also possible in the presence of shortened contacts between the C_{60} molecules in the crystals of these molecular complexes at low temperatures. Cooling of these specimens in a magnetic field below this temperature results in freezing of a completely ordered orientation of the magnetic moments of the fullerene molecules.

The intercalation of the complexes $(DB-TTF)C_{60}(C_6H_6)$, $(TMDTDM-TTF)_2 C_{60}(CS_2)_3$ and $TPDP(C_{60})_2(CS_2)_4$ with iodine results in compounds with a high content of iodine, *viz.*, $(DB-TTF)C_{60}I_9$, $(TMDTDM-TTF)_2 C_{60}I_{7.5}$ and $TPDP \cdot (C_{60})_2 I_{10}$.^{173, 174}

The intercalation of C_{60} complexes with iodine is based on the solid-phase oxidation of the donor component of these complexes with the formation of a radical cation. The solvent, for example, CS_2 , is displaced by iodine.¹⁷⁴



Ox is oxidant.

The intercalation is accompanied by noticeable changes in the ESR spectra due to the oxidation of the donor.¹⁷³ The optical absorption spectra display a shift (up to 10 nm) of the absorption bands of the basic electron transition ϵ_0 at $\lambda = 260$ and 350 nm and an increase in absorption intensity in the region of 450–620 nm.¹⁷³ These changes can be due to the formation of a radical cation by the donor.¹⁷³ The position of the absorption band of the $T_{1u}(4)$ vibrations of C_{60} (1429 cm⁻¹) in the IR spectrum of intercalated specimens is not changed, which indicates the absence of charge transfer to the fullerene molecule. The starting complexes are dielectrics. Intercalation results in an insignificant increase in the conductivity of the complexes (by a

factor of less than 100), which is apparently due to the large distances between the donor molecules in these complexes.¹⁷⁴

IV. Structure and spectral characteristics of complexes and radical ionic salts of fullerenes

1. Specific features of the crystal structure

The position of the C_{60} molecules in a crystal and the number of direct van der Waals contacts between the fullerene molecules make it possible to distinguish several structural types of fullerene compounds.¹⁷⁵

1. Three-dimensional packing of the C_{60} fullerene molecules with distances between the centres of the molecules ranging from 9.8 to 10.3 Å is observed in fullerene salts $M_x C_{60}$ ($x = 1$ –6) with alkali and alkaline-earth metals. Simple cubic, cubic face-centred, cubic volume-centred and rhombic lattices with the number of closest neighbouring C_{60} molecules from 8 to 12 correspond to this type of packing.^{13, 14}

2. Layered packing, in which two-dimensional dense or loose hexagonal layers of C_{60} molecules are formed. The number of closest neighbouring fullerene molecules ranges from 4 to 6. The layers of donor molecules in these structures also alternate with layers of C_{60} molecules. In the donor layer, *e.g.*, in the $(TMDTDM-TTF)_2 C_{60}(CS_2)_3$ complex,¹⁰³ there are also shortened contacts between the TMDTDM–TTF molecules. A shift of hexagonal layers relative to each other with transition to simple hexagonal packing of layers can be observed in compounds with small donors. This refers to compounds of C_{60} with such molecules as I_2 ,¹⁷⁰ S_4N_4 ,⁹⁵ P_4 ,⁹³ TMPD,¹²⁹ OM–TTF,⁵ TPDP¹⁰⁹ or DAN.⁴⁴

The structure of the $(DAN)C_{60}(C_6H_6)_3$ complex with layered packing of C_{60} molecules is shown in Fig. 4. Each C_{60} molecule in this complex is surrounded by four fullerene molecules with a distance of 10.07 Å between the centres.

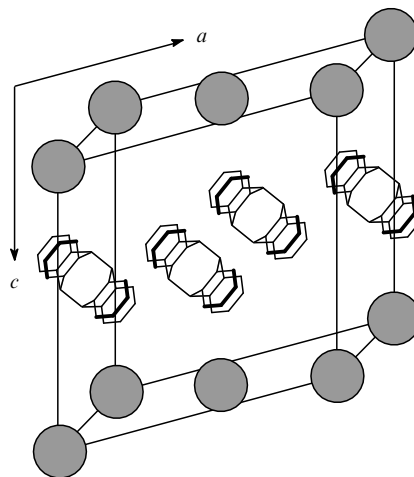


Figure 4. Projection of the crystal structure of the complex $(DAN)C_{60}(C_6H_6)_3$ (the positions of the fullerene molecules are indicated with grey spheres) along the crystallographic axis b ⁴⁴ (schematic representation). The solvate benzene molecules (not shown) are located in the dianthracene layer.⁴⁴

3. Cage packing: the fullerene molecules form various cavities or channels, in particular, hexagonal channels, which are filled with donor molecules. The number of the closest neighbouring fullerene molecules can vary from 4 to 8. This structure is represented by compounds of C_{60} with *twin*-TDAS,¹¹³ C_6H_6 ,^{68, 69} and S_8 .^{90, 91}

4. Chain packing: the fullerene molecules form densely packed chains (with two closest neighbouring fullerene molecules) or double chains (with three closest neighbouring fullerene

molecules). This structure is characteristic of complexes of fullerene with BEDT-TTF,^{98,99} *twin*-BEDT-TTF¹⁰² and C₁TET-TTF.¹¹⁰

5. Island mode of packing: in this case, there are no direct van der Waals contacts between the fullerene molecules, and all distances between the centres of C₆₀ molecules are ~12 Å. This type of packing is observed in compounds with large donor molecules (HMT,¹¹⁵ Ph₃Sb¹¹⁶) or cations (Ph₄P⁺ (see Refs 57, 136 and 153) and PPN⁺ (see Refs 58 and 155)).

The structures of some fullerene complexes, for example with such donors as DBTTF¹⁰⁵ and BTX, are intermediate between the cage and island structures.¹¹¹ Figure 5 presents the structure of the DBTTF·C₆₀·C₆H₆ complex. It is characterised by isolated packing of C₆₀ molecules, in which each of them is surrounded by six closest neighbouring fullerene molecules with a distance of 10.4–10.5 Å between the centres. This distance is larger than the van der Waals diameter of fullerene (10.18 Å) but smaller than the distance characteristic of island structures (~12 Å).

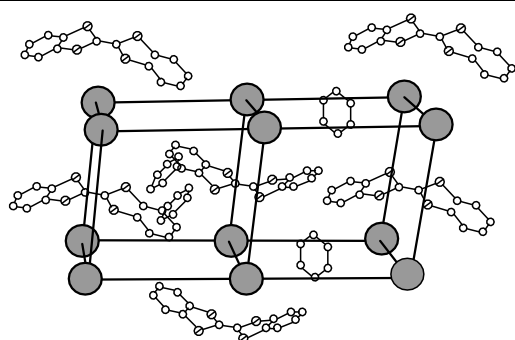


Figure 5. Crystal packing of the complex (DB-TTF)C₆₀·C₆H₆ (positions of fullerene molecules are indicated by grey spheres; crystallographic axes are shown by straight lines).¹⁰⁰

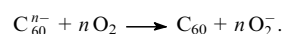
Table 7 lists the mean bond lengths of the C₆₀ fullerene molecule in its compounds. It is evident that the bond lengths in C₆₀ change with an increase in the degree of charge transfer to the fullerene molecule; in this case, the 6–5 bonds shorten while the 6–6 bonds elongate. The direction of changes in the bond lengths upon reduction of fullerene is due to the nature of the *t_{1u}* orbital, which is anti-bonding with respect to the 6–6 bonds and bonding with respect to the 6–5 bonds.¹³ This results in elongation of the fullerene molecule, and the C₆₀ sphere is distorted to become an ellipsoid.

Table 7. Lengths of 6–5 and 6–6 bonds for D–A complexes and radical ionic salts of C₆₀.

Compound	Charge on C ₆₀	6–5 Bond length/Å	6–6 Bond length/Å	Ref.
C ₆₀	0	1.467(2)	1.355(9)	176
C ₆₀ (SbPh ₃) ₆	0	1.452(5)	1.383(4)	116
C ₆₀ (BEDT-TTF) ₂	0	1.452(1)	1.389(7)	98
C ₆₀ [(C ₅ H ₅) ₂ Fe] ₂	0	1.450(5)	1.387(6)	145
(C ₆₀) ₂ TPDP(CS ₂) ₄	0	1.451(6)	1.381(6)	109
C ₆₀ (S ₈) ₂	0	1.448(8)	1.340(8)	90
C ₆₀ [Ni(C ₃ Me ₅) ₂]CS ₂	–1	1.449(3)	1.389(3)	149
C ₆₀ [Co(C ₆ H ₅) ₂]CS ₂	–1	1.453(4)	1.384(8)	47
C ₆₀ (PPN) ₂	–2	1.446(2)	1.399(2)	155
K ₃ C ₆₀	–3	1.452(1)	1.400(4)	13
K ₆ C ₆₀	–6	1.432(1)	1.445(3)	13

2. Stability

The stability of fullerenes with respect to atmospheric oxygen differs from the stability of their compounds. In solid state, fullerenes can adsorb oxygen on their surface.⁶² In solution, they can add oxygen under illumination to give epoxides C₆₀O_{*n*}, where *n* = 1, 2 and 3 (therefore, it is preferable to carry out reactions with fullerenes in the dark).¹⁹ Anionic fullerene compounds are particularly sensitive to oxygen because of the possible reaction



This reaction can also yield addition products C₆₀O₂^{·–} at the fullerene 6–6 or 6–5 bonds.¹⁷⁷

In aprotic media, the redox potential of the O₂/O₂^{·–} couple is –0.8 V,⁴⁸ while the first redox potential of fullerenes, C₆₀/C₆₀^{·–} and C₇₀/C₇₀^{·–}, is –0.4 V.³¹ With these values of redox potentials, oxidation of fullerene radical anions C₆₀^{·–} and C₇₀^{·–} is thermodynamically unfavourable, and hence radical monoanionic fullerene compounds should be stable when exposed to air. This is actually observed for salts containing the C₆₀^{·–} radical anion (KC₆₀, RbC₆₀, CsC₆₀) and salts with bulky cations.^{56–58, 152–154, 157} The instability of salts of C₆₀^{·–} with metalloporphyrins,⁴⁸ metallocenes^{48, 147} and amines^{15, 134} in the air can be due to the fact that protons or metal cations can stabilise the charge on O₂^{·–}. The redox potential of the O₂/O₂^{·–} couple becomes more positive due to stabilisation of the O₂^{·–} radical anion, which enables the oxidation of C₆₀^{·–}.

The second redox potential of fullerenes C₆₀^{·–}/C₆₀^{2–} and C₇₀^{·–}/C₇₀^{2–} is ~–0.8 V,³¹ hence the oxidation of fullerene dianions with oxygen is thermodynamically favourable. Therefore, radical anionic salts containing fullerene dianions or C₆₀^{n–} anions in higher degrees of reduction are very sensitive with respect to oxygen.⁸²

3. Thermogravimetry

Derivatography is generally used to study the thermal stability of both pure fullerene and its compounds.^{43, 44, 54, 75, 101, 104, 178} Heating in air causes complete combustion of fullerene at 650 °C. In nitrogen, fullerene starts to sublime at 600 °C, and the maximum sublimation rate is reached at 700–800 °C.¹⁷⁸

It is possible to determine the content and the strength of binding of a solvent in a complex from derivatograms of molecular complexes of fullerenes.^{43, 44, 54, 75, 101, 104} Thermogravimetric studies of fullerene complexes show that partial decomposition of donors occurs in these compounds. The decomposition temperatures of donors in complexes are close to those of the pure donors. In certain instances, the decomposition temperature of a donor increases owing to its stabilisation because of the donor-acceptor interaction with the fullerene.^{44, 54, 75} The presence of a large amount of a solvent in a molecular complex separates the fullerene molecules from each other. Therefore, the sublimation temperature of the fullerene in such complexes even after complete removal of the solvent is lower^{43, 50, 103} than that of pure C₆₀.¹⁷⁸

4. Spectroscopy of compounds based on fullerenes

A significant number of publications deal with the study of fullerenes and their compounds by spectroscopic methods (see, for example, Refs 5, 22–26, 36 and 179–195).

a. Electronic spectroscopy

Optical spectroscopy is a convenient method for the study of changes in the electronic structure of fullerenes upon formation of donor–acceptor compounds.^{5, 9, 181–185}

The optical absorption spectrum of the C₆₀ fullerene in solid state (Fig. 6) has been studied in detail.^{25, 66} In the ultra-violet region (250–400 nm), two intense bands corresponding to symmetry-allowed electronic transitions are observed. There is a rather strong band in the visible region (λ = 420–540 nm) with a maximum at λ = 450 nm (2.7 eV), the origin of which is not quite clear. This band is absent in the absorption spectra of C₆₀ solutions,²⁵ but appears, for example, upon aggregation of several

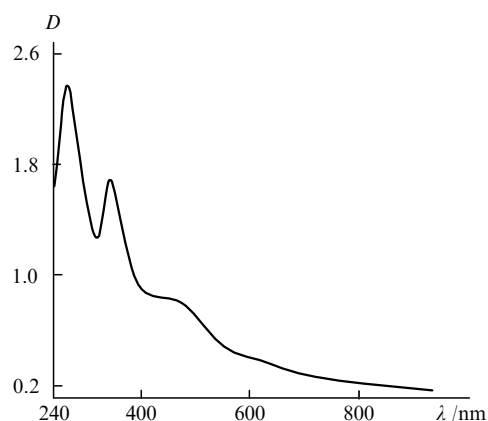
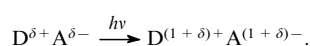


Figure 6. The absorption spectrum of C₆₀ in a KBr matrix.¹⁸¹

C₆₀ molecules in a complex with γ -cyclodextrin in aqueous solution.⁸⁴ Therefore, this band is sometimes¹⁷⁹ related to intermolecular transfer of an electron from the HOMO of the C₆₀ molecule to the LUMO of the neighbouring C₆₀ molecule. The absorption at $\lambda = 540\text{--}620\text{ nm}$ (2.2–2.0 eV) has low intensity and corresponds to the symmetry-forbidden $h_u \rightarrow t_{1u}$ transition from HOMO to LUMO of one C₆₀ molecule (see Fig. 1).²⁵ The manifestation of this forbidden transition both in liquid and in solid phase is explained by a deviation of the symmetry of C₆₀ molecules from I_h .²⁵ The absorption edge of fullerene in optical spectra is in the region of 1.95–1.75 eV, which corresponds to 640–700 nm, and it is basically related to exciton transitions.¹⁸⁰

The formation of molecular complexes does not induce considerable changes in the electronic system of fullerenes.¹⁸¹ Irrespective of the solvent, the absorption edge of fullerene in fullerene solvates shifts by 0.1 eV upfield in comparison with pure fullerene,¹⁸⁰ which is explained¹⁸⁵ by separation of fullerene molecules from each other by the solvent.

The spectra of complexes both in solution and in solid state display charge-transfer bands (CTB) from the donor to the fullerene. The process of charge transfer for complexes with an uncharged ground state upon absorption of a light quantum is described by the scheme:



The dependence of the charge transfer energy ($h\nu_{CT}$) on the donor IP for complexes of one acceptor with a series of donors is linear. This dependence is described by the equation:^{5,9}

$$h\nu_{CT} = \alpha(IP - EA) - E_C,$$

where α is a constant, IP is the ionisation potential of the donor, EA is the electron affinity of the acceptor, and E_C is the energy of electrostatic interaction between the donor and acceptor radical ions in the excited state of the complex.

Such a dependence for complexes of the C₆₀ fullerene with substituted anilines¹⁸² and naphthalenes¹⁸³ (IP = 7.2–8.13 eV) in toluene is shown in Fig. 7 and can be described by the expression: $h\nu_{CT} = 0.91IP - 4.34$ (eV).

Table 8 lists the energies corresponding to the maximum of the charge-transfer band for a number of C₆₀ complexes in the solid state. It is evident that $h\nu_{CT}$ decreases with a decrease in the redox potential ($E_{Red/Ox}$) of the donors.⁵

Irradiation of a crystalline complex (TMPD)C₆₀ with visible light (He–Ne laser) was found to cause a strong increase in the absorption at 1070 nm.⁷⁶ This is related to the formation of a long-lived radical anion C₆₀^{•−} upon transfer of an electron from TMPD to C₆₀. The lifetime of the C₆₀^{•−} radical anion in a crystal is about 1 h, which is several orders larger than the lifetime in the case of similar electron transfer in solution.⁷⁶

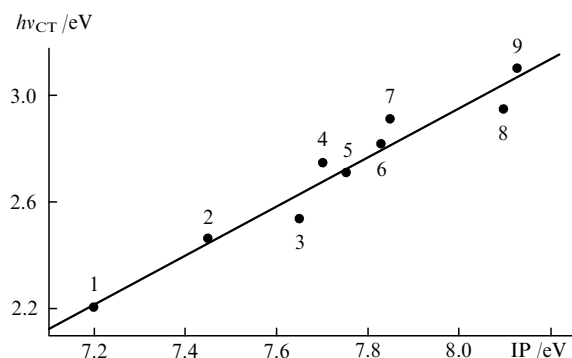


Figure 7. Dependence of charge transfer energy $h\nu_{CT}$ on ionisation potentials of donors in CTC of C₆₀ in toluene: (1), *N,N*-diethylaniline;¹⁸² (2), *N,N*-dimethylaniline;¹⁸² (3), *N*-methylaniline;¹⁸² (4), 1-methoxynaphthalene;¹⁸³ (5), 2,6-dimethylaniline;¹⁸² (6), *o*-toluidine;¹⁸² (7), 1-methylnaphthalene;¹⁸³ (8), aniline;¹⁸² (9), 1-chloronaphthalene.¹⁸³

Table 8. Position of the charge-transfer band maximum in electronic absorption spectra of C₆₀ complexes in solid state.

CTC	$h\nu_{CT}$ / eV	$E_{Red/Ox}$ of the donor / V	Ref.
[(C ₅ Me ₅) ₂ Fe] ₂ C ₆₀	1.13	−0.086	147
(OM–TTF)C ₆₀ (C ₆ H ₆)	1.35	+0.29	5
(TMDTDM–TTF) ₂ C ₆₀ (CS ₂) ₃	1.38	+0.39	104
(BEDO–TTF) ~ C ₆₀ ^a	1.51	+0.42	5
(BET–TTF)C ₆₀ (C ₆ H ₅ Me)	1.55	–	101
(BEDT–TTF) ₂ C ₆₀	1.65	+0.52	98
(<i>twin</i> -BEDT–TTF)C ₆₀ (CS ₂)	1.65	–	110

^a The exact complex composition has not been determined.

Charge transfer from the donor to the fullerene in the ground state is related to the population of the t_{1u} orbital of the C₆₀ fullerene. This enables electronic transitions from the t_{1u} orbital to vacant molecular orbitals with higher energies (see Fig. 1), which results in the appearance of new absorption bands in the near IR region. Their position corresponds to definite charge of the fullerene molecule:

Fullerene	C ₆₀ ^{•−}	C ₆₀ ^{2−}	C ₆₀ ^{3−}	C ₆₀ ^{4−}	C ₇₀ ^{•−}	C ₇₀ ^{2−}
ν (nm)	1070	950	780	730	1370	1165
			1380	1195		
Ref.	35, 48, 184	50	35	88	35	35

b. IR spectroscopy

The change in the symmetry and redistribution of the electron density upon formation of D–A complexes and radical ionic salts of fullerenes is reflected in their IR spectra.^{9, 25, 26, 184–195}

Due to its high symmetry (I_h), the C₆₀ molecule has 46 characteristic normal vibrations. Four of these are active in the IR spectra [T_{1u} (1–4) vibrations with absorption bands at 527, 577, 1183 and 1429 cm^{−1}, respectively] and ten in Raman spectra; 32 normal vibrations in the C₆₀ molecule are symmetry-forbidden in the dipole approximation.^{25, 26, 186}

In the crystalline C₆₀ fullerene¹⁸⁶ and some of its crystal solvates,^{187, 188} violation of symmetry of the environment of the C₆₀ fullerene molecules is observed, which results in partial modification of symmetry-forbidden vibrations, hence they appear in the IR spectra. This is due to the presence of defects, dislocations, admixtures or solvent molecules in the crystal structure of C₆₀ and in crystal solvates.

At room temperature, the molecules of the C₆₀ fullerene in crystals rotate quickly and isotropically, occupying positions with the T_h symmetry.¹⁸⁸ The T_{1u} vibrations, which are active in IR

spectra of the C_{60} fullerene, are threefold degenerate and appear as single bands. Cooling C_{60} crystals below 255 K results in an orientational-type phase transfer with freezing of the rotation of the fullerene molecules and a decrease in its position symmetry to S_6 .¹⁸⁹ The degeneration of the $T_{1u}(4)$ vibration of C_{60} at 1429 cm^{-1} is eliminated, and at 8 K it is split into three bands with wave numbers 1424.5, 1427.9 and 1431.2 cm^{-1} . The $T_{1u}(3)$ vibration at 1183 cm^{-1} remains unsplit.¹⁸⁹ Similar splitting of the $T_{1u}(4)$ vibration of C_{60} into three bands (Table 9) has been reported in compounds of C_{60} with amines, viz., (TMPD) C_{60} and (TPA) C_{60} .¹⁹⁰ This splitting is due to freezing of rotation of the C_{60} molecules in the crystal of the complex due to the intermolecular interaction with molecules of the donor and a decrease in the positional symmetry of the C_{60} molecules (in comparison with pure fullerene above 255 K).¹⁹⁰

Table 9. Position of the $T_{1u}(4)$ vibration band of fullerene (ν) and degree of charge transfer (δ) estimated from Eqn (2) in donor-acceptor complexes and radical ionic salts of C_{60} .

Compound	ν/cm^{-1}	Compound δ type	Ref.
C_{60}	1424, 1428, 1431, ^{a, b} 1429 ^c		189
$S_4N_4C_{60}$	1429	molecular 0	75
$(S_8)_2C_{60}(C_6H_5Cl)_{0.5}$	1429	complex the same 0	194
(TPA) C_{60}	1425, 1428, 1433 ^b	" —	190
(TMPD) C_{60}	1422, 1425, 1427 ^b	CTC —	190
$(C_5H_5)_2CoC_{60}(CS_2)$	1411	CTC ~ 0.5	47
$(C_5H_5)_2CoC_{60}(C_6H_5CN)$	1413	CTC ~ 0.5	48
$(C_6H_6)_2CrC_{60}$	1407	CTC ~ 0.7	150
$[Na(18-C-6)]C_{60}(THF)_3$	1395	salt ~ 1	48
$(Ph_4P)C_{60}(Ph_4PCl)$	1394	" ~ 1	184
$(Ph_4P)C_{60}(Ph_4PI)$	1394	" ~ 1	195
RbC_{60} ^d	1392	" ~ 1	26, 191
$(Ph_4As)C_{60}(Ph_4AsCl)$	1390	" ~ 1	184

^a Measured at 8 K; ^b splitting of the $T_{1u}(4)$ band of fullerene on freezing the rotation in the crystal; ^c measured at 293 K; ^d film.

The transfer of electron density from the donor to the C_{60} fullerene in the ground state results in a shift of some of its bands in the IR and Raman spectra.^{26, 191, 192} This is caused by the population of the t_{1u} orbital of the fullerene and interaction of the T_{1u} vibrations with virtual electronic transitions from the t_{1u} orbital to the higher t_{1g} orbital.¹⁹¹ Figure 8 shows the charge dependence of the position of absorption bands (ν) of C_{60} vibrations active in the IR spectrum.^{26, 191} The $T_{1u}(4)$ and $T_{1u}(2)$ vibrations are most sensitive to charge transfer: they are characterised by a linear increase in ν_p and an almost linear shift of ν . The $A_{1g}(2)$ vibration active at 1469 cm^{-1} in the Raman spectrum also has a linear dependence of ν on the degree of reduction of the fullerene molecule.^{26, 192} This relationship may be used for the determination of the degree of C_{60} reduction in salts,²⁶ including that occurring during intercalation. The plasma frequency (ω_p) (square root of the oscillator force) also changes linearly with the charge on the fullerene molecule (Fig. 9).

The change in frequency of absorption bands in the IR spectrum of C_{60} vibrations in D-A complexes makes it possible to estimate even a small degree of charge transfer ($0 < \delta < 1$). This method has already been used previously for the estimation of charge transfer in organic CTC.^{9, 193}

The $T_{1u}(4)$ vibration is most suitable for determination of the degree of charge transfer (δ), as the transition from C_{60} to the C_{60}^- radical anionic salts is accompanied by a strong shift of the absorption band of this vibration from 1429 cm^{-1} to $1390-1395\text{ cm}^{-1}$ (see Refs 26, 48, 184, 191 and 195) (Table 9).

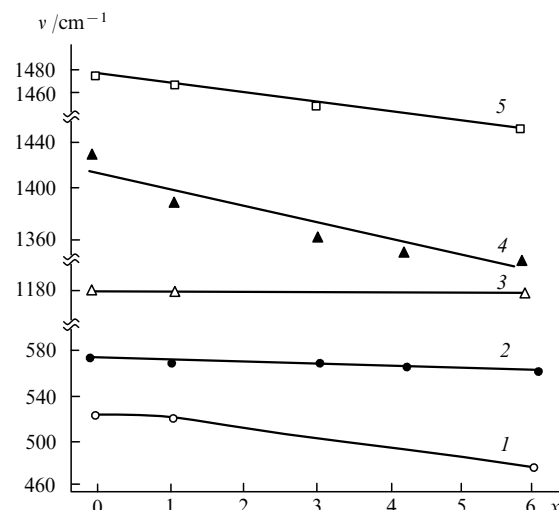


Figure 8. Wave numbers (ν) for different degrees of reduction (x) of the C_{60} fullerene molecule.¹⁹¹ (1), $T_{1u}(1)$ vibrations; (2), $T_{1u}(2)$ vibrations; (3), $T_{1u}(3)$ vibrations; (4), $T_{1u}(4)$ vibrations; (5), $A_{1g}(2)$ vibrations.

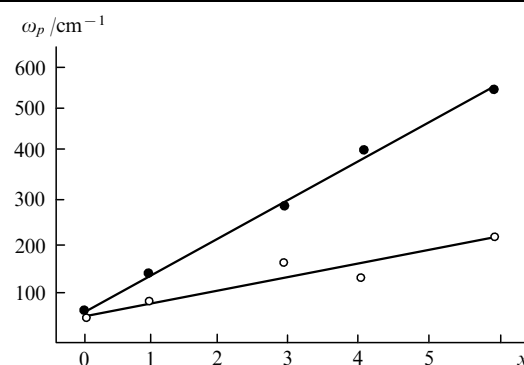


Figure 9. Plasma frequency (ω_p) for different degrees of reduction (x) of the C_{60} fullerene molecule.¹⁹¹ (1), $T_{1u}(2)$ vibrations; (2), $T_{1u}(4)$ vibrations.

The change in the positions of absorption bands of three other T_{1u} vibrations active in the IR region on transition from C_{60} to C_{60}^- is less marked.^{26, 192}

Taking into account the linear dependence of the position of the absorption band of the $T_{1u}(4)$ vibrations on the degree of reduction of the fullerene molecule, it is possible to use Eqn (1) for the estimation of the degree of charge transfer in complexes:^{9, 193}

$$\delta = \frac{2\Delta\nu}{\nu_0(1 - \nu_1^2/\nu_0^2)}, \quad (1)$$

where ν_0 is the position of the absorption band of the $T_{1u}(4)$ vibration in neutral C_{60} (1429 cm^{-1}); ν_1 is its average position in C_{60}^- salts [$1392.5 \pm 2.5\text{ cm}^{-1}$, depending on the crystal structure (Table 9)], and $\Delta\nu$ is the difference between the positions of absorption bands of $T_{1u}(4)$ vibrations in neutral C_{60} and in the corresponding complex.

The use of these values in Eqn (1) gives Eqn (2):

$$\delta \approx 0.03 \Delta\nu. \quad (2)$$

The accuracy of estimation of charge transfer δ , which is ± 0.03 , depends on the accuracy of measurement of the positions of absorption bands in IR spectra ($\pm 1\text{ cm}^{-1}$).

One can see from Table 9, which lists the positions of the $T_{1u}(4)$ vibration bands and the degree of charge transfer in C_{60} compounds estimated from Eqn (2), that the degree of charge transfer is close to zero (molecular complexes) for the majority of C_{60} compounds with organic donors. In radical ionic salts, the

degree of charge transfer is close to unity. Only the complexes of C_{60} with TMPD,¹⁹⁰ cobaltocene^{47,48} and dibenzenechromium¹⁵⁰ have intermediate degrees of charge transfer.

c. ESR spectra

The g -factors and ΔH of ESR signals of fullerenes and their compounds are listed in Table 10. In a discussion of the ESR spectra of C_{60} compounds, it is necessary to emphasise the presence of two ESR signals at room temperature in specimens of the initial, 'pure' fullerene, one with $g = 2.0025$ – 2.0021 and $\Delta H = 2$ G^{196,197} and the other with $g = 2.0006$ – 2.0012 and $\Delta H = 0.5$ – 2 G;¹⁹⁶ their widths virtually do not change down to liquid-helium temperatures. These signals originate from defects, *i.e.*, paramagnetic admixtures formed upon oxidation of fullerene with oxygen.^{177,196} The intensity of the former signal increases by an order of magnitude on heating the specimen in air at 623 K for 2 h and by two orders on heating for 24 h.¹⁹⁶ The intensity of this signal changes considerably depending on the way the fullerene has been obtained or stored.

Unlike the signals related to the oxidation of fullerenes, the ESR signals of the $C_{60}^{\cdot-}$ anions have a considerably larger line width ($\Delta H = 20$ – 60 G), which depends strongly on temperature. The ground state of the radical anion $C_{60}^{\cdot-}$ is a singlet ($S = 1/2$) with $g = 1.997$ – 1.999 . This value is smaller than the g -factor of a free electron.^{56,56,61,153} Larger g -factors (2.0008) are observed only in salts of C_{60} with amines.^{38,142} The C_{60}^{2-} anion displays a signal with $g = 2.0010$ and $\Delta H = 10$ – 30 G at room temperature. This corresponds to the triplet state ($S = 1$) with forbidden splitting $D \cong 0$: two electrons with parallel spins are so distant from each other that they behave similarly to electrons with independent spins, therefore their interaction is not displayed in the ESR spectra.⁵⁰ The radical anion C_{60}^{3-} is in a singlet basic state ($S = 1/2$) at room temperature, and its g -factor equals 2.0012–2.0017, and $\Delta H = 10$ – 30 G.⁴⁹ In the compounds M_3C_{60} , the ESR parameters (the g -factor and ΔH) of the C_{60}^{3-} radical anion depend on the nature of the metal.^{13,14} The ESR signals of all of the $C_{60}^{\cdot-}$ anions become much narrower as the temperature is decreased.^{58,153,154}

Due to the Jahn–Teller effect, the presence of fullerene radical anions in C_{60} salts with bulky counter-ions results in violation of the I_h symmetry of C_{60} .^{48–50,149} The effect can be both dynamic

and static on the ESR time scale.¹⁹⁸ At room temperature, a dynamic effect with fast transition from one static Jahn–Teller configuration to the other is observed. Based on the ESR data, the frequency of this pseudo-rotation is estimated as $\sim 10^{12}$ Hz.¹⁹⁸ If the temperature is decreased, pseudo-rotation is hindered, the ESR signal narrows, and transition to the static Jahn–Teller effect is observed. In the salt $(Ph_4P)C_{60}(Ph_4PCl)_2$, this transition occurs when the temperature is decreased to 70 K;¹⁹⁹ this is accompanied by abrupt narrowing of the signal. On further decreasing the temperature, its width almost does not change. The static Jahn–Teller effect at low temperatures (4–70 K) results in transformation of the isotropic ESR signal to anisotropic. For instance, the $Na(18\text{-crown-6})C_{60}(\text{THF})_3$ salt displays an anisotropy of the g -factor: $g_{\perp} = 1.9968$, $g_{\parallel} = 2.0023$.⁴⁸

As the symmetry of the $C_{60}^{\cdot-}$ radical anion decreases from I_h to D_{5d} , the T_{1u} state splits into two states, *viz.*, E_{1u} and A_{2u} (Fig. 10). The difference between the energies of the E_{1u} and A_{2u} states is small and equals 1 kcal, therefore thermal population of the overlying A_{2u} state can occur, and an additional 'high-temperature' signal with $g = 2.000$ appears in the ESR spectrum of $C_{60}^{\cdot-}$.⁴⁸

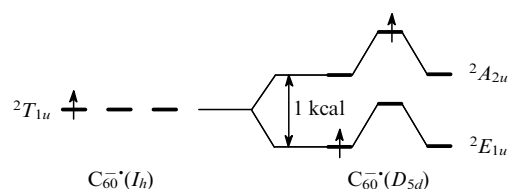


Figure 10. Scheme of partial removal of degeneracy of the t_{1u} orbital in the $C_{60}^{\cdot-}$ radical anion upon lowering the symmetry from I_h to D_{5d} .⁴⁸

The radical anion $C_{70}^{\cdot-}$ in the $(Ph_4P)_2C_{70}I$ salt gives a broad ESR signal with $g = 2.047$,¹⁵⁴ as does that in the salt $(TDAE)C_{70}$, with $g = 2.0022$.^{136,137} Higher fullerenes display a narrow signal with $g = 2.0023$,¹⁴³ which is close to the g -factor for the free electron.

The ESR signal of the $C_{60}^{\cdot-}$ radical anion in some fullerene complexes has been used to determine the degree of charge

Table 10. g -Factors and line widths (ΔH) for ESR signals in D-A complexes and radical ionic fullerene salts.

Compound	Charge on fullerene	g -Factor	T /K	ΔH /G	Ref.
C_{60}	0	2.0021	< 300 ^a	0.3–1.0	196
C_{60}	0	2.0023	< 300 ^a	0.5–2.0	197
		2.0006–2.0012	< 300 ^a	0.5–2.0	
$(Ph_4P)C_{60}(Ph_4PCl)_2$	–1	1.9991	300	45	56
$(PPN)C_{60}(C_6H_5Cl)$	–1	1.9992	300(77) ^b	35(5)	58
		2.0007	> 50 ^c	1–2	
$(Ph_4P)_2C_{60}I_{0.35}$		1.9979	300(113) ^b	50(14)	153
$KC_{60}(\text{THF})_5$	–1	1.9987	300	34	55
$Na_{0.4}C_{60}(\text{THF})_{2.2}$	–0.4	1.999	300	30	61
$(TDAE)C_{60}$	–1	2.0008	300	22	38, 142
		2.0017–2.0030	< 16 ^{a,d}	30	
$(TDAE)C_{70}$	–1	2.0022	< 300 ^a	10	136, 137
$(TDAE)C_{84}$, C_{90} , C_{96}	–1	2.0020–2.0022	< 300 ^a	1.85–2.40	143
$(DBU, \text{DBN})C_{60}$	–1	—	300(5) ^b	40(5)	127, 128
$[(C_5H_5)_2Co]C_{60}(C_6H_5CN)$	–1	1.9969	130(4.5) ^b	24(6)	48
		2.000	> 24 ^c	3	
$(Ph_4P)C_{70}(Ph_4PI)$	–1	2.047	300(4.2) ^b	600(1.5)	154
$SbCl_3 + C_{60}$	+1	2.0029	300	1.5	35
$(CB_{11}H_6Br_6)C_{76}$	+1	2.0030	300	0.5	7

^a The signal is observed below the temperature T ; ^b the ESR signal was measured at two different temperatures $T(T_1)$; ^c the signal is observed above the temperature T ; ^d ESR signal after transition of the compound to ferromagnetic state.

transfer from the donor to C_{60} (based on the number of $C_{60}^{\cdot-}$ spins per formula unit).^{123, 127, 128}

d. X-ray photoelectron spectroscopy

X-Ray photoelectron spectroscopy (XPS) is a sensitive method for the determination of the valence state of elements in thin (0.5–4.0 nm) surface layers. Based on the position of lines corresponding to internal electronic shells of heteroatoms of the donors contained in the complex and their shift relative to the lines of the individual donor, it is possible to estimate the redistribution of the electron density upon formation of a D–A compound and the atomic composition of the compound.^{200–205}

The C(1s) X-ray photoelectron spectrum of the C_{60} fullerene consists of the main singlet peak with an energy of 285 eV. The higher energy region contains a satellite shifted by 5.9 eV from the main C(1s) peak. It originates from excitation of a π -plasmon, *i.e.*, coordinated vibrations of π -electrons of the C_{60} molecules in a crystal.²⁰⁶ The density of valence electrons is determined from the electron energy loss spectra (EELS). The loss function has two peaks in the case of the C_{60} fullerene,^{203, 206} which correspond to the π -plasmon with a maximum at 5.8 eV originating from excitation of plasma vibrations of π -electrons and the $(\pi + \sigma)$ -plasmon with a maximum at 26.1 eV originating from excitation of all valence electrons in C_{60} .^{203, 206}

The position of the C(1s) peak in the XPS spectra of molecular complexes and salts of fullerenes remains unchanged, but some changes in its satellite structure occur.^{44, 205} The disappearance of $\pi - \pi^*$ transitions of phenyl substituents of the donors in the satellite structure of C_{60} compounds, *e.g.*, in (DAN) $C_{60}(C_6H_5)_3$ ⁴⁴ and in salts with bulky cations,²⁰⁵ has been reported. This is due to the strong interaction of the phenyl substituents of the donor with the fullerene or to the fact that, upon formation of a compound with fullerene, the $\pi - \pi^*$ transitions in the donor molecule become less favourable than the excitation of plasma vibrations of π -electrons of the fullerene itself.^{44, 205} In many compounds, a decrease in the energy of the $\pi + \sigma$ -plasmon is observed: 24.0 eV in $(S_8)_2C_{60}$,²⁰³ 25.2 eV in (BTX) $C_{60}(CS_2)$ ^{54, 119} and 25.5 eV in TPDP(C_{60}) $_2(CS_2)_4$.⁴³

The shift in the position of the S(2p), N(1s) and Te ($3d_{5/2}$) lines of the donor heteroatoms in various fullerene complexes by 0.1–1.0 eV towards higher energies can be caused^{200, 201, 204} by the electron density shift from the donor to the fullerene. However, in some cases a similar shift in fullerene complexes in comparison with the individual donors can also be due to the calibration of spectra of the complex and the donor with respect to the C(1s) line, as the exact position of this line in the spectra of the donor and C_{60} can differ.²⁰⁰ A shift in the position of the S(2p) peak in compound $(S_8)_2C_{60}$ towards lower energies by 0.4 eV has been reported.²⁰³

e. ^{13}C NMR spectroscopy

The ^{13}C NMR spectrum of crystalline C_{60} fullerene at room temperature contains a narrow singlet at δ 143.²⁹ This is caused by fast rotation of the C_{60} molecule and isotropic averaging of the signal. As the temperature is decreased, the rotation of fullerene molecules is hindered, and broadening of the signal is observed.²² The observed phase transitions in fullerene at 255 and 90 K result in stepwise changes in the line width. The formation of molecular complexes does not change the position of the ^{13}C NMR signal of the fullerene.^{93, 98, 114} The formation of fullerene anions, C_{60}^{n-} ($n = 1, 2, 3$), causes a shift of the ^{13}C NMR signal towards lower magnetic field, which can be due to the paramagnetic state of these ions.^{50, 207, 208} However, the salts containing the $C_{60}^{\cdot-}$ and C_{60}^{2-} anions have close chemical shifts of signals in the ^{13}C NMR spectra (δ 187 and 183, respectively), though their magnetic susceptibilities differ strongly.^{207, 208} A shift of the ^{13}C NMR signal to δ 156 is also observed in the diamagnetic state of the C_{60}^{6-} anion.²⁰⁸

V. Conclusion

Based on the survey of the most important results concerning the synthesis and properties of the D–A complexes and radical ionic salts of fullerenes obtained over the last years, one can distinguish the most important directions of the development in this field and evaluate some possibilities of using fullerene compounds, both for obtaining new materials and for solving fundamental problems.

The ability of molecules of the C_{60} fullerene, its molecular complexes and salts to synchronise their rotation in crystals results in the appearance of unusual magnetic properties in these compounds. The existence of the frozen glassy magnetic state of fullerenes and molecular complexes of fullerenes with halogens has been established; radical anionic salts of $C_{60}^{\cdot-}$ with unsaturated amines possess ferromagnetic properties with the highest T_c among organic materials; various magnetic properties are displayed by complexes of C_{60} with metallocenes. Obviously, synthesis of D–A complexes of fullerenes with strong organic and organometallic donors, *viz.*, unsaturated amines, metallocenes and metalloporphyrins, and the study of their structure and properties will lead to new interesting results.

Another important direction includes the synthesis of conducting and superconducting materials based on fullerene compounds. By now, several dozens of superconductors with $T_c \leq 40$ K have already been obtained based on C_{60} and some specific features of their superconductivity have been rationalised. Superconducting phases can exist in fullerene compounds with alkali or alkaline-earth metals, lanthanides, and in salts of C_{60} with strong organic donors: they can be obtained both by direct chemical synthesis and by intercalation in the gas phase.

Fullerenes are weak acceptors, and the range of donors capable of reducing them to radical anions is limited. In addition, the essential drawback of both superconducting and ferromagnetic compounds of fullerenes is their instability in air. This restricts considerably the possibilities of obtaining and applying the fullerene-based materials with specific conducting and magnetic properties.

One possible way to solve these problems is the synthesis of three-component systems. The systems ‘organic donor – fullerene radical anion – alkali metal cation’ include a wider range of ionic compounds of fullerenes. In some of them, the fullerene radical anion can be stabilised because the bulky organic donor sterically hinders the approach of oxygen molecules to the fullerene radical anion.

In the majority of fullerene complexes that have been obtained, in particular in the complexes with tetrathiafulvalenes, charge transfer is insignificant because of the weak acceptor properties of C_{60} and C_{70} . However, in a three-component system ‘donor radical cation – neutral fullerene – halide anion’, fullerene compounds with radical cations of the donors can be obtained. Similar compounds can also possess conducting and magnetic properties.

Three-component systems can be obtained by intercalation of fullerene complexes (with either alkali metals or halogens) or by direct synthesis in solution. In the latter case, it is probably possible to obtain single crystals of these compounds.

Synthesis of complexes of chemically modified fullerenes, in particular, brominated, chlorinated and fluorinated ones, seems to be a promising direction. Unlike the C_{60} and C_{70} molecules, these derivatives have strong acceptor properties and can apparently yield molecular complexes and radical ionic salts with strong organic donors (*e.g.*, tetrathiafulvalenes).

The significant delocalisation of electrons in C_{60} upon photo-induced electron transfer results in the formation of free charge carriers and high photoconductivity. In the near future, this phenomenon can find application for the development of energy phototransducers and other devices that use photoconductivity. Therefore, the study of electron photoconduction in fullerene compounds is an important direction. The most promising compounds for the development of materials with high photo-

conductivity can include both the composites 'C₆₀ – conducting polymer' and D–A complexes of fullerenes with organic donors, in which charge separation with significant life time is possible. The use of the combination 'organic donor – C₆₀ – conducting polymer' is also promising.

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

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^d — *Russ. J. Phys. Chem. (Engl. Transl.)*

^e — *Russ. Crystallography (Engl. Transl.)*

^f — *Russ. J. Gen. Chem. (Engl. Transl.)*

Recyclisation of carbo- and heterocyclic compounds involving malononitrile and its derivatives[†]

V P Litvinov

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Abstract. Published data on recyclisation reactions of carbo- and heterocycles with participation of malononitrile and recyclisation of compounds containing a malononitrile fragment or fragments with malononitrile as a synthon are surveyed, described systematically and analysed. The bibliography includes 206 references.

I. Introduction

Recyclisation of carbo- and especially heterocyclic compounds occupies an important place in organic chemistry. Recyclisation in the presence of various nucleophilic, electrophilic or dipolar reagents occurs as opening of the ring in the initial molecule and its subsequent closure. This process is often accompanied by ring expansion or contraction, introduction of a heteroatom in the ring or its replacement by another heteroatom, *etc.* Nevertheless, from the preparative viewpoint, all these complex transformations occur during a one-stage reaction, which makes possible relatively easy synthesis of compounds that are difficult to obtain by other methods or modification of heterocyclic fragments in complex, including natural, molecules. The latter is fairly important for the synthesis of new biologically active products. At present, a large number of transformations of this type are known; they include name reactions, for example, the Yur'ev, Zincke–Konig and Hafner reactions, the Dimroth, Boulton–Katritzky, Cornforth and Kost–Sagitullin rearrangements, *etc.* The problem of recyclisation is considered in numerous publications and reviews (see, for example, Refs 1–24).

Malononitrile **1**, containing highly reactive methylene and cyano groups,²⁵ is of special interest as a reagent for recyclisation of carbo- and heterocyclic compounds. In this review, we consider recyclisation reactions with participation of malononitrile and its derivatives including carbo- and heterocyclic compounds with vicinal cyano groups. Primary attention is paid to the synthetic potential of these reactions and less space is given to the reaction mechanisms, because the data on the mechanisms are quite limited and often contradictory.

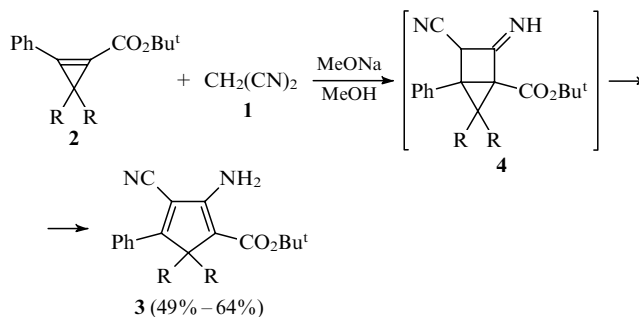
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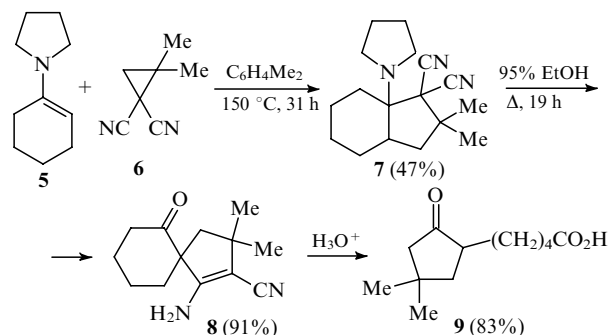
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II. Recyclisation of three- and four-membered rings

In 1983, a group of German scientists found that cyclopropene derivatives **2** react with the malononitrile anion, generated by treatment of malononitrile with sodium methoxide in methanol, to give functionally substituted cyclopentadienes **3**. Bicyclic derivatives **4** were postulated as intermediates in this reaction.²⁶



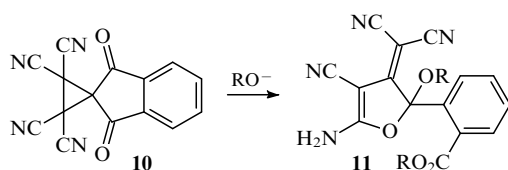
Cycloaddition of *N*-cyclohexenylpyrrolidine **5** to 2,2-dimethyl-1,1-cyclopropanedicarbonitrile **6** has been reported.²⁷ The reaction follows an S_N2 mechanism and yields adduct **7**. On partial hydrolysis, this product rearranges into spiro compound **8**, which is further hydrolysed to give 5-(4,4-dimethyl-2-oxocyclopentyl)pentanoic acid **9**.



The reactivity of substituted tetracyanocyclopropanes has attracted considerable attention of researchers in recent years. Thus it was found that treatment of 3,3-phthaloylcyclopropane-1,1,2,2-tetracyanitrile **10** with nucleophiles (alcohols or ketox-

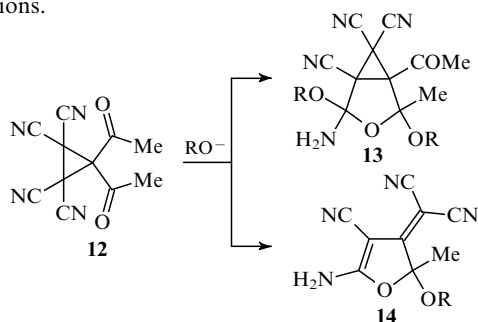
[†] This review is dedicated to the memory of Professor Yu A Sharanin.

imes) induces recyclisation of the cyclopropane fragment in **10** and results in the formation of 2-alkoxy-2-(2-alkoxycarbonylphenyl)-5-amino-4-cyano-3-dicyanomethylene-2,3-dihydrofurans **11**.^{28,29}



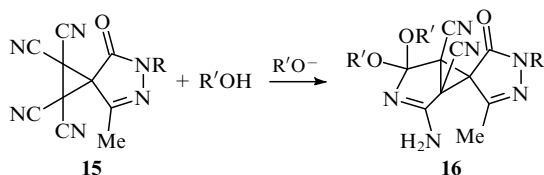
R = Me, Et, (CH₂)₂OH, N = CMe₂, N =

Unlike the cyclopropane **10**, 3,3-diacetylcyclopropane-1,1,2,2-tetracyanonitrile **12** reacts with alcohols or ketoximes in the presence of catalytic amounts of the corresponding sodium alkoxides or oximates with retention of the cyclopropane ring to give substituted 3-oxabicyclo[3.1.0]hexane-1,6,6-tricyanonitriles **13**.^{28,30} However, when a twofold excess of the catalyst is used, 2,3-dihydrofuran derivatives **14** are formed under similar conditions.



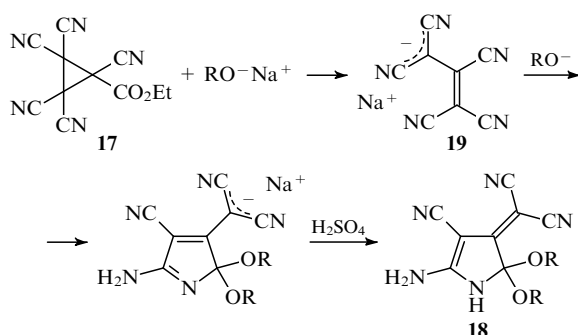
R = Me, Et, N = CMe₂, N = CMeEt, N = CMeBu, (CH₂)₂OH,
N = , N =

The cyclopropane ring is also retained when substituted pyrazoline-4-spirocyclopropanetetracyanonitriles **15** are treated with alcohols and ketoximes under the same conditions; this reaction affords adducts **16**.³¹



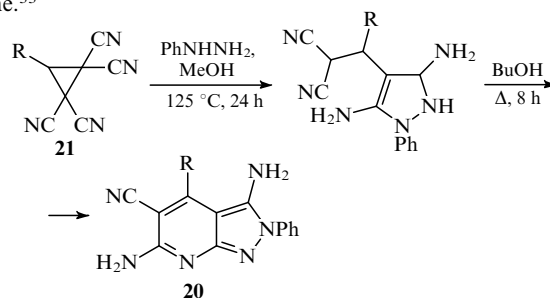
R = Pri, Ph; R' = Me, Et, N = CMe₂, N = CMeEt, N = , N =

When ethyl pentacyanocyclopropanecarboxylate **17** is made to react with alcohols in the presence of an equimolar amount of the corresponding alkoxide, it undergoes recyclisation to give 5,5-dialkoxy-2-amino-4-dicyanomethylene-2-pyrroline-3-carbonitriles **18**. The formation of a stable intermediate, sodium pentacyanopropenide **19**, was noted.³²



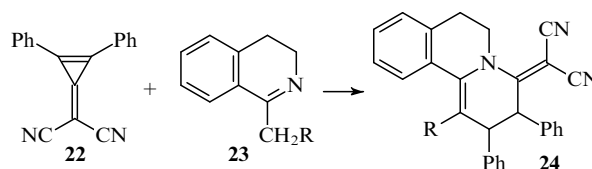
R = Me, Et.

2*H*-Pyrazolo[3,4-*b*]pyridines **21** have been prepared by recyclisation of tetracyanocyclopropanes **20** involving phenylhydrazine.³³

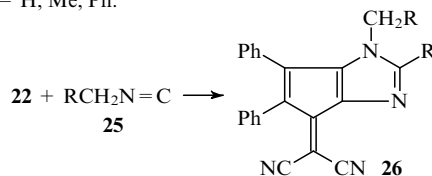


R = Me, Et, Ph, 4-ClC₆H₄, 4-NO₂C₆H₄.

The reaction of 3-dicyanomethylene-1,2-diphenylcycloprop-1-ene **22** with 3,4-dihydroisoquinolines **23** in ethanol is accompanied by recyclisation giving rise to 4-dicyanomethylene-2,3-diphenyl-4*H*-2,3,6,7-tetrahydropyrido[2,1-*a*]isoquinolines **24** in 73%–78% yields.³⁴ Refluxing of the compound **22** with isonitriles **25** in acetonitrile results in the formation of 4-dicyanomethylene-4*H*-cyclopenta[2,3-*b*]imidazole derivatives **26** in 43%–58% yields.³⁵

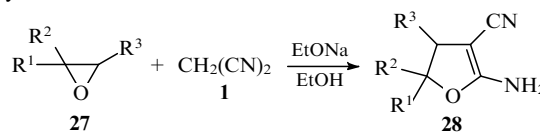


R = H, Me, Ph.



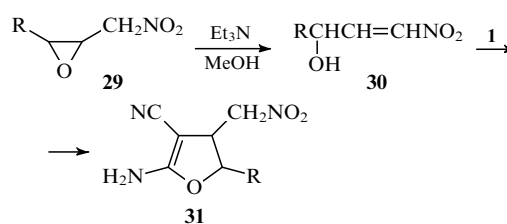
R = Ph, CO₂Et.

Various three-membered heterocycles, oxiranes,^{1,36} thiiranes^{1,36–38} and aziridines,^{38,39} can also undergo recyclisation on treatment with nucleophiles. Thus it was found that the reaction of oxiranes **27** with malononitrile in the presence of sodium ethoxide in ethanol occurs as recyclisation yielding 2-amino-4,5-dihydrofuran-3-carbonitrile **28**.^{40–42}



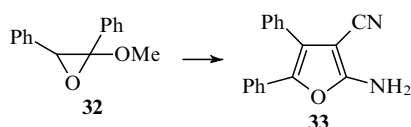
R¹ = H, Me, Et, Ph; R², R³ = H, Me.

In the case of oxiranes **29**, recyclisation proceeds *via* acyclic intermediates **30**, which were treated with malononitrile after isolation. This afforded 2-amino-4-nitromethyl-4,5-dihydrofuran-3-carbonitrile **31** in yields of up to 60%.^{43–45}

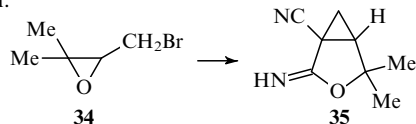


R = H, Me.

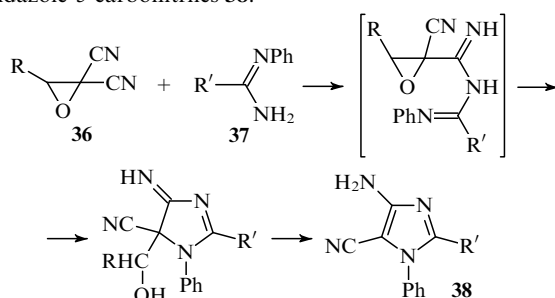
2-Methoxy-2,3-diphenyloxirane **32** recyclises in the presence of sodium malononitrile giving rise to 2-amino-4,5-diphenylfuran-3-carbonitrile **33**.⁴⁶



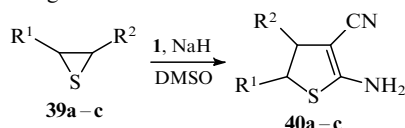
The γ -iminolactone **35** has been synthesised by treatment of the oxirane **34** with potassium malononitrile in *tert*-butyl alcohol.⁴⁷



It has also been reported^{48,49} that recyclisation of 2,2-dicyano-oxiranes **36** in the presence of amidines **37** affords 4-aminoimidazole-5-carbonitriles **38**.

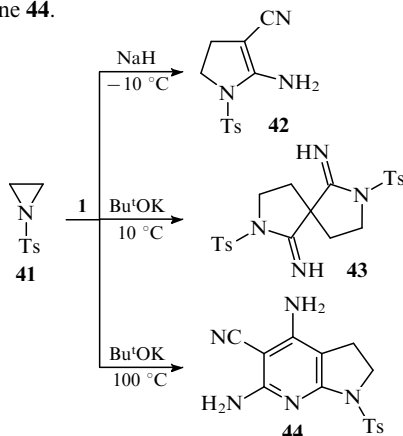


Thiiranes also enter into recyclisation reactions.^{1, 38, 42, 50–52} For example, thiiranes **39a–c** react with malononitrile in the presence of sodium hydride in DMSO giving 2-amino-4,5-dihydrothiophene-3-carbonitriles **40a–c** in 50%–62% yields. Note that in the case of the thiiranes **39a,b**, ring opening occurs in conformity with Krasuski's rule, while in the case of **39c**, the ring opens against this rule.^{38,50}

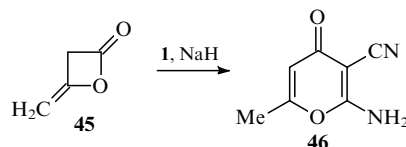


$R^1 = H$; $R^2 = H$ (**a**), Me (**b**), Ph (**c**).

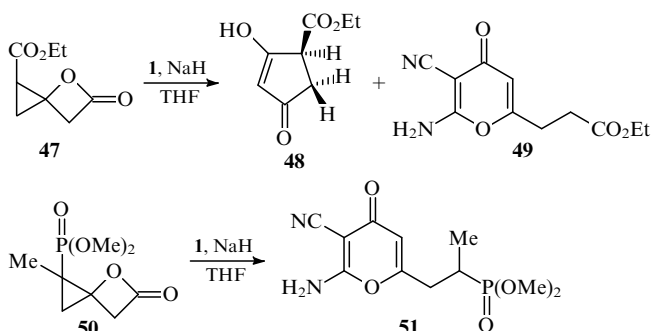
Recyclisation reactions for three-membered nitrogen-containing heterocycles have been reported.^{42,52–54} The reaction of aziridines **41** with malononitrile in the presence of sodium hydride affords different products depending on the reaction conditions and the ratio of the reactants.⁴² When the compounds **1** and **41** are taken in equimolar amounts, 2-amino-1-(toluene-*p*-sulfonyl)-4,5-dihydropyrrole-3-carbonitrile **42** is formed. The reaction with a twofold excess of the initial aziridine **41** (Bu^tOK , 10 °C) yields spiro compound **43**, whereas the use of a twofold excess of malononitrile and an increase in the reaction temperature to 100 °C results in the formation of 2,3-dihydropyrrolo[2,3-*b*]pyridine **44**.



Recyclisation of four-membered heterocycles with participation of malononitrile is also known. Thus the reaction of 2-oxetanone **45** with malononitrile in the presence of sodium hydride affords 2-amino-3-cyano-6-methyl-4-pyrone **46**.⁵⁵

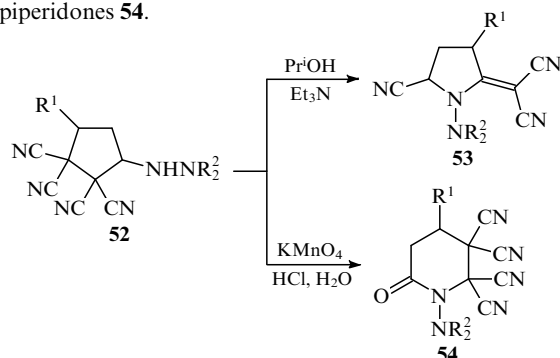


Treatment of 1-ethoxycarbonyl-5-oxo-4-oxaspiro[2.3]hexane **47** with malononitrile under similar conditions gives rise to a mixture of cyclopentenone **48** and 2-amino-4-pyrone **49** (yields 49% and 24%, respectively).⁵⁶ 1-Dimethoxyphosphoryl-1-methyl-5-oxo-4-oxaspiro[2.3]hexane **50** reacts with malononitrile under the same conditions to afford 2-amino-3-cyano-6-(2-dimethoxyphosphorylpropyl)-4-pyrone **51** in 58% yield.⁵⁶



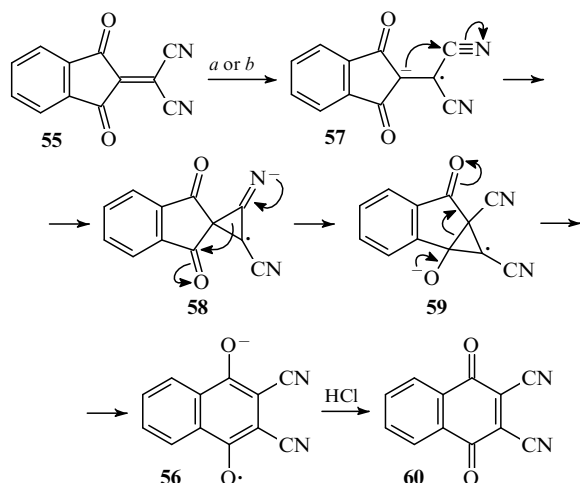
III. Recyclisation of five-membered rings

Recyclisation of tetracyanocyclopentanes **52** has been reported.^{57,58} Depending on the reaction conditions, they are transformed into 2-dicyanomethylene-pyrrolidines **53** or tetracyanopiperidones **54**.



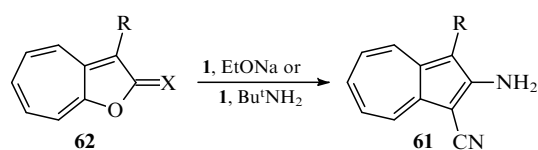
$R^1 = Me$; $R^2 = Me, Et$; $R^1 = Pr$, $R^2 = Me$.

A scheme for the transformation of 2-dicyanomethyleneindane-1,3-dione **55** into salts **56** has been proposed.⁵⁹ The transformation is attained by refluxing **55** in acetonitrile in the presence of lithium iodide or methyltriphenylphosphonium iodide or by stirring it in dry THF with finely divided sodium. The reaction scheme includes a single-electron transfer in the indanedione **55** resulting in symmetrical radical anion **57**, which cyclises to give spirocyclopropane intermediate **58**. The rearrangement of the compound **58**, accompanied by cyclopropane ring opening, and subsequent cyclisation result in the formation of cyclopropane intermediate **59**. This compound also recyclises to afford salts **56**. Treatment of the lithium or methyltriphenylphosphonium salt **56** with concentrated hydrochloric acid gives 2,3-dicyano-1,4-naphthoquinone **60** in 65% and 40% yields, respectively.⁵⁹



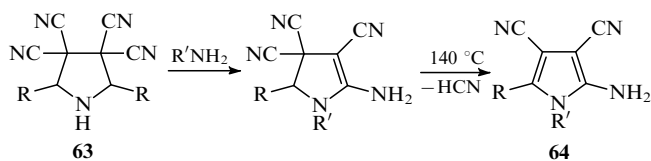
(a) M^+I^- , MeCN, Δ , $M = Li, Ph_3PMe$; (b) Na, THF, 20 °C, 48 h.

The review on molecular rearrangements of five-membered heterocycles¹¹ published in 1984 presents virtually no data on recyclisation with participation of malononitrile or recyclisation of heterocyclic systems containing malononitrile fragments. Meanwhile, an original pathway to aminoazulenes **61** consisting in recyclisation of lactones or iminolactones, 2*H*-cyclohepta[*b*]-furan derivatives **62**, on treatment with methylene active nitriles, including malononitrile, had been reported in the literature.^{36, 60–63}

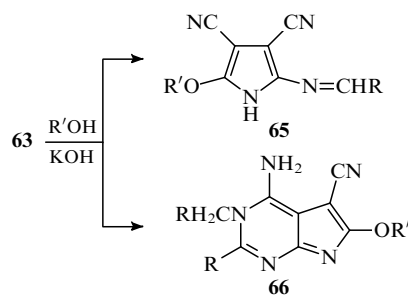


X = O, NAc; R = CO₂Et, COMe.

2,5-Disubstituted pyrrolidine-3,3,4,4-tetracarboxitriles **63** react with aromatic amines to give 2-aminopyrrole-3,4-dicarbonitriles **64**.⁶⁴ Depending on the ratio of the reactants, the reactions of the compounds **63** with primary alcohols in the presence of KOH yield either 3,4-dicyanopyrroles **65** or substituted 3*H*-pyrrolo[2,3-*d*]pyrimidines **66**.^{65, 66}



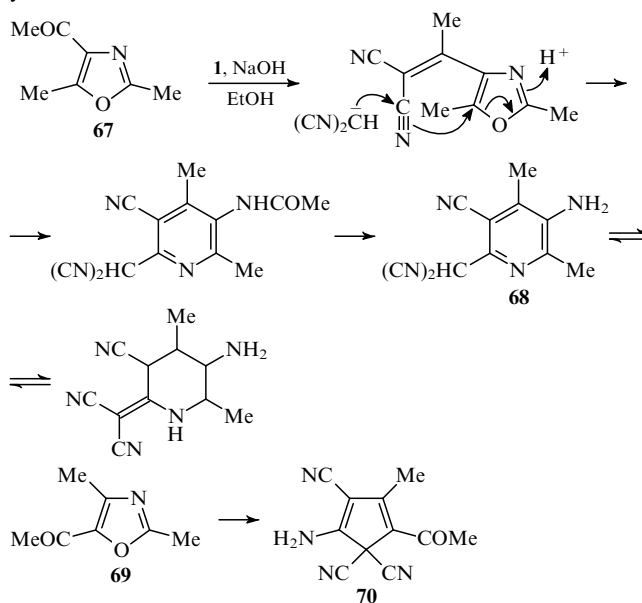
R = Ph; R' = Ph, 3-MeC₆H₄.



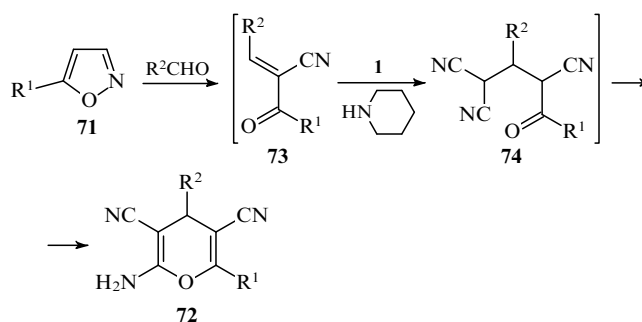
R = Ph, 4-BrC₆H₄, 4-FC₆H₄, 4-MeC₆H₄, O-C₆H₄; R' = Me, Et, Pr.

4-Acetyl-2,5-dimethyloxazole **67** also reacts with malononitrile with recyclisation of the oxazole ring. This reaction results in the formation of 3-amino-6-dicyanomethyl-2,4-dimethylpyridine-5-carbonitrile **68** in 33% yield. 5-Acetyl-2,4-dimethyloxazole **69**, which is an isomer of the compound **67**, reacts with malononitrile

under similar conditions being thus converted into 2-acetyl-5-amino-3-methylcyclopentadiene-1,1,4-tricarbonitrile **70** in 60% yield.⁶⁷

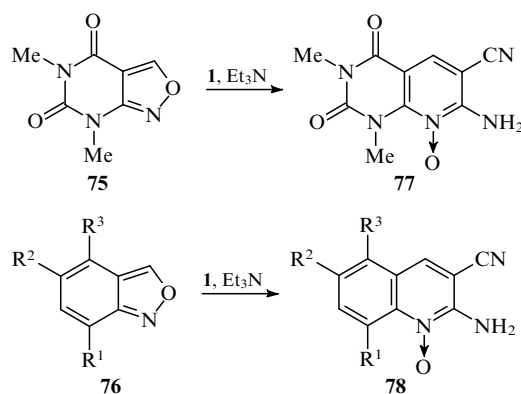


It has been noted^{68–71} that isoxazoles **71** recyclise to give 2-amino-4*H*-pyran-3,5-dicarbonitriles **72**. Opening of the isoxazole ring in the compound **71** under the action of an aldehyde and EtONa in ethanol gives rise to substituted nitriles **73**. The subsequent nucleophilic attack on the compounds **73** by malononitrile followed by cyclisation of the Michael adducts **74** affords aminopyrans **72**.⁶⁹



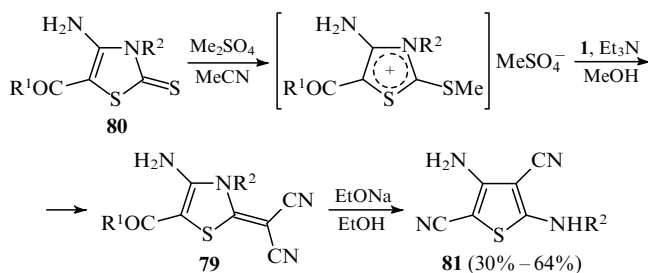
R¹ = Me; R² = Ph, 4-MeC₆H₄, 4-MeOC₆H₄, Bu^t;
R¹ = Ph; R² = Prⁱ, Bu^t, CH₂Et₂.

In turn, when fused isoxazoles **75** and **76** are made to react with malononitrile in the presence of triethylamine, the corresponding annelated 2-amino-3-cyanopyridine 1-oxides **77** and **78** are formed in high yields.^{70–72}



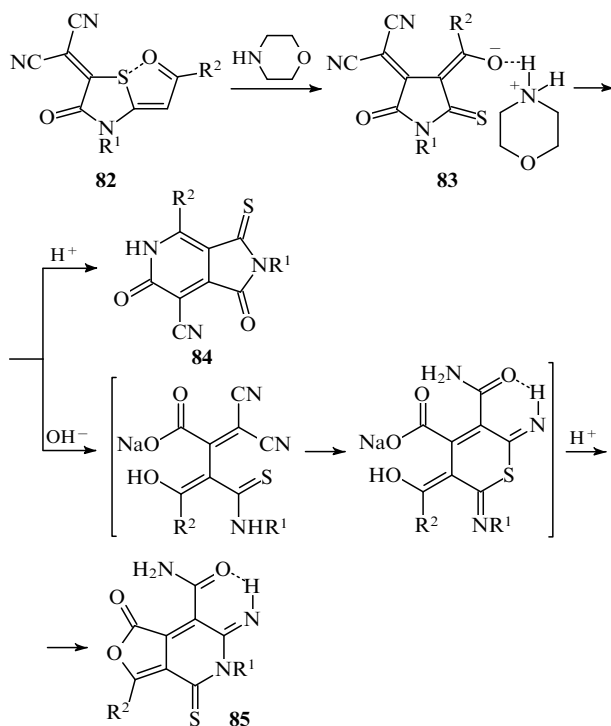
R¹ = H, Me; R² = H, NO₂; R³ = H, Cl, NO₂.

Recyclisation of 4-aminothiazolin-2-ylidenemalononitriles **79**, prepared from 4-aminothiazoline-2-thiones **80**, in the presence of sodium ethoxide in ethanol giving substituted 3,5-diaminothiophene-2,4-carbonitriles **81** has been described.⁷³



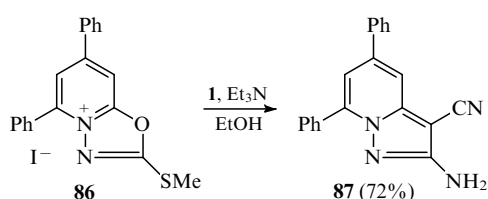
$\text{R}^1 = \text{OEt}, \text{NH}_2$; $\text{R}^2 = \text{Me}, \text{Ph}, \text{Bn}, \text{CH}_2\text{CH}=\text{CH}_2$.

Substituted 4-dicyanomethylenethiazolidin-5-ones **82** form complexes **83** with morpholine. Hydrolysis of these complexes with hydrochloric acid affords pyrrolo[3,4-*c*]pyridine derivatives **84**, whereas their interaction with NaOH followed by acidification gives rise to furo[3,4-*c*]pyridine derivatives **85**.⁷⁴



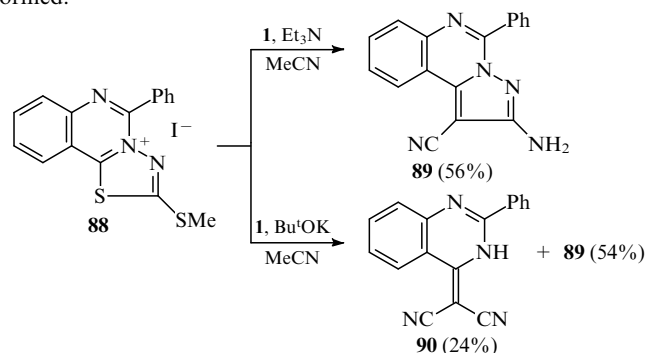
$\text{R}^1 = \text{Ph}, 4\text{-MeC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4$; $\text{R}^2 = \text{Ph}, 4\text{-MeC}_6\text{H}_4$.

It was also shown that 2-methylthio-5,7-diphenyl-1,3,4-oxadiazolo[3,2-*a*]pyridinium iodide **86** reacts with malononitrile in ethanol in the presence of triethylamine to give 2-amino-5,7-diphenylpyrazolo[1,5-*a*]pyridine-3-carbonitrile **87**.⁷⁵

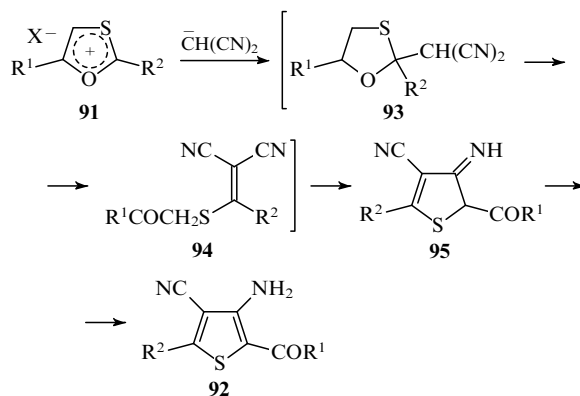


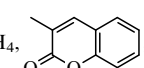
2-Methylthio-5-phenyl-1,3,4-thiadiazolo[3,2-*c*]-4-quinazolinium iodide **88** reacts with malononitrile in a similar way, with elimination of one heteroatom from the five-membered ring. Thus it was shown that the salt **88** reacts with malononitrile in dry

acetonitrile in the presence of triethylamine to give 2-amino-3-cyanopyrazolo[1,5-*c*]quinazoline **89**.⁷⁶ When potassium triethylamine is replaced by potassium *tert*-butoxide, a mixture of the pyrazoloquinazoline **89** and 3,4-dihydroquinazoline **90** is formed.⁷⁶



Recyclisation of 1,3-oxathiolium salts **91** on treatment with malononitrile has been used successfully in the synthesis of functionally substituted thiophenes **92**.^{36, 77–81} In the general form, the mechanism of this reaction includes the attack on the 2-position of the salt **91** by the malononitrile anion to give adduct **93**. The subsequent cleavage of the ring at the C(2)–S(3) bond in the compound **93** gives intermediate **94**, which then cyclises according to the Thorpe reaction pathway to give imine **95**; this product isomerises into more stable 3-aminothiophene **92**.

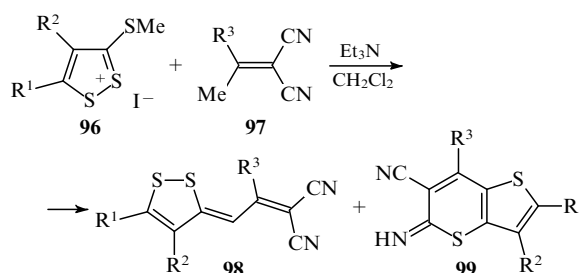


$\text{R}^1 = \text{Ph}, 4\text{-BrC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4$,


$\text{R}^2 = \text{Ph}, 4\text{-MeOC}_6\text{H}_4, 4\text{-Me}_2\text{NC}_6\text{H}_4$.

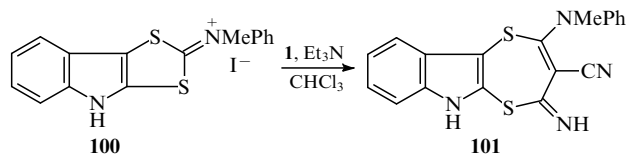
1,3-Oxathiolidene-2-immonium salts recyclise in a similar way to give functionally substituted thiophenes.^{81,82}

The reaction of 3-methylthio-1,2-dithiolium iodides **96** with ylidenemalononitriles **97** in dichloromethane in the presence of triethylamine has been shown⁸³ to afford dithiolyldenemalononitriles **98** and recyclisation products — 2-iminothieno[3,2-*b*]thiopyran-3-carbonitriles **99**.

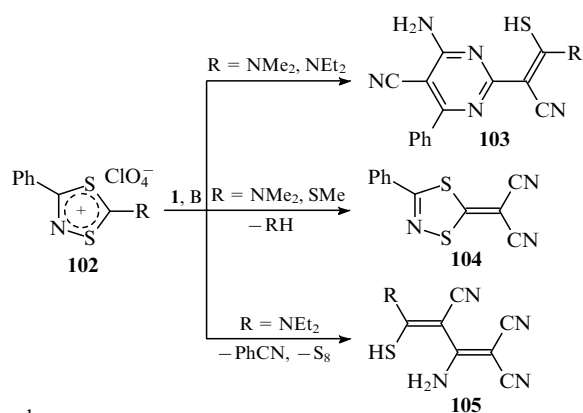


$\text{R}^1 = \text{Ph}, \text{SMe}, 4\text{-MeOC}_6\text{H}_4$; $\text{R}^2 = \text{H}, 4\text{-MeC}_6\text{H}_4$;
 $\text{R}^3 = \text{Ph}, 4\text{-MeOC}_6\text{H}_4$.

The reaction of iodide **100** with malononitrile in the presence of triethylamine in chloroform is also accompanied by recyclisation of the dithiole fragment. Simultaneously, ring expansion occurs and 2-imino-4-(*N*-methylanilino)-2*H*-[1,4]dithiapyrino-[2,3-*b*]indole-3-carbonitrile **101** is formed in 83% yield.⁸⁴

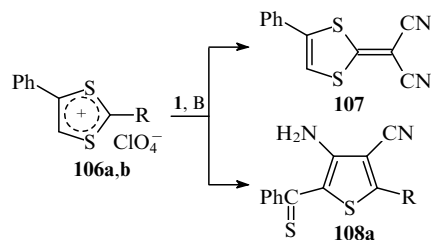


1,3,4-Dithiazolium perchlorates **102** react with malononitrile in the presence of a base (Et_3N , NaH, pyridine, γ -picoline) in EtOH, THF, CH_2Cl_2 or MeCN. Depending on the substituent at the C(5) atom, the base used and the ratio of the reactants, this gives 4-amino-2-(1-cyano-2-dialkylamino-2-sulfanylviny)-6-phenylpyrimidine-5-carbonitriles **103**, 2-dicyanomethylene-5-phenyl-1,3,4-dithiazole **104** or substituted 1,3-butadiene **105**.⁸⁵



B is a base.

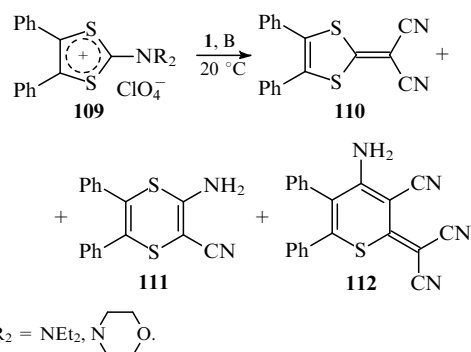
The pathway of the reactions of 1,3-dithiolium perchlorates with malononitrile also depends substantially on the nature of the substituents in the heterocycle and the solvent used. For example, the reaction of 2-diethylamino-4-phenyl-1,3-dithiolium perchlorate **106a** with malononitrile in the presence of a weak base (γ -picoline) results in the formation of 2-dicyanomethylene-4-phenyl-1,3-dithiole **107**, whereas in the presence of a strong base (triethylamine), 3-amino-5-diethylamino-2-thiobenzoylthiophene-4-carbonitrile **108a** is formed.⁸⁵



R = NEt_2 (a), NMe_2 (b).

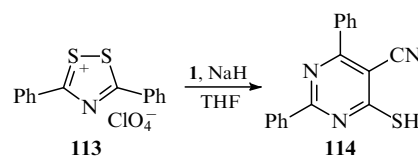
However, when 2-dimethylamino-derivative **106b** is used as the substrate, 1,3-dithiole **107** is formed in the presence of the strong base, triethylamine.

Similarly, the final products formed in the reaction of 4,5-diphenyl-1,3-dithiolium perchlorates **109** with malononitrile depend on the reaction conditions; this reaction can yield (in various proportions) 2-dicyanomethylene-4,5-diphenyl-1,3-dithiole **110**, 2-amino-5,6-diphenyl-1,4-dithiine-3-carbonitrile **111** and 4-amino-2-dicyanomethylene-5,6-diphenyl-2*H*-thiine-3-carbonitrile **112**.⁸⁵

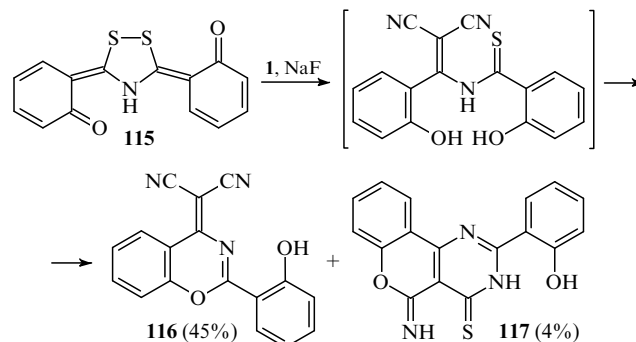


$\text{NR}_2 = \text{NEt}_2, \text{N} \begin{array}{c} \diagup \diagdown \\ \text{O} \end{array}$.

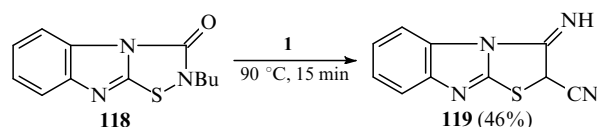
The reaction of 3,5-diphenyl-1,2,4-dithiazolium perchlorate **113** with malononitrile on refluxing in THF in the presence of sodium hydride is accompanied by recyclisation and gives 2,6-diphenyl-4-sulfanylpurine-5-carbonitrile **114** in 92% yield.⁸⁶



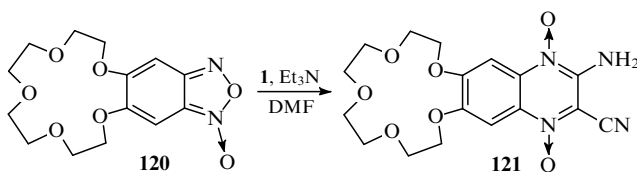
2-(2-Hydroxyphenyl)-4-dicyanomethylene-4*H*-1,3-benzoxazine **116** and 5-imino-2-(2-hydroxyphenyl)-1-benzopyrano-[4,3-*d*]pyrimidine-4-thione **117** have been synthesised by recyclisation of 1,2,4-dithiazolidine **115** involving malononitrile in the presence of NaF (refluxing for 2 min in a 1:1 DMSO:Pr₂O mixture).⁸⁷



On fusion with malononitrile (15 min, 90 °C), 2-butylbenzimidazo[1,2-*d*][1,4]thiadiazol-3(2*H*)-one **118** undergoes recyclisation with elimination of isocyanate to give 3-imino-2,3-dihydrobenzimidazo[2,1-*b*][1,3]thiazole-2-carbonitrile **119**.^{88,89}

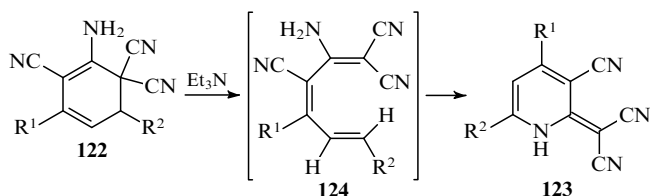


In a series of studies,^{90–93} it has been found that benzofuroxans recyclise on treatment with malononitrile giving rise to substituted 2-amino-3-cyanoquinoxaline *N,N*-dioxides. Recyclisation of benzofuroxan-15-crown-5 **120** during the reaction with malononitrile in DMF in the presence of triethylamine, resulting in the formation of 2-amino-3-cyanoquinoxaline *N,N*-dioxide **121**,⁹³ can be cited as an example.



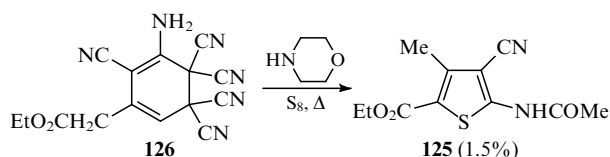
IV. Recyclisation of six-membered rings

For six-membered carbocycles containing a malononitrile fragment, base-induced recyclisation of 1-amino-1,3-cyclohexadiene-2,6,6-tricarbonitriles **122**, resulting from dimerisation of alkylidenemalononitriles, has been reported. This reaction yields 2-dicyanomethylene-1,2-dihydropyridine-3-carbonitriles **123** and involves intermediate formation of *cis(trans)*-2-amino-1,3,5-hexatriene-1,1,3-tricarbonitriles **124**.^{94–101}

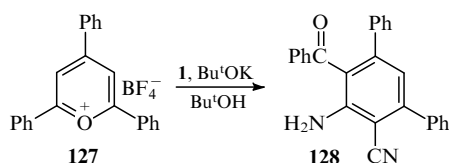


$\text{R}^1 = \text{Ph}, 4\text{-MeC}_6\text{H}_4$; $\text{R}^2 = \text{Ph}, 4\text{-FC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, \text{cyclo-C}_3\text{H}_5$.

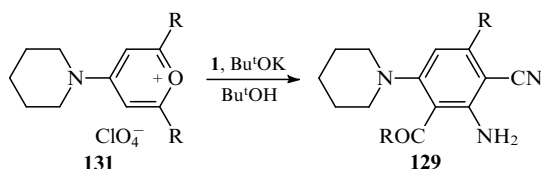
The formation of acetylaminothiophene **125** in a low yield in the recyclisation of hexa-1,3-diene **126** upon refluxing with morpholine polysulfide in ethanol for 4 h has been described.¹⁰²



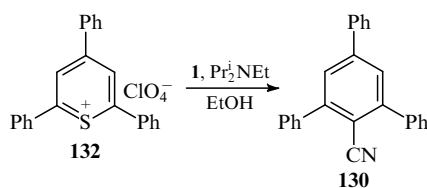
Recyclisation of six-membered heterocycles with participation of malononitrile possesses a substantially greater synthetic potential. First of all, mention should be made of recyclisation of heterocyclic compounds to carbocyclic compounds. For example, recyclisation of 2,4,6-triphenylpyrylium salt **127** during its reaction with malononitrile in *tert*-butyl alcohol in the presence of potassium *tert*-butoxide affords 2-amino-3-cyano-4,6-diphenylbenzophenone **128**, which is difficult to obtain by other methods, in a high yield.^{103–106}



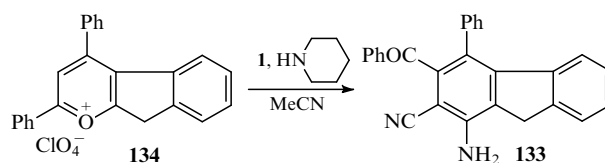
Later, this reaction was used to prepare 2-amino-3-cyano-4-methyl(or phenyl)-6-piperidylaceto(or benzo)phenones **129**¹⁰⁷ and 2,4,6-triphenylbenzonitrile **130**¹⁰⁸ from pyrylium salts **131** and 2,4,6-triphenylthiapyrylium perchlorate **132**.



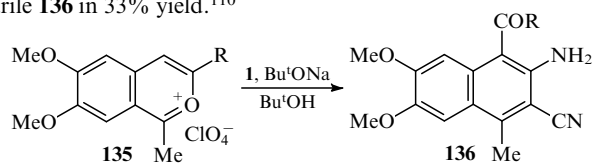
$\text{R} = \text{Me}, \text{Ph}$.



The synthesis of 4-amino-2-benzoyl-1-phenylfluorene-3-carbonitrile **133** in 89% yield by the reaction of 2,4-diphenyl-5*H*-indeno[2,1-*b*]pyrylium perchlorate **134** with malononitrile in acetonitrile in the presence of piperidine has been reported.¹⁰⁹

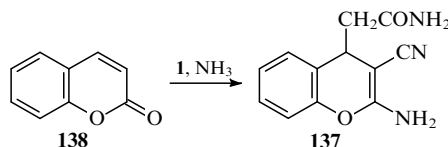


2-Benzopyrylium salt **135** undergoes similar recyclisation on treatment with malononitrile in the presence of sodium *tert*-butoxide in *tert*-butyl alcohol. This gives 2-amino-1-(3,4-dimethoxybenzoyl)-4-methyl-6,7-dimethoxynaphthalene-3-carbonitrile **136** in 33% yield.¹¹⁰

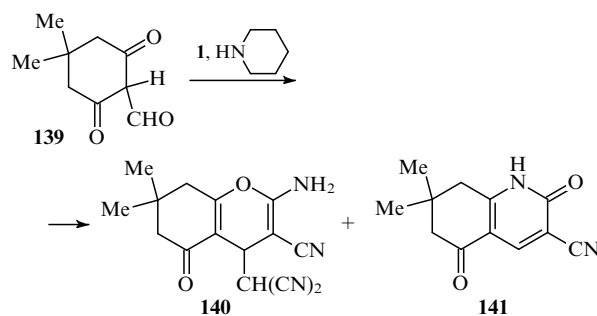


$\text{R} = 3,4\text{-(MeO)}_2\text{C}_6\text{H}_3$.

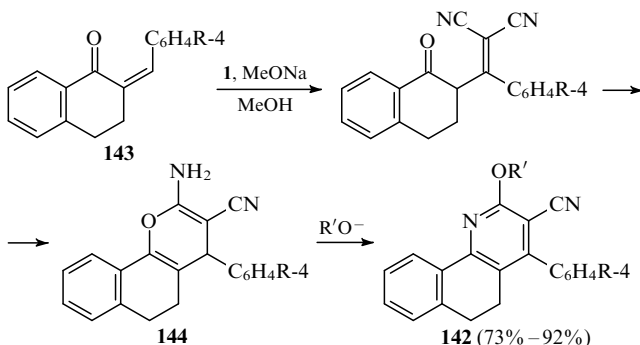
Of other examples of recyclisation of six-membered oxygen-containing heterocycles with malononitrile, the formation of (2-amino-3-cyano-4*H*-1-benzopyran-4-yl)acetamide **138** from coumarin **137** should be mentioned.¹¹¹



It has been reported¹¹² that 2-formyldimedone **139** reacts with malononitrile in the presence of piperidine in methanol or ethanol to give 2-amino-4-dicyanomethyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrobenzopyran-3-carbonitrile **140** in 78% yield and 3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-2(1*H*)-quinolone **141** in 20% yield.

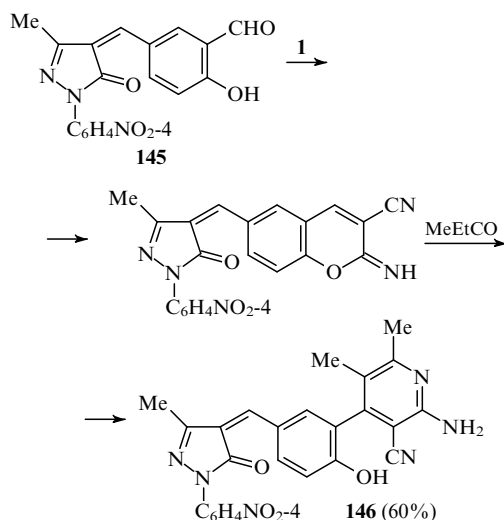


A new method for the synthesis of compounds of the benzo[*h*]quinoline series **142** has been proposed.¹¹³ The method is based on the Michael addition of malononitrile to 2-arylidene-1-tetralones **143** in the presence of sodium methoxide in methanol. The reaction mechanism was confirmed by isolation of the reaction intermediate, 4*H*-naphtho[1,2-*b*]pyran **144**.

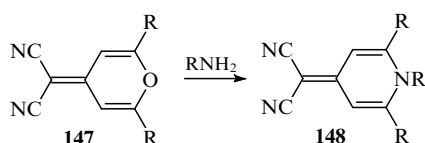


$\text{R} = \text{H}, \text{Me}, \text{Cl}, \text{OMe}, \text{NO}_2$; $\text{R}' = \text{Me}, \text{Et}$.

The condensation of pyrazolinone **145** with malononitrile in the presence of ammonium acetate and methyl ethyl ketone on refluxing in ethanol for 3 h gives rise to substituted nicotinonitrile **146**.^{114,115}

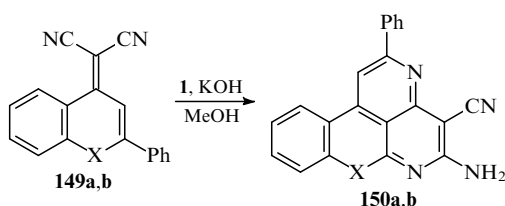


The reaction of 4*H*-pyrans **147**, incorporating a dicyanomethylene fragment, with amines is accompanied by recyclisation and results in the formation of 4-dicyanomethylene-1,4-dihydropyridines **148**.^{116–118}



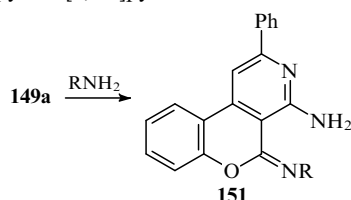
R = Alk, Ar.

However, the reactions of 4-dicyanomethylene-2-phenyl-4*H*-benzo[*b*]pyran **149a** and the corresponding thiopyran **149b** with malononitrile in methanol in the presence of KOH gives 5-amino-4-cyano-2-phenylbenzo[*b*]pyrano[4,3,2-*de*][1,6]naphthiridine **150a** or the corresponding thiopyranonaphthiridine **150b**.¹¹⁹



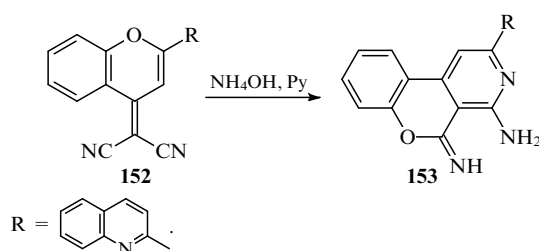
X = O (a), S (b).

The benzopyran **149a** reacts with primary amines under mild conditions giving rise to 4-amino-5-*R*-imino-2-phenyl-4*H*-[1]benzopyrano[3,4-*c*]pyridines **151**.¹²⁰

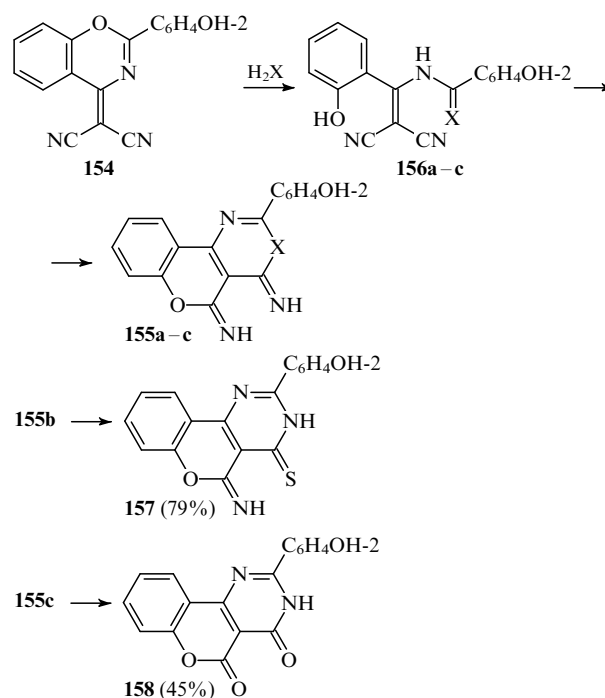


R = Ph, Bn, PhNH.

In order to synthesise analogues of the antitumour antibiotic streptonigrin, recyclisation of 4-dicyanomethylene-2-(2-quinolyl)-4*H*-[1]benzopyran **152** in pyridine in the presence of NH₄OH has been studied. This reaction gave 4-amino-5-imino-2-(2-quinolyl)-4*H*-[1]benzopyrano[3,4-*c*]pyridine **153** in 91% yield.¹²¹

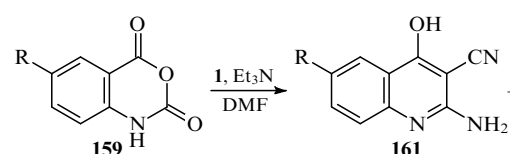


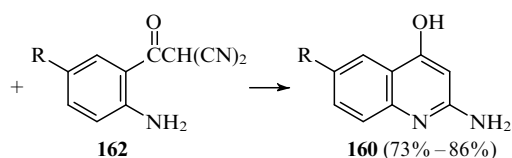
Recyclisation of 4-dicyanomethylene-2-(2-hydroxyphenyl)-4*H*-[1,3]benzoxazine **154** induced by various nucleophiles follows a similar pathway. Thus refluxing of the benzoxazine **154** in 2-methoxyethanol in the presence of ammonium acetate affords 2-(2-hydroxyphenyl)-4,5-diimino-3,4-dihydro-5*H*-[1]benzopyrano[4,3-*d*]pyrimidine **155a** in 91% yield.¹²² The thiazine **155b** was prepared by treatment of the benzoxazine **154** with hydrogen sulfide in the presence of triethylamine, and the 1,3-oxazine **155c** was synthesised by treatment of the compound **154** with hydrochloric acid in 2-methoxyethanol. It was noted that adducts **156a–c** are formed as intermediates in this reaction; in the case of the thiazine **155b** and oxazine **155c**, the Dimroth rearrangement occurs under the reaction conditions, yielding 2-(2-hydroxyphenyl)-5-imino-4-thio-3,4-dihydro-5*H*-[1]benzopyrano[4,3-*d*]pyrimidine **157** and 2-(2-hydroxyphenyl)-4,5-dioxo-3,4-dihydro-5*H*-[1]benzopyranopyrimidine **158**.¹²²



X = NH (a), S (b), O (c).

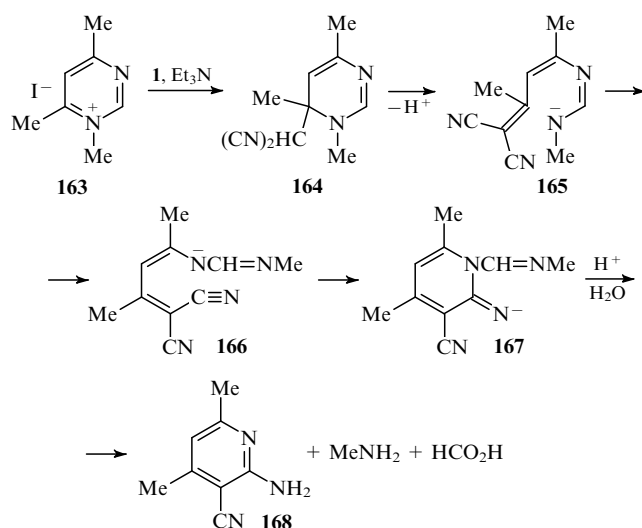
When isatic anhydride [2*H*-3,1-benzoxazine-2,4(1*H*)-dione] and its substituted derivatives **159** react with malononitrile in DMF in the presence of triethylamine and then the reaction mixture is hydrolysed with 48% HBr or 6*N* KOH, they are converted into 2-amino-4-hydroxyquinolines **160**.^{123,124} Compounds **161** and **162** were identified as reaction intermediates.



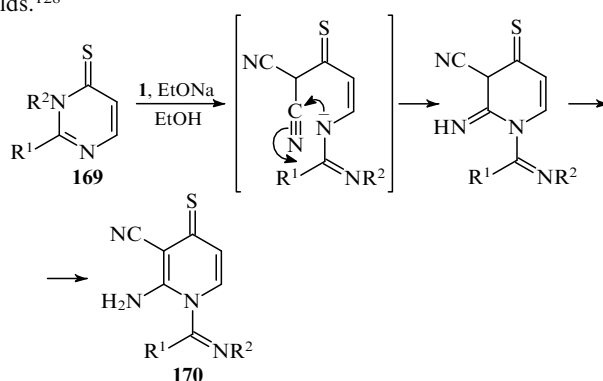


R = H, Cl, Me, OMe.

Recyclisation of pyrimidines involving malononitrile has been studied comprehensively.^{19, 125–136} For the reaction of 1,4,6-trimethylpyrimidin-2-yl iodide **163**, it was found that first the 4(6)-position of the pyrimidine nucleus in the compound **163** is attacked by the malononitrile anion, which gives adduct **164**. Then the pyrimidine ring in the compound **164** is cleaved at the N(3)–C(4) bond. Due to the presence of both nucleophilic [the N(1) atom] and electrophilic [the nitrile group carbon atom] reaction sites, the intermediates **165** and **166** thus formed cyclise to give pyridine **167**. The latter is stabilised by being converted into aminopyridine **168** upon abstraction of an aminomethylene fragment as methylamine and formic acid.¹²⁵

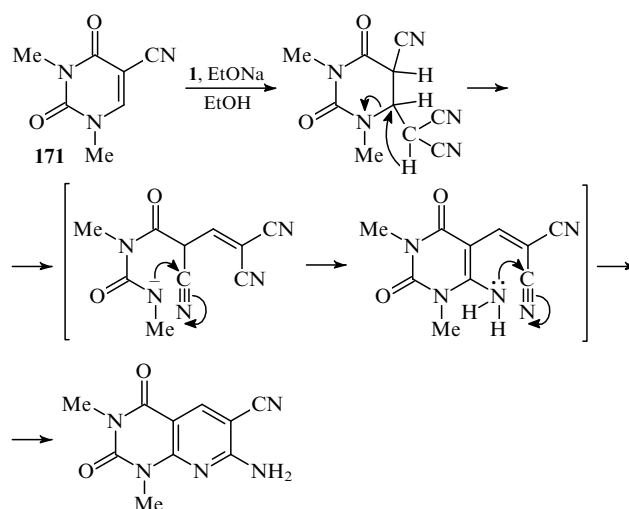


Recyclisation of 2,3-disubstituted 4(1*H*)-pyrimidinethiones **169** on treatment with malononitrile in ethanol in the presence of sodium ethoxide affords pyridinethiones **170** in 78%–93% yields.¹²⁸

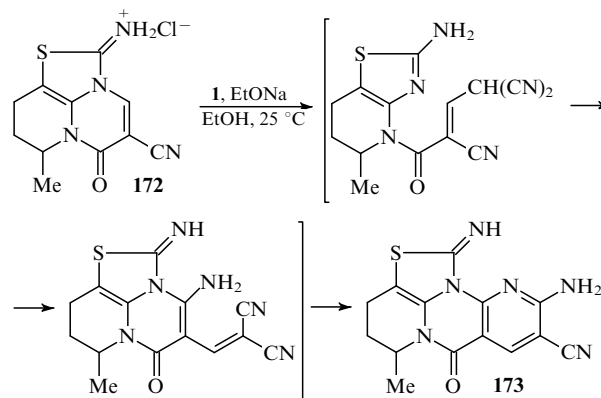


R¹ = Ph; R² = Ph, 3-MeC₆H₄, 4-MeC₆H₄; R¹ = R² = 4-MeC₆H₄.

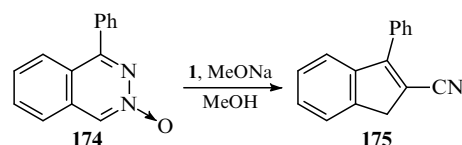
Recyclisation of 2(1*H*)-pyrimidinediones¹²⁹ and fused pyrimidines, such as quinazolines,¹³² 1*H*-pyrazolo[3,4-*d*]pyrimidines¹³¹ and their 3-oxides¹³⁰ occurs in a similar way. The scheme for the recyclisation of pyrimidinediones can be represented in relation to the interaction of 5-cyano-1,3-dimethyluracil **171** with malononitrile.^{134, 135}



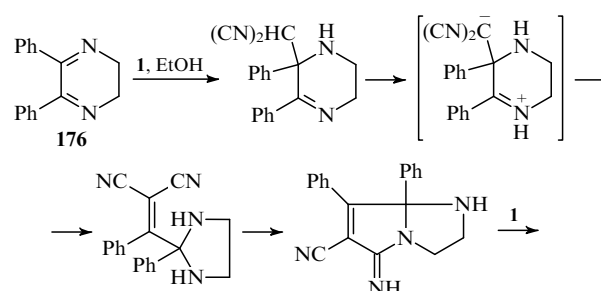
Recyclisation of 1-thia-2*a*,5*a*-diazacacenaphthene system **172** on treatment with malononitrile in ethanol in the presence of sodium ethoxide giving fused tetracyclic heterocyclic compound **173** in 88% yield has been described.¹³⁶

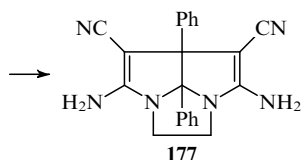


The recyclisation of 1-phenylphthalazine 3-oxide **174** during its reaction with malononitrile in methanol in the presence of sodium methoxide is accompanied by the loss of two nitrogen atoms and gives 3-phenylindene-2-carbonitrile **175**.¹³⁷

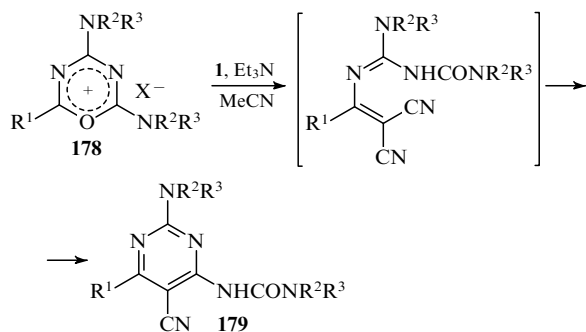


The recyclisation of 2,3-diphenyl-5,6-dihydropyrazine **176** occurring on refluxing with malononitrile in ethanol over a period of 1 h follows a peculiar pathway and affords 2,6-diamino-4,10-diphenyl-1,7-diazatricyclo[5.2.1.0^{4,10}]deca-2,5-diene-3,5-dicarbonitrile **177** in 70% yield.¹³⁸



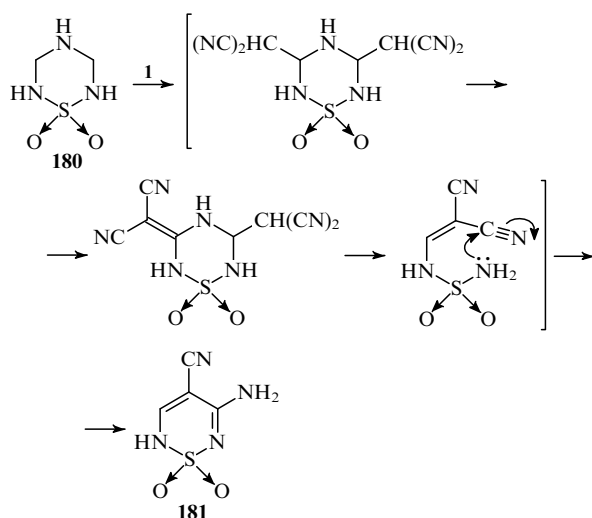


Recyclisation of 1,3,5-oxadiazinium salts **178** with participation of malononitrile carried out in acetonitrile in the presence of triethylamine has been reported. 2-Amino-6-aryl-4-carbamido-pyrimidines **179** were obtained in this way in 65%–83% yields.¹³⁹



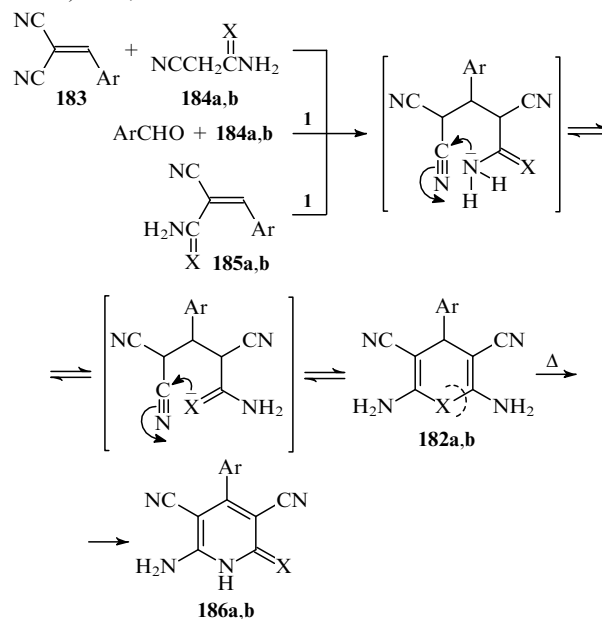
$R^1 = \text{Ph}; R^2 = \text{Me}, R^3 = \text{Me}; R^2, R^3 = (\text{CH}_2)_5, (\text{CH}_2)_2\text{O}(\text{CH}_2)_2.$

When reacting with malononitrile, 1,3,5-triazine undergoes recyclisation, similar to the transformation of pyrimidines into pyridines. This gives 4-aminopyrimidine-5-carbonitrile in 80% yield.^{140, 141} Recyclisation of 4*H*-1,2,4,6-thiatriazine 1,1-dioxide **180** yielding 3-amino-4-cyano-1,2,6-thiadiazine 1,1-dioxide **181** should be classified as the same type of reaction.¹⁴²



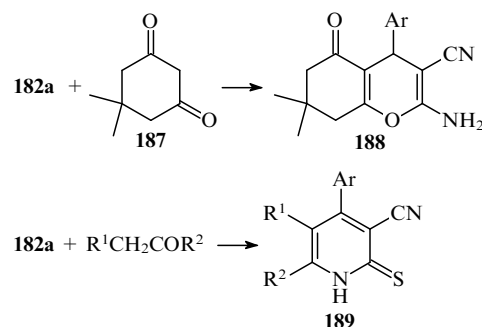
3-Cyanopyridin-2(1*H*)-ones, -thiones, -selenones and their derivatives represent an important class of heterocyclic compounds because of the diversity of their chemical transformations and the possible practical applications.^{36, 76, 143–154} These bifunctional compounds, which contain the nitrile and the oxo-hydroxy, thione–thiol or selenone–selenol functional groups in the vicinal positions, proved to be promising starting compounds in the preparation of annelated heterocyclic systems difficult to obtain by other methods.^{143, 144} The strategy of the synthesis of 3-cyano-2-pyridinones, -thiones and -selenones and their hydrogenated analogues is based, first of all, on cyclisation of functionally substituted carbonyl compounds or their derivatives with malononitrile or other derivatives of cyanoacetic acid.^{155–164} During these studies it was found that thio(seleno)pyrans **182a,b** are formed in the reactions of arylidenemalononitriles **183** with cyanothio(or seleno)acetamides **184a,b**, or in a one-step procedure involving aromatic aldehydes, malononitrile, and the amides **184a,b**, or in the reactions of arylidenecyanothio(or seleno)-

acetamides **185a,b** with malononitrile. The compounds **182a,b** readily recyclise to give the corresponding pyridinethiones (or selenones) **186a,b**.^{143, 144, 155, 157, 159, 161, 164–179}

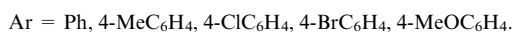


$X = \text{S (a)}, \text{Se (b)}.$

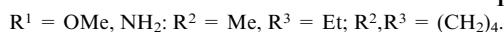
According to the results of physicochemical studies, including X-ray diffraction analysis, the thio(or seleno)pyran ring in the compounds **182a,b** occurs in the flattened boat conformation in which the aryl substituent at the 4-position is equatorial.^{159, 168, 180–183} The steric overcrowding of the thio(or seleno)pyran molecules **182a,b** with bulky electron-withdrawing substituents hampers the bond inversion in the ring and inversion of the substituents and thus makes impossible the conformational transitions in the heterocycle at higher temperatures. Therefore, on heating, ring cleavage at the weakest bond occurs (it is denoted by a dashed line in the scheme) and the compounds **182a,b** are then converted into pyridinethiones(or selenones) **186a,b**. In some studies,^{165, 184–186} faulty data on the structures of the thiopyrans **182a** and the pyridinethiones **186a** are presented. The structure of the thiopyrans **182a** ($\text{Ar} = 4\text{-ClC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4$) was attributed to the corresponding pyridinethiones **186a**.^{165, 168} The structures of 5-acetyl-2-amino-4-(4-methoxyphenyl)-6-methyl-4*H*-thiopyran-3-carbonitrile and 2,4-diamino-5-cyano-3-(2-furyl)-methylene-3,6-dihydropyridine-6-thione reported in the literature^{185, 186} are also erroneous. In addition, it has been found that the thiopyrans **182a** recyclise on treatment with dimedone **187** to give 2-amino-4*H*-pyran-3-carbonitriles **188**, whereas on treatment with ketones, **182a** are converted into pyridinethiones **189**.¹⁸⁷



An original pathway to substituted pyridinethiones **190** has been proposed.¹⁸⁸ The reaction of β -enaminothioamides **191** with malononitrile under kinetically controlled conditions gives substituted thiopyrans **192**; on heating with a base under thermodynamically controlled conditions, these products are converted into pyridinethiones **190**, their yields being more than 80%.


$$\begin{array}{c}
 \text{H}_2\text{N} \\
 | \\
 \text{NC} - \text{C}_6\text{H}_3\text{S} = \text{S} \\
 | \\
 \text{Cyclohexyl}
 \end{array}
 + \text{HN} \begin{array}{c} \diagup \diagdown \\ \diagdown \diagup \end{array} \text{X} \xrightarrow{-\text{H}_2\text{S}} \begin{array}{c} \text{S} \\ || \\ \text{NC} - \text{C}_6\text{H}_3\text{N} = \text{N} - \begin{array}{c} \diagup \diagdown \\ \diagdown \diagup \end{array} \text{X} \\
 | \\
 \text{Cyclohexyl}
 \end{array}
 \quad \text{193} \qquad \qquad \qquad \text{194}$$

The ylidene-derivatives of 6-amino-2*H*-thiopyran-5-carbonitrile **195**, prepared from thiopyrylium salts, are converted into 2,6-dicyano-3-sulfanylanilines **196**; this reaction is similar to the reactions of pyrylium salts with nucleophiles.¹⁸⁷



the pyridimethionones **200** and **201**.

Reaction of **199** with $R^1 = R^2 = \text{Me}$ in MeOH at 20–25 °C yields **200**, while reaction in DMF at 150–160 °C yields **201**.

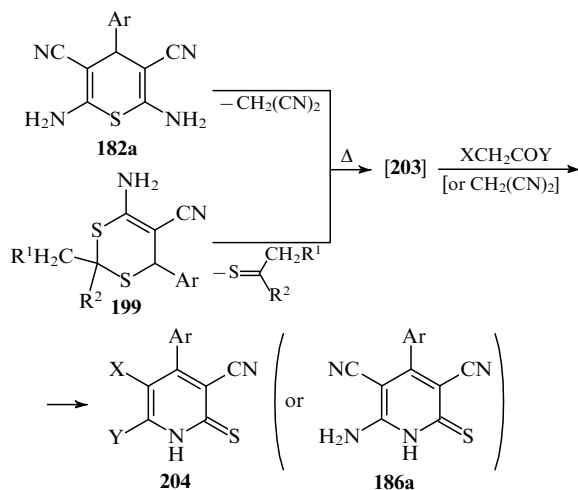
NC1=C(C#N)C(=S)SC1(C)C(R2)C(R1)C (**199**, $R^1 = R^2 = \text{Me}$)

 In MeOH, 20–25 °C → Cc1c(C)c(C#N)c(=S)n1C(=S)C2=CC=C(C)C=C2 (**200**)

 In DMF, 150–160 °C → CCc1c(C)cc(C#N)c(=S)n1C(=S)C2=CC=C(C)C=C2 (**201**) + **200**

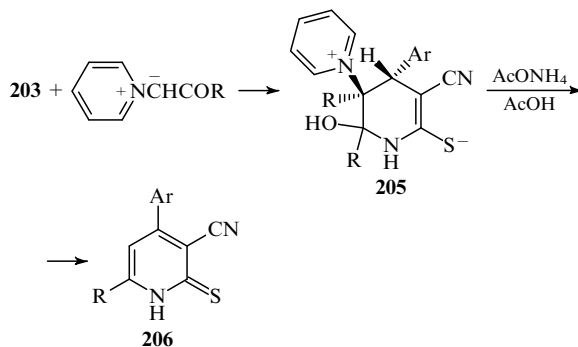
R^1H_2C(R^2)S(=O)(=O)c1c(N)cc(C#N)c(Ar)c1 (**199**) $\rightarrow$ R^1H_2C(R^2)S(=O)(=O)c1c(N)cc(C#N)c(Ar)c1 (**202**) + NC(=O)C(R^2)=C(Ar) (**203**) $\rightarrow$ $\left[\text{Intermediate} \right] \xrightarrow{-H_2S}$ R^1C1=C(C#N)C(=S)N(C1)C2=CC(=CC=C2)Ar (**189**)

The mechanism of recyclisation of 4*H*-thiopyrans and 1,3-dithiacyclohex-4-enes **199** was confirmed by studying their cross-recyclisation with various CH acids, α -methylene ketones, 1,3-dicarbonyl compounds and their enamines, ethyl cyanoacetate and malononitrile.^{25, 143, 144, 181–183} Under thermodynamically controlled conditions, cycloelimination of heterocyclic compounds **182** and **199** occurs, yielding arylidenecyanothioacetamides **203** and either malononitrile or thioketones, respectively. The subsequent competing transformations of the amides **203** involving malononitrile or carbonyl compounds give rise to substituted pyridinethiones **204** or **186a**.



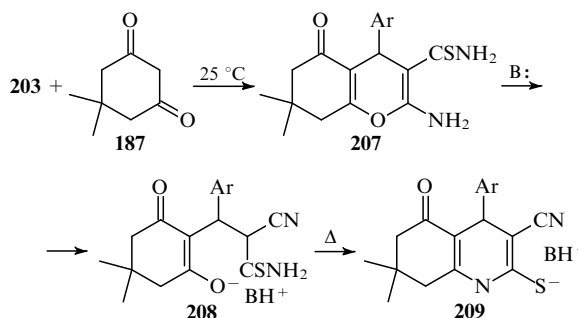
X = Alk, OAlk; Y = Alk.

To elucidate the mechanism and stereochemistry of transformations of the heterocyclic compounds **182a** and **199**, their reactions with pyridinium ylides have been studied.^{144, 156, 181, 182} It was found that in this case, too, arylidenecyanothioacetamides **203** are formed as intermediates; they react stereoselectively with pyridinium ylides to give 3,4-*trans*-1,2,3,4-tetrahydropyridine-2-thiolates **205**. The latter are converted into pyridinethiones **206** on heating with ammonium acetate in acetic acid.



The results obtained demonstrated that the stereochemistry and the electronic structures of heterocyclic compounds **182a** and **199** have similar features, namely, (1) both molecules contain a planar enamionitrile fragment with a well-developed system of p,π-conjugation; (2) they are partially hydrogenated; (3) they contain a nonplanar ring sterically overcrowded with alkyl and aryl substituents; (4) they contain one or several electron-withdrawing groups as substituents. Due to these features, when the enthalpy increases, the compounds **182a** and **199** cannot decrease their energy upon conformational transitions; instead, they undergo cycloelimination involving the weakest bonds.

The reactions of arylidenecyanothioacetamides **203** with dimedone afford substituted pyrans **207**, which recyclise in the presence of bases to give intermediates **208** and then quinoline-thiolates **209**.^{203–206}



V. Conclusion

The data on recyclisation of carbo- and heterocyclic compounds with participation of malononitrile and its derivatives considered here clearly demonstrate the high synthetic potential of these reactions and good prospects for using them in the syntheses of various compounds, including products that are difficult to obtain by other methods, which possess a broad spectrum of useful properties.

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^f — *Russ. Chem. Bull. (Engl. Transl.)*

Reductive amination of oxygen-containing organic compounds

V A Tarasevich, N G Kozlov

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Abstract. The data dealing with reductive amination of oxygen-containing organic compounds of different classes are systematised. New data on the amination agents and the catalysts used are presented. The dependence of the reactivity of reagents on their structures is considered. The bibliography includes 249 references.

I. Introduction

Reductive amination or hydroamination is widely used for the synthesis of amines. This method is based on the reaction between oxygen- and nitrogen-containing compounds on the surface of a catalyst under a hydrogen atmosphere or in solution in the presence of hydrogen donors.

In the literature, this reaction is often referred to as 'reductive alkylation', which does not reflect exactly its chemical essence.

It has been shown in numerous studies that during the reaction with oxygen-containing compounds in the presence of hydrogen donors, some nitrogen-containing compounds, namely, nitro and nitroso compounds, nitriles and oximes, are first reduced to amines, and then the latter react with oxygen-containing compounds. Thus, this reaction occurs successfully when an amino group is present; therefore, it is more correct to call this reaction 'reductive amination' or 'hydroamination' rather than 'reductive alkylation'.

This review deals with reductive amination reactions involving hydrogen or hydrogen donors; the reaction conditions and the catalysts used are discussed.

II. Reductive amination of carbonyl compounds with ammonia and amines

The ability of ammonia and amines to form imines with aldehydes and ketones and the fact that imines can be reduced relatively easily to the corresponding amines permitted the synthesis of amines by direct amination of carbonyl-containing compounds

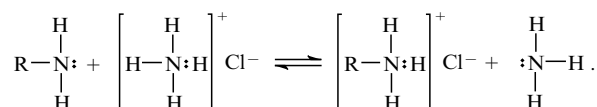
with ammonia or amines. Hydrogen (in the presence of a catalyst) or formic acid and its derivatives are used most often as the reducing agents in this process. This reaction is widely employed to prepare amines from various aldehydes and ketones.

Mignonac^{1,2} was the first to carry out the reductive amination of aldehydes and ketones with ammonia. Mixtures of the corresponding primary, secondary and tertiary amines were obtained from aliphatic aldehydes and ammonia in the presence of nickel catalysts.

In the first stage of the reaction, ammonia adds to the carbonyl compound (Scheme 1, pathway *a*); this is followed by the reduction of either the product of nucleophilic addition itself, α -amino alcohol **1** (pathway *d*), or the product of its dehydration, imine **2** (pathways *b* and *c*).³ In some cases, the imines formed in the condensation of carbonyl compounds with ammonia can be isolated, whereas the α -amino alcohol **1** could not be isolated.⁴

As the primary amine is accumulated in the reaction mixture, it enters into reaction with the initial carbonyl compound similarly to ammonia (Scheme 1, pathway *e*). The imine **3**, which is formed upon dehydration of the condensation product, is converted into secondary amine (pathways *f* and *g*). In addition, primary amine can react with the imine **2** to give addition product **4**, the reduction of which also gives a secondary amine (pathways *h–j*). Secondary amines also can enter into this type of reactions (pathways *k–n*); this gives tertiary amines. Thus, the process occurs as a set of consecutive and parallel reactions yielding a mixture of primary, secondary and tertiary amines.

To suppress the formation of secondary and tertiary amines, the reductive amination of carbonyl compounds is carried out in the presence of ammonium salts.⁵ Under these conditions, only primary amines are formed. Apparently, an excess of ammonium salts shifts equilibrium towards primary amines; in addition, the formation of secondary amines is suppressed because primary amines lose their nucleophilic properties upon transformation into alkylammonium ions



For example, the introduction of ammonium chloride into the reaction mixture during hydroamination of 1-(2,5-dimethoxyphenyl)propan-2-one **5** with ammonia in methanol in the presence of Raney nickel permitted the synthesis of 2-amino-1-(2,5-dimethoxyphenyl)propane **6** in 95% yield.⁶

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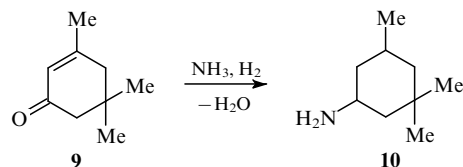
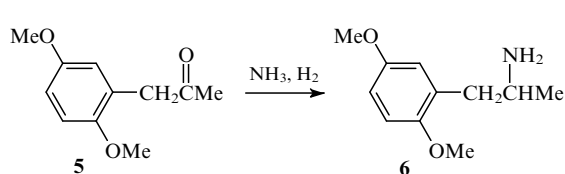
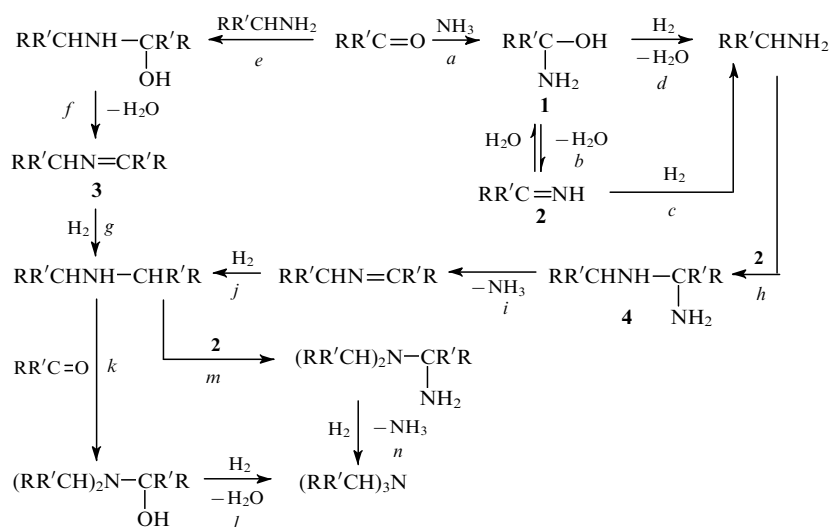
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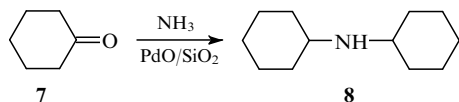
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Scheme 1



Most often, hydroamination of carbonyl-containing compounds with ammonia is carried out in the presence of nickel catalysts.^{7–9} When metallic rhenium and rhodium supported on alumina are used as the catalysts, the total yield of primary and secondary amines reaches 93%–95%.¹⁰ In order to direct the process at the formation of secondary amines, catalysts are often modified by various oxides. Thus the reaction of cyclohexanone **7** with ammonia catalysed by the 0.35% PdO/SiO₂ catalyst modified by Ag, Mn, K, Na and Al oxides gives dicyclohexylamine **8** in 97% yield.¹¹

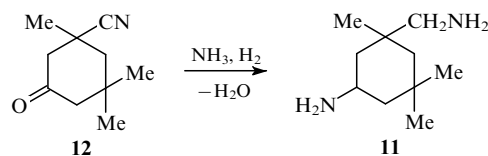


Synthesis of 2,2-disubstituted 1,5-diaminopentane derivatives by the reaction of the corresponding aldehydes containing a terminal nitrile group with excess ammonia over acid catalysts has been reported.^{12,13} The imino nitrile formed in the first stage is hydrogenated over catalysts based on Co, Ni, Ru and other noble metals at 60–150 °C and 5–15 MPa. The yields of diamines amount to 50%–72%.

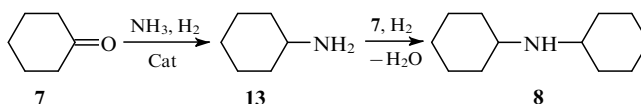
The use of reduced promoted fused iron catalysts (RPFIC) in various reactions, most of all, in reductive amination of carbonyl-containing compounds, has been described in a review.¹⁴ Among other reactions, the reductive amination of octan-2-one with ammonia has been studied in detail.^{15–18} The kinetic isotope effect observed after replacement of H₂ by D₂ made it possible to propose a stepwise mechanism of reductive amination of carbonyl compounds, the addition of hydrogen to ketimine being the rate-determining step.

Hydroamination of 3,5,5-trimethylcyclohex-2-enone (isophorone, **9**) with ammonia in the presence of a copper–zinc–aluminium catalyst (SNM-1) and RPFIC at 160–230 °C has been reported.^{19,20} The yield of 3,3,5-trimethylcyclohexylamine **10** reaches 90%–95%.

3-Aminomethyl-3,5,5-trimethylcyclohexylamine **11** is prepared by reductive amination of 1,3,3-trimethyl-5-oxocyclohexanecarbonitrile **12** with simultaneous reduction of the cyano group at 50–150 °C on Raney nickel or cobalt using anhydrous Ni, Co, Y, and La halides as co-catalysts. The yield of the amine **11** was 83%.²¹

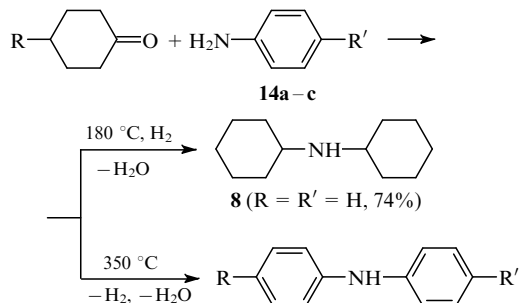


Transformation of aldehydes and ammonia into secondary amines was attained²² by using a three-component catalyst based on Cu, a metal of the series Cr, Mn, Fe and Zn and a platinum group metal (Pt, Pd, Ru, Rh). The predominant formation of either primary or secondary amines from ketones and ammonia can depend significantly on the procedure used to prepare the catalysts and on the catalyst composition, all other factors being the same. Study of hydroamination of cyclohexanone **7** with ammonia in the presence of various catalysts has demonstrated²³ that in the presence of a nickel catalyst, the primary amine, cyclohexylamine **13**, is formed predominantly, whereas the use of colloidal platinum results in the secondary amine **8** being formed as the major product.



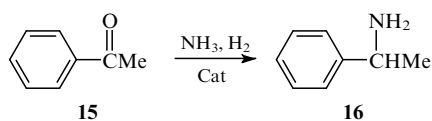
However, later,²⁴ it was found that in the presence of platinumated silica gel, the ketone **7** is readily converted into the primary amine **13** rather than into the secondary amine **8**, as noted in the study²³ cited above. Thus, depending on the method for the preparation of the platinum catalyst, either secondary or primary amines can be synthesised. Hydroamination of alicyclic ketones with aromatic amines in the presence of catalysts containing Ru, Rh, Pd or Ni supported on γ -Al₂O₃ yields, depending on the temperature conditions, either cycloaliphatic or aromatic sec-

dary amines. For example, at 180 °C and $p_{H_2} = 5$ MPa,²⁵ dicyclohexylamine was obtained from cyclohexanone **7** and aniline **14a** over a nickel catalyst, whereas the reaction between the same compounds or their *para*-substituted derivatives at temperatures of dehydration of alicyclic compounds (above 300 °C) gives²⁶ only the corresponding diarylamines.

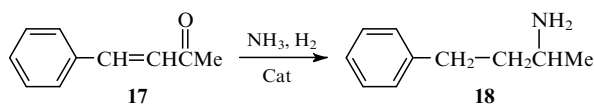


R, R' = H (**a**), Hal (**b**), Alk (**c**).

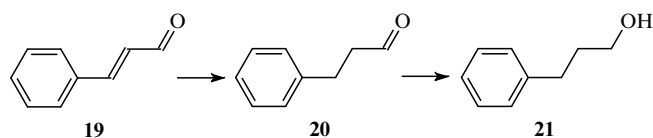
The reductive amination of arylaliphatic aldehydes and ketones with ammonia results in the formation of primary aliphatic-aromatic amines.^{9,27,28} The reaction is complicated by the reduction of the corresponding carbonyl compounds to hydrocarbons. The yield of the amination products is influenced by the location of the carbonyl group with respect to the aromatic ring of the initial aldehyde or ketone. The yields of amines produced from aromatic aldehydes or alkyl aryl ketones are much lower than the yields of amines formed upon hydroamination of ketones in which the carbonyl group is removed from the aromatic nucleus. Thus over a nickel catalyst at 150 °C and 8 MPa, acetophenone is converted into 1-phenylethylamine **16** in 50% yield.²⁸



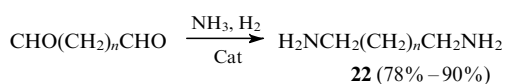
Under the same conditions, benzylideneacetone **17** gives 2-amino-4-phenylbutane in 84% yield.²⁹



In this case, it should be borne in mind that the reaction starts with hydrogenation of the alkene double bond. This eliminates the conjugation between the carbonyl group and the aromatic nucleus. Thus it has been shown³⁰ that hydrogenation of 3-phenylacrolein **19** at 80 °C and $p_{H_2} = 2$ MPa gives initially aldehyde **20** and then alcohol **21**.

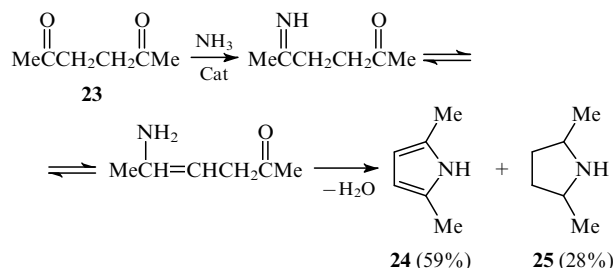


A method has been proposed^{31,32} for the synthesis of diamines **22** from aliphatic dialdehydes containing four to ten carbon atoms; according to this method, they are treated with excess ammonia and hydrogen in the presence of Ni, Co, Pd or Ru catalysts at 40–150 °C and a pressure of 10 MPa.

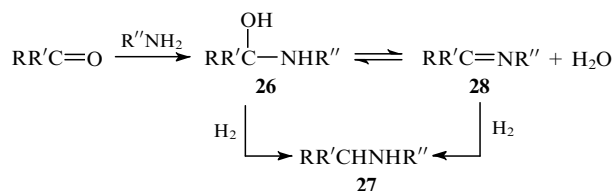


In order to prevent the formation of secondary amines and possible intramolecular cyclisation giving a heterocyclic deriva-

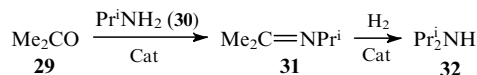
tive, excess ammonia is used (the ammonia : aldehyde molar ratio is 5 : 1). Conversely, an excess of the initial dicarbonyl compound is favourable for the formation of heterocyclic systems. Thus the reaction of acetonylacetone **23** with ammonia [the diketone : ammonia molar ratio is (2–3) : 1] in the presence of Raney nickel at $p_{H_2} = 15$ MPa resulted in the synthesis of a mixture of 2,5-dimethylpyrrole **24** and 2,5-dimethylpyrrolidine **25**, *i.e.* amination and cyclisation were accompanied by hydrogenation of the pyrrole ring.³³ Esters of 4-oxo acids behave in a similar way.



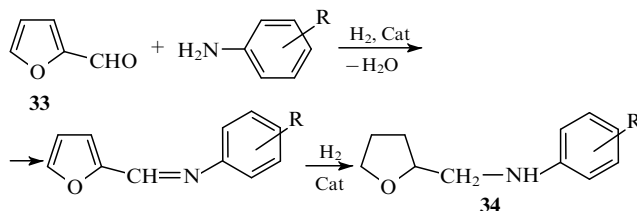
Hydroamination with primary amines, like hydroamination with ammonia, involves evidently the intermediate formation of addition product **26**, which is either hydrogenated to amine **27** or is converted initially into imine **28** and then into the amine.³⁴



A kinetic study of the catalytic reductive amination of acetone **29** with isopropylamine **30** in aqueous alcohol over a platinum catalyst at 29 °C has demonstrated³⁵ that the reaction consists of two steps: the formation of imine **31** and its subsequent hydrogenation, giving rise to diisopropylamine **32**.

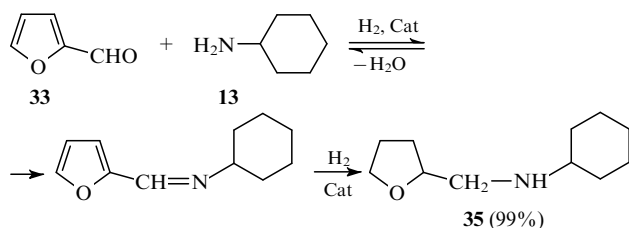


This pathway to secondary amines, which includes the formation of imines, has also been confirmed in studies dealing with hydroamination of furfural **33** with aromatic amines. It was shown that the reaction over palladium catalysts includes the initial formation of the corresponding imines, which are then hydrogenated, in particular, in the furan ring.^{36–38} The yields of substituted *N*-(2-tetrahydrofurylmethyl)anilines **34** vary from 10% (for *o*-bromoaniline) to 85% (for aniline). When palladium immobilised in the polymeric matrix of the AB-17-8 or AN-1 anion exchanger is used, the yield of *N*-(2-tetrahydrofurylmethyl)aniline reaches 100%.



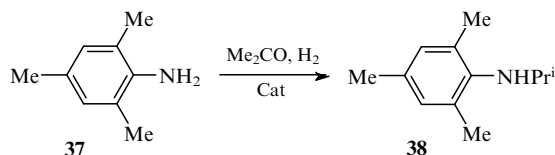
R = H, *m*-Me, *p*-Me, *o*-Me, *m*-Hal, *p*-Hal, *o*-Hal.

The reductive amination of furfural **33** with cyclohexylamine over the same catalysts at 20–60 °C and $p_{H_2} = 0.98-1.03$ MPa in a solvent (an alcohol or a hydrocarbon) affords *N*-(2-tetrahydrofurylmethyl)cyclohexylamine **35** in a high yield.



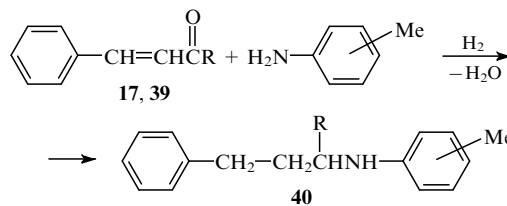
Palladium catalysts immobilised in an anion-exchanger polymeric matrix are inferior to Pd/C regarding the rate of formation of the amine **35** but are superior regarding the selectivity and the service stability. The rate of reductive amination of the aldehyde **33** was found³⁹ to be directly proportional to the dielectric constant of the solvent.

N,N-Diethylaminophenols are prepared⁴⁰ in high yields by reductive amination of acetaldehyde with *o*-, *m*- and *p*-aminophenols at 150 °C and $p_{H_2} = 2$ MPa in the presence of Pt, Pd or Ni catalysts in the medium of an aliphatic alcohol (MeOH, EtOH, Pr^nOH). For example, in the case of *m*-aminophenol, the yield of *N,N*-diethyl-*m*-aminophenol was 98.4%. In a study of reductive amination of aliphatic ketones with primary amines, it has been found^{41–43} that the product yield is substantially influenced by steric factors caused by the structures of both the ketone and the initial amine. Steric restrictions were considered⁴⁴ to be the only reason for the fact that the yields of amines upon the hydroamination of ketones with cyclohexylamine **13** decrease in the sequence acetone > methyl ethyl ketone > diethyl ketone. When ethanolamine is used instead of cyclohexylamine, steric hindrance markedly diminishes, and the yields of hydroamination products obtained from acetone and diethyl ketone **36** become almost identical. Study of the influence of steric factors on the reductive amination of acetone with aniline and 2,4,6-trimethylaniline **37**⁴⁵ has shown that the sterically hindered amine **37** is converted into secondary amine, *N*-isopropyl-2,4,6-trimethylaniline **38**, in 36% yield (when aniline is used, the yield of the corresponding secondary amine increases to 98%).



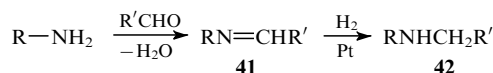
The yield of the product of reductive amination of benzylideneacetone **17** and benzylideneacetophenone **39** with toluidines⁴⁶

varies as a function of the position of the methyl substituent in the aromatic amine. The yields of secondary amines **40** in the hydroamination of the ketone **17** were 14.0, 35.0 and 52.4% for *o*-, *m*- and *p*-toluidine, respectively. Meanwhile, it was found that the yields of secondary amines formed from aliphatic amines increase with an increase in the basicity of the amine used.



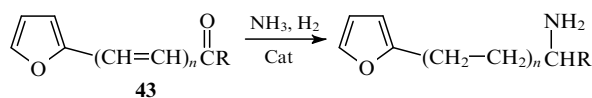
$R = Me$ (**17**), Ph (**39**).

Secondary amines of the aliphatic series have been prepared in two stages from primary amines and aldehydes.⁴⁷ In the first stage, imines were synthesised; after isolation, they were hydrogenated over a platinum catalyst in anhydrous EtOH. The total yields of the imines **41** and the amines **42** were 40%–63%.⁴⁸



$R = R' = Et, Pr^n, Pr^i, Bu^n, Bu^i$.

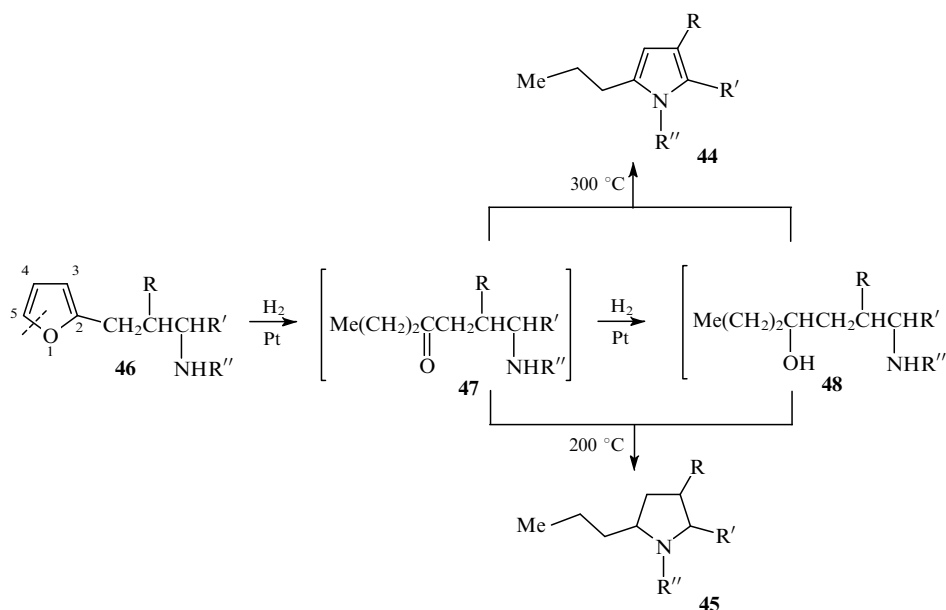
Reductive amination of carbonyl compounds of the furan series has been studied only occasionally. Reductive amination of unsaturated ketones **43** with ammonia has been reported.^{49–51} The reaction was carried out in methanol saturated with ammonia over skeletal nickel–aluminium catalyst and under a hydrogen pressure of 12–14 MPa.⁵²



$n = 1, 2$; $R = Alk$.

The synthesis of pyrrole (**44**) and pyrrolidine (**45**) homologues from furan derivatives **46**, containing an amino group in the alkyl substituent, over platinum catalysts should be regarded as a peculiar intramolecular reductive amination reaction (Scheme 2). The reaction consists of two stages: hydrogenolysis of the furan ring at the O(1)–C(5) bond to give amino ketones **47** and amino alcohols **48** and their intramolecular hydroamination leading to the formation of a heterocycle.^{53–55} Selective hydrogenolysis at the O(1)–C(5) bond is possible only with platinum catalysts

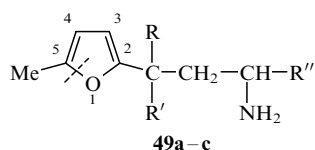
Scheme 2



$R = R' = H, Me, Et$; $R'' = H, Me$.

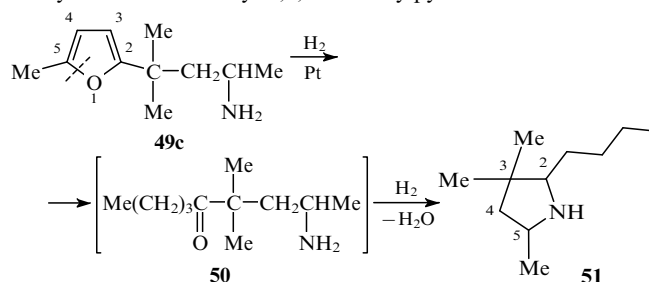
(Pt/C, Pt/asbestos); in this case, the mixture of reaction products contains pyrrolidines and pyrroles with a propyl radical at the 5-position. Pyrrolidine homologues are formed at 200–220 °C, their yields being 85%–90%, whereas pyrrole homologues are produced at 300 °C in ~85% yield. The yields of *N*-methyl-substituted pyrrolidines and pyrroles are somewhat lower (70% and 73%–75%). High-boiling nitrogen-containing compounds (2%–3%) and the recovered amine (~23%) were also detected in the product mixture.⁵⁵

The structure of the pyrrolidines and pyrroles formed is determined by the structure of the aminoalkyl side chain.^{54,55} The influence of the structure of alkyl and aminoalkyl groups in the molecules of the furan derivatives **49** on the course of hydrogenolysis and the formation of pyrrole and pyrrolidine trialkyl derivatives was studied.⁵⁵



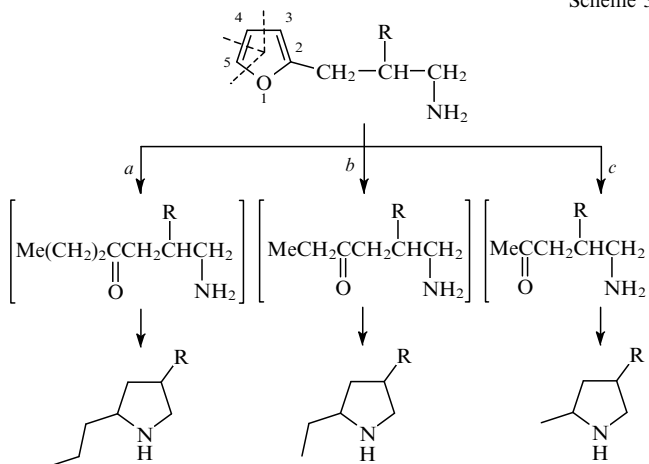
$R = R' = R'' = H$ (a); $R = Me, R' = R'' = H$ (b); $R = R' = R'' = Me$ (c).

When the substituents R and R' at the carbon atom attached directly to the furan ring in **49** are methyl groups, hydrogenolysis of the furan ring is more selective, due to the shielding effect, and involves the $O(1)–C(5)$ bond. In addition, in the presence of these substituents, the formation of the pyrrole ring is impossible. As a result, catalytic hydrogenation of 2-(3-amino-1,1-dimethylbutyl)-5-methylfuran **49c** over platinum catalysts at 250 °C resulted in the synthesis of 2-*n*-butyl-3,3,5-trimethylpyrrolidine **51**.⁵⁶



Whereas the reaction on platinum catalysts gives only one series of pyrrolidine homologues owing to the selective rupture of the $C(5)–O(1)$ bond at 200–220 °C, in the presence of skeletal nickel–aluminium catalysts, three series of pyrrolidine homologues containing methyl, ethyl or *n*-propyl groups at the 2-position can be obtained (Scheme 3).⁵⁷

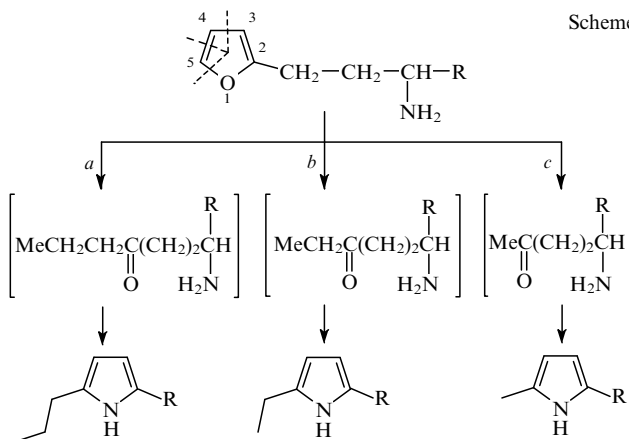
Scheme 3



(a) rupture of the $O(1)–C(5)$ bond; (b) rupture of the $O(1)–C(5)$ and $C(4)–C(5)$ bonds; (c) rupture of the $O(1)–C(5)$ and $C(3)–C(4)$ bonds.

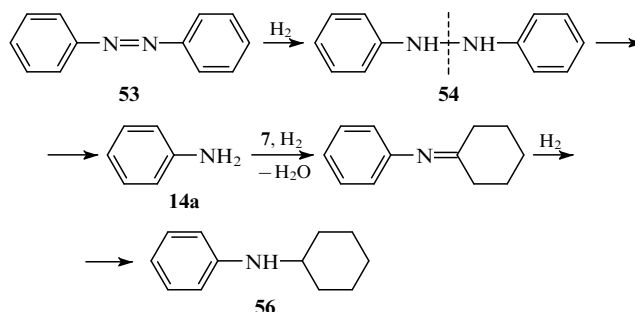
The yield of pyrrolidines in the hydrogenolysis products was, on the average, 70%–75% based on the consumed amine. The pyrrolidines formed contained 35% of 2-methyl-4-*R*-pyrrolidines, 20% of 2-ethyl-4-*R*-pyrrolidines and 45% of 2-*n*-propyl-4-*R*-pyrrolidines. The formation of a particular pyrrolidine homologue depends substantially on the reaction temperature. For example, when the temperature is raised to 270 °C, the proportion of 2-methyl-4-*R*-pyrrolidines increases to approximately 50%–60%; however, the overall content of pyrrolidines in the reaction products diminishes to 30%–40%. The synthesis of pyrrole homologues over skeletal nickel–aluminium catalyst is carried out at 300 °C;⁵⁸ in this case, the mixture of pyrroles contains 30% of 2-methyl-5-*R*-pyrroles, 25% of 2-ethyl-5-*R*-pyrroles and 45% of 2-*n*-propyl-5-*R*-pyrroles (Scheme 4).

Scheme 4



(a) rupture of the $O(1)–C(5)$ bonds; (b) rupture of the $O(1)–C(5)$ and $C(4)–C(5)$ bonds; (c) rupture of the $O(1)–C(5)$ and $C(3)–C(4)$ bonds.

Hydroamination of cyclohexanone **7** and cyclopentanone **52** was performed⁵⁹ using azobenzene **53**, 1,2-diphenylhydrazine **54** and cyclohexanone phenylhydrazone **55**. It is known that hydrazines are able to undergo hydrogenolysis over nickel–alumina or copper–alumina catalysts at 250 °C to give primary amines.⁶⁰ It was found that in all cases, hydrogenolysis of the $N–N$ bond and the formation of secondary cycloalkylamines (in 18% to 75% yields) is a typical reaction pathway. Since the $N=N$ bond in azobenzene **53** is relatively stable, it can undergo hydrogenolysis only after saturation; therefore, the use of the hydrazine **54** results in higher yields of the reductive amination products; for example, the yields of *N*-cyclohexylaniline **56** obtained upon hydroamination of cyclohexanone with azobenzene and 1,2-diphenylhydrazine are 45% and 75%, respectively.

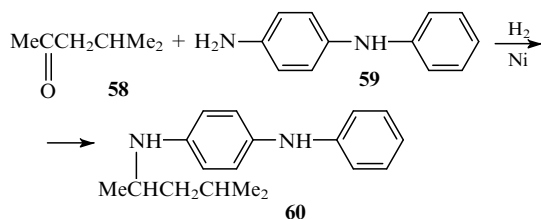


Several studies,^{14,61–70} 'generically' related to hydroamination, deserve special attention. They describe the synthesis of various amines in the presence of RPFIC in the Fischer–Tropsch synthesis. These catalysts are used to prepare various hydrocarbons and oxygen-containing organic compounds from CO and H_2 .^{71,72} The use of the modified Fischer–Tropsch reaction for the synthesis of oxygen-containing compounds and their reductive amination with ammonia, alkylamines and piperidine **57** have led to the development of a number of one-step proce-

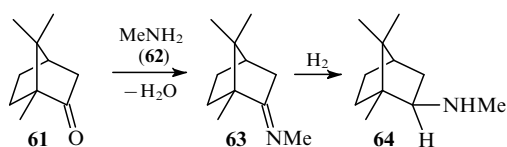
dures for the synthesis of various amines. Thus hydrogenation of CO at 169–195 °C, 10–12 MPa and at an H₂:CO ratio of (2–6):1 in the presence of HNMe₂ (1 vol. %–10 vol. %) over RPFIC gives rise to dimethylalkylamines.⁷⁰ The yield of liquid amines reaches 73%. The use of piperidine and RPFIC in the modified Fischer–Tropsch synthesis permitted the preparation of *N*-alkylpiperidines with alkyl substituents consisting of one to fifteen C atoms at the nitrogen atom (the selectivity of the reaction with respect to amines reaches 97%).^{64–69} The highest activity was found for RPFIC containing V₂O₅, Al₂O₃ or Cr₂O₃ and CuO.⁶⁸ Two pathways to *N*-alkyldimethylamines are possible: (1) hydroamination of a surface oxygen-containing intermediate, precursor of an aldehyde, ketone or alcohol; (2) direct hydroamination of alkanals or alkyl methyl ketones, primary components of the Fischer–Tropsch synthesis.

Synthesis of alkylamines from CO, H₂ and N₂ in the presence of RPFIC has been carried out. The process included two alternating reactions performed in one catalytic area: first NH₃ was obtained from H₂ and N₂ and then it was used to aminate the oxygen-containing or olefinic products of the Fischer–Tropsch synthesis, formed after the introduction of CO. Primary terminal C₄–C₉ amines were the major reaction products.^{73,74}

Reductive amination of aldehydes and ketones is usually carried out at high (up to 50 MPa) pressures of hydrogen.⁷⁵ Various solvents have been used in this process, MeOH, EtOH, PrⁱOH, BuⁱOH, THF and cyclohexanol.^{76–78} Nickel or cobalt catalysts^{34,77,79–81} and platinum group metals (Pt, Pd) supported on activated carbon^{79,82–85} are used most often. Some metals (Ni, Pt, Ru, Rh) supported on an active material, for example, on alumina or kieselguhr, are also employed.^{77,86–88} Catalysts based on copper and chromium oxide mixtures have been patented.⁸⁹ Rhenium and palladium sulfides (Re₂S₇, PdS) as well as Fe, Co, Ni, W and Mo sulfides supported on alumina proved to be highly active catalysts of reductive amination.^{90,91} In some studies, catalysts modified with sulfur or other organic or inorganic sulfur-containing compounds have been considered. Thus reductive amination of 4-methylpentan-2-one **58** with *N*-phenyl-1,4-phenylenediamine **59** over nickel supported on kieselguhr (63% Ni) at 165 °C and a hydrogen pressure of 5.2–7.0 MPa gave *N*-phenyl-*N'*-(1,3-dimethylbutyl)-1,4-phenylenediamine **60** in 58% yield. The addition of Bu₂S increased the yield of the diamine **60** to 97%.⁸⁸

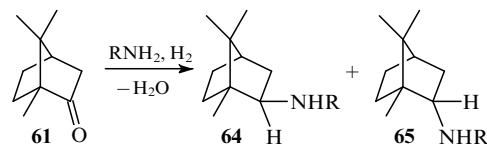


Sulfoxides, thiols and sulfur-containing heterocycles have also been used to modify the catalysts.⁹² The influence of the nature of the catalyst on the yield of the final product can be followed in relation to the reductive amination of camphor **61** with methylamine **62**. Thus when Raney nickel is used as the catalyst, *N*-methylbornan-2-imine **63** (yield 82.8%) is formed predominantly, whereas the reaction over 5% Pd/C yields a mixture of the imine **63** and *N*-methylbornan-2-ylamine **64** (30.4% and 65.7%, respectively).



If platinum oxide is used as the catalyst, the yield of the amine **64** reaches 92.7%.⁸² High stereoselectivity of RPFIC, unusual for metallic heterogeneous catalysts, has been noted.^{93–95} Thus the

degree of transformation of *d,l*-camphor into *endo*- (**65**) and *exo*-bornan-2-ylamines (**64**) during hydroamination reaches 92%, the *endo* to *exo* ratio being (1.4–1.8):1. Apparently, this stereoselectivity is due to the 'imine–enamine' tautomerisation occurring on the acid–base sites of the catalyst.



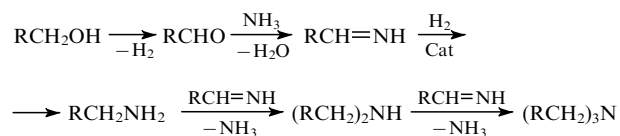
R = H, Alk.

Highly effective and selective catalysts for hydroamination of aldehydes and ketones with ammonia, amines and nitro compounds have been developed. These catalysts, which make it possible to conduct this reaction under mild conditions (20–60 °C, and *p*_{H₂} = 0.1 MPa), are Pd, Pt, Rh, Co, Fe, Ni and Cu complexes with dimethyl- and dibenzylglyoximes and with polymeric macroligands such as polyacrylic acid, polyethyleneimine, copolymers, anion exchangers, cation exchangers, *etc.*^{96–106} The rate of hydroamination in the presence of these catalysts depends appreciably on the nature of the polymeric matrix. The major contribution to the activity is made by the rigidity of those sections of the macromolecule which bear the active metal sites. The activity and selectivity of these catalysts can be controlled by changing the 'local rigidity'; this can be attained by increasing the temperature, by using a different solvent or exchangeable ion, by varying the particle size of the support, by irradiating the polymeric matrix or by introducing microadditives of another solvent.^{99,106}

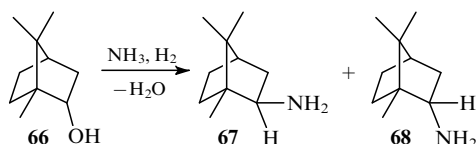
III. Reductive amination of alcohols with ammonia and amines

The reaction of ammonia with alcohols results in the formation of mixtures of primary, secondary and tertiary amines. In the vast majority of cases, alcohols react with ammonia or amines only in the presence of catalysts. Heterogeneous acidic catalysts have found wide application in industry. In the presence of these catalysts, the process is carried out in the gas phase at 350–450 °C. Their influence consists in the activation of the C–OH bond due to adsorption of the alcohol on the catalyst acid sites.

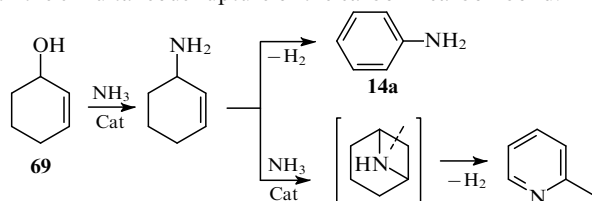
The reactions between ammonia and alcohols are carried out using dehydrating catalysts (copper, nickel and cobalt on alumina, fused iron, copper chromites)^{107–111} and hydrogen. In this case, the reaction follows a mechanism other than the acid–base one. First, the alcohol is dehydrogenated to give aldehyde, and then the aldehyde condenses with ammonia, and the imine thus formed undergoes hydrogenation coupled with dehydration.



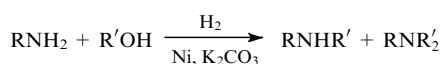
The mechanism of dehydration of alcohols followed by amination has been comprehensively studied by Bashkirov *et al.*^{112–117} Secondary and tertiary amines are formed upon the reactions of primary and secondary amines with aldimines. RPFIC modified with various oxides have been successfully used in reactions with amines. For example, hydroamination of a number of alcohols (2-ethylhexan-1-ol, octan-1-ol, octan-2-ol, heptan-4-ol) with dimethylamine at 210–240 °C gave the corresponding *N,N*-dimethylalkylamines in ~80% yields. The highest yield of tertiary amine was observed in the presence of RPFIC promoted by 10% Al₂O₃ + 1% CuO.¹¹⁸ The same catalyst was used in the reductive amination of borneols **66** with ammonia, which afforded bornylamines **67** and **68**, mostly as *endo*-isomers.¹¹⁹



Copper-containing catalysts exhibit high activity in the amination of various alcohols with ammonia and amines. When bifunctional catalysts, $\text{Cu}/\text{Al}_2\text{O}_3$ or $\text{Ni}/\text{Al}_2\text{O}_3$, were used in hydroamination of alicyclic alcohols, the yields of primary amines reached 80%. To suppress cyclisation and isomerisation, lithium and potassium hydroxides were introduced into the alumina.¹²⁰ Hydroamination of cyclohex-2-enol **69** in the presence of $\text{Cu}/\text{Al}_2\text{O}_3$, $\text{Ni}/\text{Al}_2\text{O}_3$ and $\text{Pt}/\text{Al}_2\text{O}_3$ has been studied.¹²¹ In the case of the copper catalysts, cyclohexylamine is mostly formed (yield 65%), whereas the reaction carried out at 310 °C over active dehydrating Pt and Ni catalysts containing 10%, 15% and 20% of the metal gives aniline. In the presence of copper and nickel catalysts at 310 °C, pyridine bases are formed, mostly 2-methylpyridine (60%–62% of the total amount of pyridine bases). Presumably, in the latter case, the reaction passes through the formation of an unstable bicyclic compound resulting from insertion of the nitrogen atom of the amino group into the ring with the simultaneous rupture of the carbon–carbon bond.



When alkanols are hydroaminated with dimethylamine, 2-ethylhexylamine and cyclohexylamine over the industrial copper–zinc–aluminium oxide-type catalyst (SNM-1) and over RPFIC,^{122–125} the highest yields of non-symmetrical secondary and tertiary amines (up to 90%) are attained at 175–195 °C and at an amine:alcohol molar ratio of 0.2. Secondary amines containing an alkyl radical ($\text{C}_{10}\text{--C}_{22}$) are prepared by hydroamination of alcohols with primary amines at $p_{\text{H}_2} = 0.3\text{--}0.5$ MPa in the presence of the Ni or Ni–Cu catalyst containing some K_2CO_3 ; the yields of non-symmetrical secondary alkylamines can be as high as 85%.



$\text{R} = \text{C}_{10}\text{H}_{21}\text{--C}_{22}\text{H}_{45}$, $\text{R}' = \text{CH}_3\text{--C}_8\text{H}_{17}$.

When K_2CO_3 is not added, the content of secondary amine in the amination products is 17%, and the content of tertiary amine is 45%.¹²⁶

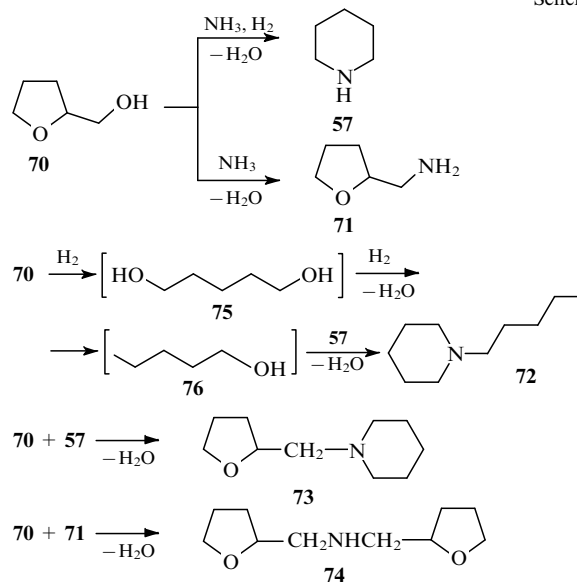
To increase the yield of amines, nickel catalysts are modified with various additives. Thus the activity of nickel oxides prepared by various methods and their mechanical mixtures with titanium dioxide, quartz and Aerosil has been studied in the vapour-phase amination of n-butanol in the presence of hydrogen under atmospheric pressure.¹²⁷ Synergism of nickel–titanium and nickel–silicon binary oxide catalysts in this reaction was found. It is noteworthy that in some cases, in order to attain higher yields of amines, two-stage synthetic procedures are used, which include a separate stage of dehydration of alcohols to aldehydes.¹¹¹

Non-symmetrical dialkylamines are prepared in 75%–90% yields¹¹² by the reaction of a primary amine with an alcohol in the presence of a catalyst containing copper chromite at 180–210 °C and $p_{\text{H}_2} = 4.0\text{--}12.0$ MPa. When copper catalysts are used, the reaction between ethanol and ammonia at $p_{\text{H}_2} = 15.0$ MPa affords triethylamine (yield 90%).¹²⁸

Unlike hydroamination of primary and secondary aliphatic alcohols with ammonia, which mainly yields primary amines, hydroamination of tetrahydrofurfuryl alcohol **70** gives rise to a

heterocyclic compound, piperidine **57**. This reaction, which is of interest from the practical viewpoint, has been studied in detail.^{129–135} Scheme 5 shows the possible pathways to the main products (**57**, **71–74**) formed from the alcohol **70**, ammonia and hydrogen. It was found that, irrespective of the catalyst used, the reaction products contain piperidine, tetrahydrofurfurylamine **71**, *N*-(n-pentyl)piperidine **72**, *N*-(tetrahydrofurfuryl)piperidine **73** and bis(tetrahydrofurfuryl)amine **74**.

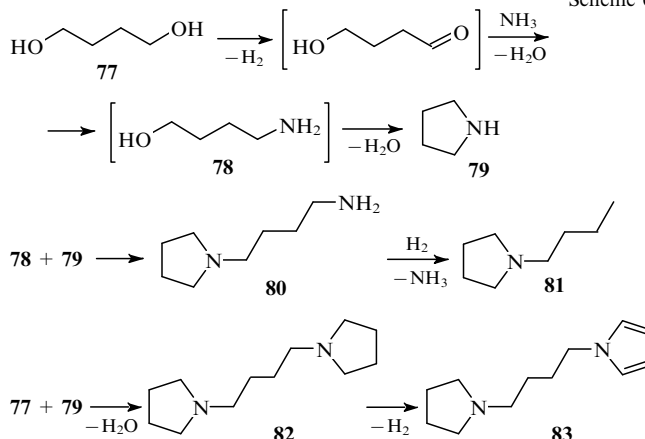
Scheme 5



When this reaction is carried out in the presence of the SNM-1 catalyst, the yield of the amine **71** reaches 62% at a virtually complete conversion of tetrahydrofurfuryl alcohol. When Co- and Ni-based catalysts are used, the formation of piperidine is the predominant reaction route (its yield reaches 51%). The compounds **73** and **74** result from intermolecular amination of the alcohol **70** with piperidine and with the amine **71**, respectively. The presence of *N*-(n-pentyl)piperidine **72** among the reaction products was explained¹³⁵ by hydrogenolysis of the alcohol **70** at the intracyclic C–O bond with the intermediate formation of pentane-1,5-diol **75**, its partial hydrodeoxygenation to n-pentan-1-ol **76** and subsequent interaction of the alcohol **76** with piperidine.

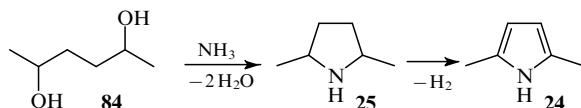
Nitrogen-containing five-, six- and seven-membered heterocyclic compounds have been prepared by hydroamination of the corresponding diols with ammonia over the industrial SNM-1 catalysts and RPFIC.^{136–139} The formation of the heterocycle in the reaction of butane-1,4-diol **77** with a mixture of NH_3 and H_2 (Scheme 6) occurs in two stages. First, the initial diol **77** is aminated to give 4-aminobutan-1-ol **78**, and then this product undergoes intramolecular amination (cyclisation) to give pyrrolidine **79**.

Scheme 6

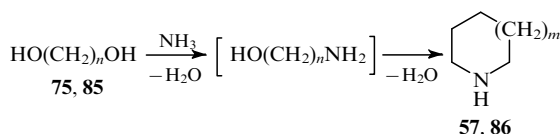


The yield of the compound **79** on the SNM-1 catalyst at 220 °C reaches 85.5%.¹³⁹ The appearance of *N*-4-aminobutylpyrrolidine **80** in the product mixture can be interpreted as being due to the reaction between 4-aminobutan-1-ol **78** and pyrrolidine. Partial hydrodeazotisation of the compound **80** affords *N*-(*n*-butyl)pyrrolidine **81**. 1,4-Dipyrrolidinobutane **82** is formed upon exhaustive amination of butanediol with pyrrolidine. The highest yield of the compound **82** (22.5%) was attained with RPFIC. Dehydrogenation of one heterocycle in the molecule of **82** gives rise to *N*-(4-pyrrolidinobutyl)pyrrole **83**.

The reaction of hexane-2,5-diol **84** with a mixture of NH₃ and H₂ is highly selective. The yield of 2,5-dimethylpyrrolidine **25** over RPFIC at 200 °C amounts to 93%.¹³⁹ The subsequent dehydrogenation of pyrrolidine **25** yields 2,5-dimethylpyrrole **24**.

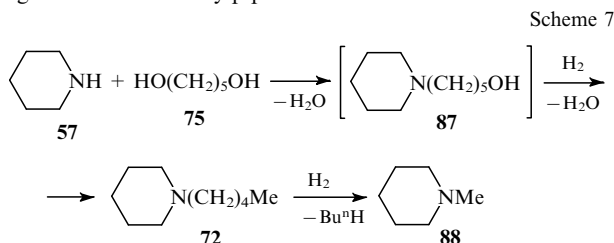


Hydroamination of pentane-1,5-diol **75** and hexane-1,6-diol **85** with ammonia follows a similar route, resulting in the formation of piperidine **57** and perhydroazepine **86**, respectively.



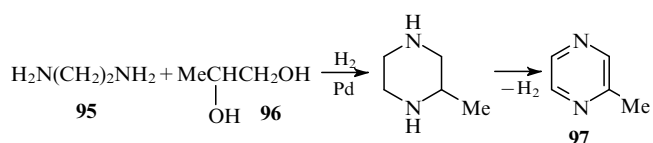
$n = 5$ (**75**), 6 (**85**); $m = 1$ (**57**), 2 (**86**).

The main pathways of the catalytic transformations of the diol **75** during its interaction with NH₃ and H₂ can be illustrated by Scheme 7. The presence of *N*-(*n*-pentyl)piperidine **72** in the reaction products is due to the alkylation of piperidine **57** with the diol **75** involving the intermediate formation of *N*-(5-hydroxypentyl)piperidine **87** and its subsequent hydrodeoxygenation. Hydrogenolysis of the C–C bond in the alkyl substituent of the compound **72** accompanied by elimination of an *n*-butane molecule gives rise to *N*-methylpiperidine **88**.

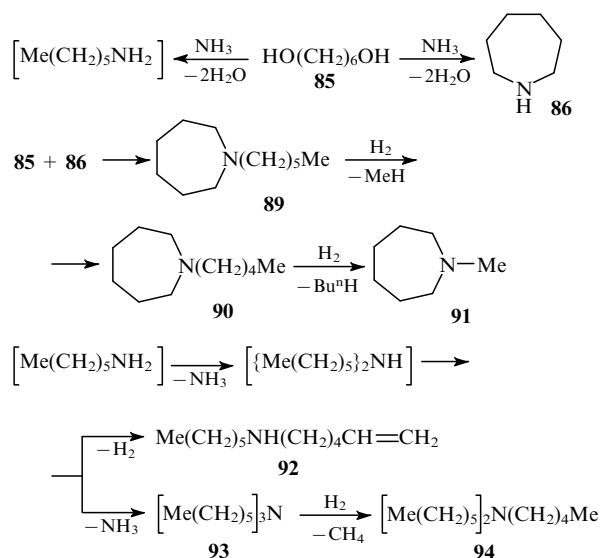


A typical feature of the transformation of the diol **85**¹³⁹ (Scheme 8) is relatively high yields of *N*-alkyl-substituted perhydroazepines **89**–**91** and secondary and tertiary alkylamines **92**–**94**. For example, when the diol **85** is hydroaminated over the SNM-1 catalyst at 180°C, the total contents of perhydroazepines **89** and **91** in the reaction products reaches 22%.

Piperazine and 1-alkyl- and 1,4-dialkyl-piperazines have been synthesised by hydroamination of diethanolamine or *N*-alkyldiethanolamines in the presence of RPFIC.¹⁴⁰ Cyclisation of ethylenediamine **95** with propane-1,2-diol **96** giving 2-methylpyrazine **97** over a catalyst containing 1% of Pd supported on a mixture of zinc and chromium oxides (Zn : Cr = 3 : 1) has been studied.¹⁴¹ The highest selectivity of this process is observed at 38°C.

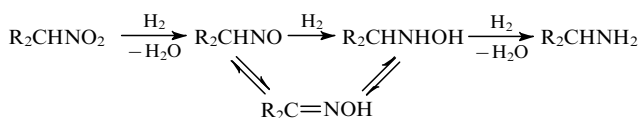


Scheme 8



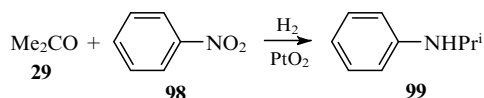
IV. Reductive amination of aldehydes and ketones with nitro compounds and pyridine bases

Reduction of nitro compounds, which is carried out in a variety of ways (catalytic hydrogenation; reduction with iron in the presence of hydrochloric acid, with metal sulfides, zinc or iron in a strongly alkaline medium, lithium aluminium hydride and hydrazine; and electrochemical reduction) is among the methods used most widely for the synthesis of amines. These reactions occur *via* several intermediate stages; for most of the reducing agents listed above, they include the formation of nitroso compounds and hydroxylamines.



Catalytic hydrogenation has found wide application in industry. Most often, it is used to convert aromatic nitro compounds into the corresponding amines.^{142, 143}

The ability of nitro compounds to be reduced to amines under the conditions of reductive amination has permitted the use of this ample class of nitrogen-containing organic compounds for direct amination of aldehydes and ketones. This reaction was first performed by Emerson.¹⁴⁴ A mixture of acetone **29** and nitrobenzene **98** was reduced by hydrogen in an autoclave over platinum oxide; the yield of *N*-isopropylaniline **99** reached 59%.^{144–147}



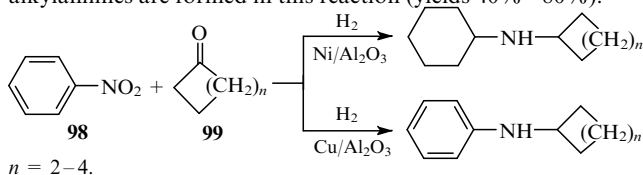
Subsequently this reaction has been widely used to synthesise secondary amines. Hydroamination by nitro compounds is normally carried out in autoclaves over platinum catalysts under a pressure of hydrogen.^{86, 148} Thus reductive amination of acetone by 4-nitrodiphenylamine at 120 °C and $p_{H_2} = 2.0$ – 2.5 MPa on the Pt/C catalyst gave *N*-phenyl-*N'*-isopropyl-*p*-phenylenediamine in 95% yield.¹⁴⁹ To increase the yield of secondary amines the catalysts are modified by various additives. For example, the reaction catalysed by platinum supported on carbon containing phosphorous acid gives amines in preparative yields.⁷⁸ Other acids or acidic compounds — H₃BO₃, organic acids or anhydrides, CO₂

— are also used as modifying agents. Acidic additives form salts with primary amines and thus prevent side reactions.

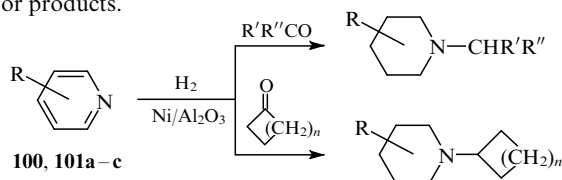
Apart from platinum, nickel catalysts are also widely used in this reaction. The use of a catalyst containing 63% of Ni supported on kieselguhr permits preparation of secondary amines from nitro compounds and ketones in yields of up to 57%. Modification of this catalyst by sulfur-containing compounds (sulfides, disulfides, sulfoxides, thiols) made it possible to increase the yields of amines to 75%.⁸⁷ Hydroamination carried out with aromatic nitro compounds is accompanied in some cases by hydrogenation of the aromatic ring.^{150,151} To prevent this process, mixtures of ketones with aromatic nitro compounds are reduced over various catalysts containing Pt, Pd, Ni, Rh, Os, Sr or Co on silica or alumina in the presence of SO₂.¹⁵⁰ The same can be attained by using metal sulfides. Amines can be obtained in preparative yields by conducting the reaction at 250 °C at a pressure of hydrogen of up to 10.0 MPa in the presence of cobalt, nickel or molybdenum selenide or telluride as the catalyst.¹⁵²

Palladium-containing anion exchangers are efficient catalysts of hydroamination of aldehydes and ketones by nitro compounds (mostly, aromatic ones).^{99,106} A study of the influence of the substrate structure on the rates of hydroamination of oxygen-containing compounds by nitro compounds of the aromatic series has shown that the reaction rate decreases following an increase in the magnitude of the Hammett constant.¹⁵³

Several studies^{151, 154–156} have been devoted to hydroamination of alicyclic and heterocyclic ketones by nitro compounds of aliphatic and aromatic series over nickel- and copper–alumina catalysts. It was found¹⁵¹ that hydroamination of alicyclic ketones **99** with nitrobenzene at 250 °C and at $p_{H_2} = 2.0$ MPa over nickel catalysts gives rise to *N*-cycloalkylcyclohexylamines in yields of up to 82%. In the presence of copper catalysts, *N*-cycloalkylanilines are formed in this reaction (yields 40%–80%).



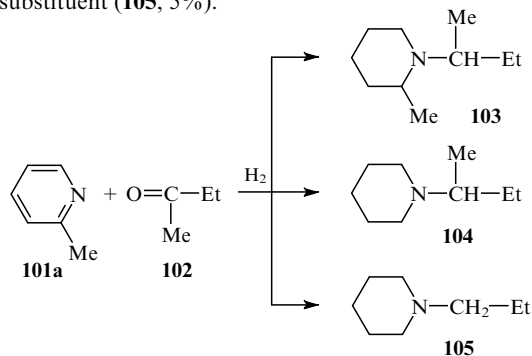
The capability of pyridine and its alkyl-substituted derivatives to be reduced to piperidines permits the use of these nitrogen-containing heterocycles in the reductive amination of ketones. Thus reductive amination of aliphatic and alicyclic ketones with pyridine and its monomethyl derivatives over nickel catalysts under a pressure of hydrogen has been studied.^{157, 158} The reactions of pyridine **100** and α -, β - and γ -picolines **101a–c** with ketones afford the corresponding *N*-substituted piperidines as the major products.



R = H (**100**), 2-Me (**101a**), 3-Me (**101b**), 4-Me (**101c**);
R' = Me, Et, Bu^t; R'' = Me, Et; $n = 2, 3$.

It was assumed^{157, 158} that this reaction can follow two pathways. One of them includes simultaneous reduction of the ketone to the corresponding secondary alcohol and hydrogenation of pyridine **100** to piperidine **57**. The subsequent interaction of the alcohol with piperidine accompanied by dehydration affords *N*-substituted piperidine derivatives. In the second pathway, pyridine is reduced to piperidine and the latter reacts directly with the ketone, without its intermediate transformation into the alcohol. This pathway, like the first one, affords *N*-substituted piperidine as the final product.

The use of α -picoline as the aminating agent demonstrated that the methyl group located in the vicinity of nitrogen has a substantial influence on the reaction route. For example, hydroamination of methyl ethyl ketone **102** with this compound, in addition to the expected product **103** (yield 4%), gave the products resulting from elimination of the methyl group from the pyridine ring (**104**, 9%) and elimination of the methyl group from the *N*-substituent (**105**, 5%).



The course of hydroamination of aliphatic ketones with pyridine bases depends substantially on the ketone structure. Thus the highest yield of the final reaction products is achieved when pyridine is made to react with alkyl methyl ketones; for example, the yield of *N*-butan-2-ylpiperidine in the reaction with methyl ethyl ketone amounts to 50%. When pyridine reacts with diethyl ketone **36** and propyl ethyl ketone **106**, the yields of the target reaction products sharply decrease (32%, for the ketone **36**) due to the substantial steric hindrance created by the two alkyl radicals attached to the carbonyl group. *tert*-Butyl methyl ketone does not enter into hydroamination at all.¹⁵⁸ The optimum conditions for the synthesis of *N*-alkylpiperidines are the following: temperature 220–230 °C, $p_{H_2} = 2.0$ MPa; $v = 0.3$ h^{−1}, catalyst — 20% Ni/Al₂O₃.¹⁵⁸

V. Reductive amination of aldehydes, ketones and alcohols with nitriles and oximes

1. Nitriles and oximes as aminating agents

Owing to the progress in the chemistry of nitrogen-containing organic compounds achieved in recent years, nitriles can be considered to be readily available starting compounds for the synthesis of diverse and valuable organic products.

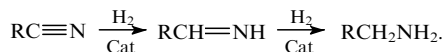
Methods of catalytic ammonolysis occupy a special place in the synthesis of nitriles. They include, first of all, oxidative ammonolysis of saturated and unsaturated hydrocarbons, methylbenzenes, naphthalene and pyridine. Linear hydrocarbons, for example, butane and butenes, can be converted by ammonolysis into saturated and unsaturated mono- and dinitriles.^{159–167} Thus oxidative ammonolysis of butadiene gives rise to a mixture of nitriles of fumaric and maleic acids (total yield 67%).¹⁶⁸ Oxidative ammonolysis of toluene, xylenes, mesitylene or dimethylnaphthalenes can be used to synthesise nitriles of the corresponding mono-, di-, and tri-carboxylic acids, their yields being 70%–95%.^{169, 170} Halotoluenes, toluidines and cresols can also be introduced into ammonolysis; this gives rise to the corresponding benzonitrile. Methylpyridines are converted into the nitriles of pyridinecarboxylic acids in 70%–95% yields.^{171–175}

At present, ammonolysis is employed in industry to produce acrylonitrile, benzonitrile and nitriles of methacrylic, terephthalic, and nicotinic acids. These processes have been patented and considered in several reviews (see, for example, Refs 176–179).

Thus, the development of this line of research has extended substantially the range of raw materials used for the production of diverse amines.

Hydrogenation of carbonitriles has been studied in detail, because the products of their reduction are important for practical purposes. Nitriles are converted into primary amines upon the

addition of two hydrogen molecules. However, the first molecule is added faster than the second one. Therefore, the reduction intermediately gives aldimines, which are converted into primary amines during subsequent hydrogenation. In some cases aldimines can be isolated in a pure state. The general pattern of hydrogenation of nitriles can be written as follows:



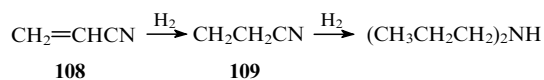
Aldimines are highly reactive and are able to react with the resulting primary amines; this gives rise to secondary and tertiary amines. Therefore, hydrogenation of nitriles can yield different products, depending on the reaction conditions.¹⁸⁰

Catalytic reduction of nitriles with molecular hydrogen is the most interesting process. A fairly broad range of catalysts have found practical application in the nitrile hydrogenation — monometallic (Pt, Pd, Ni, Co, *etc.*) and bimetallic (Ni–Co, Co–Cr, *etc.*) catalysts; bifunctional metallic catalysts supported on various materials (Al₂O₃, TiO₂, SiO₂, MgO) modified with various additives (acids, alkalis); and metals (Pt, Pd, Ni, Co) immobilised on polymers. For example, synthesis of 3-amino-5-aminomethyl-2-methyl-4-methoxymethylpyridine by coupled hydrogenation and dehalogenation of 6-chloro-2-methyl-4-methoxymethyl-3-nitropyridine-5-carbonitrile over palladium-containing anion exchanger AB-17-8 has been described.¹⁸¹ The yield of the target product (20–60 °C, p_{H_2} = 0.98–1.03 MPa, EtOH as the solvent) reaches 99%. The catalyst proposed for this reaction proved to be much more stable and active than Pd/C.

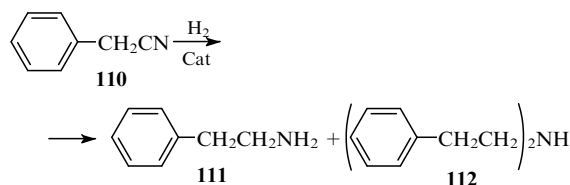
Data on the liquid-phase hydrogenation of hexanenitrile to amines have been reported.¹⁸² Reduced metals (Ni, Co, Ru, Pd, Pt, Os, Cu) on γ -Al₂O₃ were used as the catalysts in this reaction. In terms of their activity in hydrogenation, the studied catalysts can be arranged in the sequence Ru > Ni > Os > Co > Pd > Pt > Cu; the selectivities of these catalysts were also dissimilar. Thus the cobalt catalyst exhibited the highest selectivity (91%) with respect to primary amine (hexylamine). The highest selectivity with respect to secondary amine was found for Ru and Pt catalysts (81%–89%). In the presence of the Pd catalyst, the yields of di- and tri-hexylamines are 65.4% and 34.6%, respectively. Hydrogenation of hexanenitrile over the industrial nickel–chromium catalyst at 120–140 °C and p_{H_2} = 5.0 MPa gave a mixture of amines containing 64% of the secondary amine and 36% of the primary and tertiary amines (the total yield). By varying the reaction temperature, the pressure of hydrogen and the chemical composition of the catalyst, the ratio of the reaction products can be controlled. Thus at 145 °C and p_{H_2} = 0.35–0.50 MPa, 100% conversion of acetonitrile was attained; the reaction products were found to contain 3.1% of primary amines, 45.4% of secondary amines and 51.5% of tertiary amines. At higher temperatures, the yield of secondary amines increases.¹⁸⁰ The use of Pd, Pt and Ru catalysts supported on lithium aluminium spinel in this reaction permits the preparation of an amine mixture containing 99.7% of tertiary amine.¹⁸³

Numerous studies dealing with hydrogenation of acetonitrile **107** and acrylonitrile **108** over a series of copper and copper–nickel catalysts with various metal contents (5% Cu; 8% Cu + 2% Ni; 15% Cu + 2% Ni, *etc.*) have been carried out. Gumbrin was used as the support. Some catalyst specimens were modified with NaOH (3%). Hydrogenation was carried out at 100–200 °C under atmospheric pressure. The reduction of the nitriles **107** and **108** affords mixtures of the corresponding primary, secondary and tertiary amines. The copper–nickel catalyst (8% Cu + 2% Ni) annealed at 900 °C proved to be the most active towards hydrogenation of acrylonitrile; the total yield of amines on this catalyst was 69.7%. The modification of the Cu–Ni catalyst with alkali increases its stability.¹⁸⁴ The nitrile **108** was converted into dipropylamine in two stages with a high yield.¹⁸⁵ In the first stage, acrylonitrile was hydrogenated to propionitrile **109** in the presence of a catalyst containing Pd, Bi and K on silica gel, and in the second stage, the resulting

propionitrile was converted into dipropylamine using 50%–56% Ni supported on kieselguhr at p_{H_2} = 0.1–2.0 MPa and 140–200 °C.



To increase the yield of primary amines, hydrogenation is carried out in the presence of ammonia. The role of ammonia or alkali is to retard the reaction of aldimines with amines and deamination.^{186–188} The addition of ammonia markedly increases the yields of higher primary amines (C₈–C₂₄) produced in the hydrogenation of the corresponding individual nitriles or their mixtures.^{189–191} The introduction of LiOH, NaOH, KOH or Na₂CO₃ (0.1 mass %–2.0 mass % relative to the catalyst) leads to higher yields of primary amines. Thus hydrogenation of phenylacetone nitrile **110** over Raney nickel gave 2-phenylethylamine **111** in 51.2% yield, the yield of the corresponding secondary amine **112** being 37.5%. When 2.0 mass % NaOH was introduced into the catalyst, the yield of the primary amine became 92.5%–95.5%.^{192, 193}

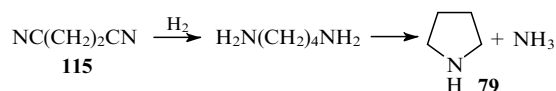


Since benzylamine **113** is a valuable compound for fine organic synthesis, a large number of studies dealing with catalytic hydrogenation of benzonitrile have been carried out. Hydrogenation of benzonitrile in dioxane in the presence of ammonia at 70–80 °C has been studied.¹⁹⁴ Nickel supported on kieselguhr was used as the catalyst. The benzene ring was not hydrogenated under these conditions; the yield of benzylamine was 76%–79% and the selectivity was 82.5%. Interesting results have been obtained in a study of hydrogenation of benzonitrile on the Pt/C, Pd/C and Ru/C catalysts.¹⁹⁵ The reaction rate was found to increase on increasing the pressure of hydrogen; however, the yield of toluene also increased (from 0.3%–3.0% to 8%–9%).

Hydrogenation of nitriles and dinitriles in methanol or cyclohexane¹⁹⁶ is carried out on cobalt catalysts supported on Fe, Co, Mn or Cr metal powders at 80–120 °C and p_{H_2} = 25.0–35.0 MPa in the presence of ammonia. The yields of the corresponding primary amines were 90%–95%. It was noted that the service life of metal-supported catalysts is longer than those of catalysts supported on oxides.

Dinitriles of the aliphatic and aromatic series are hydrogenated under the same conditions as mononitriles. For example, octamethylenediamine (yield 91%) is prepared by catalytic reduction of the dinitrile of the corresponding acid in the presence of a ruthenium catalyst in an inert solvent containing an additive of NH₃, at p_{H_2} = 3.0 MPa.¹⁹⁷ By varying the reaction conditions, the reduction of dinitriles can be terminated at the stage of formation of amino nitrile as the major reaction product. Thus the dinitriles CN(CH₂)_nCN (where n = 1–10) can be converted on a rhodium catalyst into the corresponding amino nitriles, formed in high yields.^{198, 199} Data on the conditions and the mechanism of this reaction and various factors that influence its course have been described systematically.²⁰⁰ The mechanisms of the formation of primary, secondary and tertiary amines were described in detail. In terms of their activity in this reaction, known catalysts can be arranged in the following sequence: Pt > Pd > Ni > Co > Fe > Cu. The reduction of aliphatic dinitriles containing CN groups at the 1,2-, 1,3- and 1,4-positions, in addition to the corresponding diamines, yields five-, six- and seven-membered saturated heterocyclic compounds, resulting from intramolecular heterocyclisa-

tion. For example, succinodinitrile **115** is converted into pyrrolidine **79**.

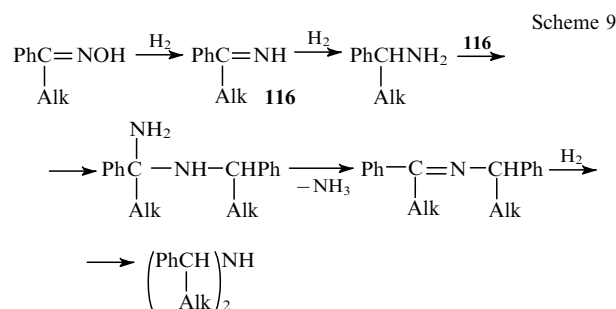


Data on the hydrogenation of nitriles in the presence of homogeneous or heterogeneous catalysts in the liquid phase have been described systematically.²⁰¹ The reaction mechanisms and the pathways to side products were considered. The effects of the solvent, temperature, the pressure of hydrogen and the nature of the catalyst on the course of this reaction carried out over heterogeneous catalysts were studied.

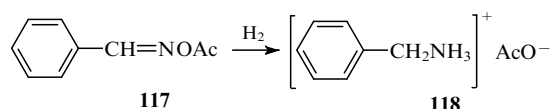
Oximes are also hydrogenated using nickel catalysts. Thus hydrogenation of acetone oxime gives a mixture of amines in which the secondary amine predominates.²⁰²



Hydrogenation of a number of alkylaromatic oximes has been studied.²⁰³ It was found that the formation of primary amines is preceded by the intermediate formation of imines **116**; in some cases, they can be isolated from the reaction mixture (Scheme 9). The reaction products contain primary, secondary and tertiary amines.^{204–207} Secondary amines result from interaction of the imine **116** with primary amines. They can also arise upon deamination of primary amines in the presence of a catalyst.²⁰⁸



Rosenmund *et al.*²⁰⁹ were the first to use an oxime acetate for preventing the formation of a secondary amine. Hydrogenation of the benzaldehyde oxime acetate **117** gave a primary amine (formed as acetate **118**) in 91% yield.



Primary amines are also prepared by hydrogenation of oximes in acetic anhydride. Thus hydrogenation of benzaldehyde oxime under these conditions resulted in the synthesis of *N*-benzylacetamide; hydrogenation of acetone oxime gave *N*-(1-phenylethyl)acetamide.²⁰⁴ Free amines are obtained by hydrolysis of these amides. Good yields of primary amines, formed as hydrochlorides, are attained when oximes are hydrogenated on a palladium catalyst in anhydrous ethanol with three equivalents of HCl.²¹⁰ Hydrogenation of oximes in the presence of ammonia,²¹¹ which increases the yield of primary amines, has found a wider practical application.

In the case of catalytic hydrogenation of oximes, nickel, cobalt and rhodium supported on alumina are used most often as the catalysts.²⁰⁴ In the reduction of oximes of α,β -unsaturated ketones, platinum dioxide is used as the catalyst and MeOH is used as the solvent.²⁰⁵ The solvent has a substantial influence on the composition of the products of oxime reduction in the liquid phase. For example, when a more polar solvent was used, aziridine was obtained from benzylideneacetone oxime, in addition to the corresponding amine.²¹² Study of hydrogenation of cyclohexa-

none oxime in various solvents in the presence of Pt, Pd, Rh and Ru supported on finely dispersed carbon made it possible to elucidate the influence of the solvent and the catalyst on the reaction rate and the product composition. The reaction does not occur in dioxane; the reaction in methanol proceeds in the presence of the rhodium catalyst, while in acetic acid, it proceeds over a platinum catalyst. When the reaction is carried out in water, cyclohexanol is produced as the major product.²¹²

Apart from the platinum Group metals listed above, cobalt is also used to catalyse hydrogenation of oximes. In some cases Raney cobalt is more active than the nickel catalyst.²¹³ Alumina is usually employed as the support.^{204, 214}

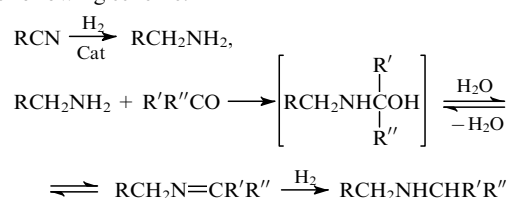
When oximes are reduced over copper catalysts, together with amines, side products are formed, in particular, the Beckmann rearrangement product, the corresponding ketones, aldehydes, nitriles and imines.²¹⁵

Apart from molecular hydrogen, the hydrazine–Raney nickel system is also widely used as the reducing agent in the hydrogenation of oximes.^{208, 216} This system permits easy and selective reduction of oximes to primary amines.

2. Reductive amination of oxygen-containing compounds with nitriles and oximes

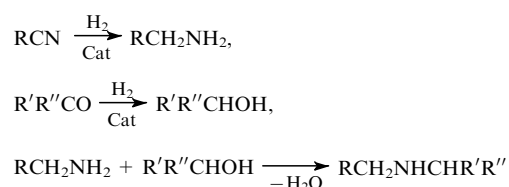
Significant progress in the development of new methods for the synthesis of amines was associated with the use in the reductive amination of nitriles and oximes, which had not been used previously as direct aminating agents. Hydroamination of oxygen-containing compounds with nitriles extends still further the potential of this reaction.

The ability of nitriles to be reduced to amines under the conditions of catalytic hydrogenation made it possible to aminate various ketones and aldehydes in one stage.^{217–221} The reaction is carried out in the vapour phase over a heterogeneous catalyst in a flow-type setup operating under a pressure of hydrogen. The process of hydroamination of oxygen-containing compounds with nitriles includes several successive coupled reactions resulting in the formation of secondary amines. In the carbonyl compound–nitrile–hydrogen system, this reaction occurs in accordance with the following scheme:^{218, 219}



R, R' = H, Alk, Ar; R'' = Alk, Ar.

Under the reaction conditions, carbonyl compounds are partly reduced to the corresponding alcohols. The possibility of hydroamination of alcohols with nitriles, as shown below, also cannot be ruled out.

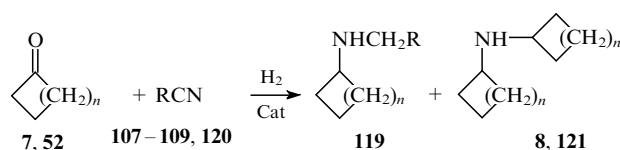


R = H, Alk, Ar; R' = H, Alk, Ar; R'' = Alk, Ar.

The reaction pathway depends on the structures of the reactants and on the rate of each particular stage. The above reactions might also occur simultaneously.

Hydroamination of cyclic ketones by aliphatic nitriles under a pressure of hydrogen has been studied.^{218, 219} Nickel–alumina and copper–alumina catalysts with a metal content of 15%–20%, both non-modified and modified by the addition of Li, Na

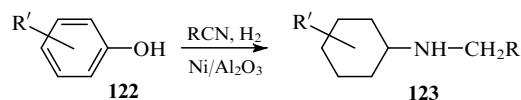
and K, were used. The main reaction pathway is the formation of alicyclic secondary amines **119**.



R = Me (**107**), CH=CH₂ (**108**), Et (**109**), Prⁿ (**120**); *n* = 3 (**7**, **8**), 2 (**52**, **121**).

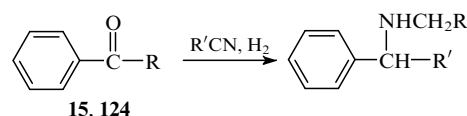
The yields of the corresponding amines **119** with the 15% Cu/Al₂O₃ catalyst at 240 °C and *p*H₂ = 1.5 MPa reaches 75%. The introduction of alkaline additives (Li, Na, K) in the copper–alumina catalyst increases the total yield of amines by 5%–12%. The di(cycloalkyl)amines **8** and **121** are formed as side products. It was assumed²¹⁸ that the main reason for the formation of the amines **8** and **121** is the low stability of *N*-alkylcycloalkylamines **119** under the conditions employed. In fact, when *N*-ethylcyclohexylamine is passed over the catalyst under the conditions of hydroamination, it partly decomposes to give a mixture of cyclohexylamine **13** and dicyclohexylamine **8** (up to 30%). Study of the reductive amination of the alicyclic ketones **7** and **52** with aceto- (**107**), acrylo- (**108**), propio- (**109**) and butyro-nitriles (**120**) showed that the yield of *N*-alkylcycloalkylamines **119** decreases following an increase in the number of the carbon atoms in the nitrile molecule.

N-Alkylcyclohexylamines **123** have been prepared in good yields (up to 73%) by hydroamination of phenols **122** with nitriles on nickel–alumina catalysts. In this case, amination is accompanied by hydrogenation of the aromatic ring.²²²



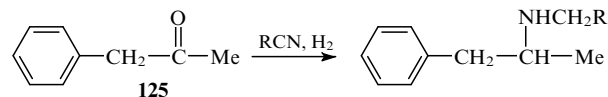
R = Me, Et, Pr; R' = H, *o*-Me, *m*-Me, *p*-Me.

In order to synthesise aromatic amines which contain the amino group in the side chain and form a number of important biologically active compounds, hydroamination of acetophenone **15**, benzophenone **124** and benzyl methyl ketone **125** with nitriles has been carried out.²²³ In the presence of copper–alumina catalysts, the highest yields (31%–72%) of secondary amines were attained with 20% Cu/Al₂O₃ at 220 °C, *p*H₂ = 1.5–2.0 MPa. The reactivity of ketones in the amination by nitriles decreases in the order **125** > **15** > **124**.²²³ The conjugated system of bonds present in acetophenone results in a lower positive charge on the carbonyl carbon atom; this accounts for the decrease in the reactivity of the ketone **15**. In the case of hydroamination of benzophenone with acetonitrile, the yield of *N*-ethylbenzhydrylamine is influenced not only by conjugation but also by steric factors. Ethylbenzene and diphenylmethane were isolated as side products upon hydroamination of aceto- and benzophenone. Virtually no propylbenzene is formed on hydroamination of benzyl methyl ketone.



15, 124

R = Me, Ph; R' = Me, Et, Prⁿ.



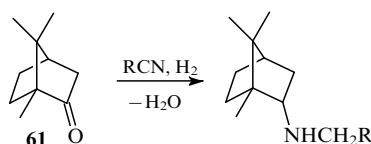
125

R = Me, Et, Prⁿ.

Unsaturated ketones, aliphatic nitriles, phenylacetone, aliphatic and alicyclic ketones, benzonitrile and aldehydes have been used successfully for the synthesis of aliphatic-aromatic amines^{219, 223–227} (Table 1). *N*-Alkylbornan-2-ylamines were synthesized in 45%–55% yields by hydroamination of camphor **61** by aliphatic nitriles.²²⁸

Table 1. Synthesis of aliphatic-aromatic secondary amines by hydroamination of ketones and aldehydes with nitriles

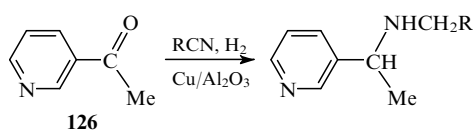
Ketone, aldehyde	Nitrile	Catalyst	The resulting amine	Yield (%)	Ref.
<i>T</i> = 220 °C, <i>p</i> H ₂ = 1.5 MPa, <i>v</i> = 0.25 h ^{−1}					
Acetophenone	acetonitrile	15% Cu/Al ₂ O ₃ + 2% LiOH	<i>N</i> -ethyl- α -phenylethylamine	58	223
Benzophenone	"	15% Cu/Al ₂ O ₃ + 2% LiOH	<i>N</i> -ethylbenzhydrylamine	28	223
Benzyl methyl ketone	"	20% Cu/Al ₂ O ₃	<i>N</i> -ethyl- α -methyl- β -phenylethylamine	72	223
Benzylidenacetone	"	36% Cu/MgO	<i>N</i> -ethyl-1-methyl-3-phenylpropylamine	65	224
Acetone	benzonitrile	20% Cu/Al ₂ O ₃	<i>N</i> -isopropylbenzylamine	58	219
Methyl ethyl ketone	"	20% Cu/Al ₂ O ₃	<i>N</i> -(butan-2-yl)benzylamine	42	219
Diethyl ketone	"	20% Cu/Al ₂ O ₃	<i>N</i> -(pentan-3-yl)benzylamine	46	219
Cyclopentanone	"	20% Cu/Al ₂ O ₃	<i>N</i> -cyclopentylbenzylamine	36	219
Cyclohexanone	"	20% Cu/Al ₂ O ₃	<i>N</i> -cyclohexylbenzylamine	54	219
<i>T</i> = 230 °C, <i>p</i> H ₂ = 1.5 MPa, <i>v</i> = 0.20 h ^{−1}					
Benzylidenacetone	acrylonitrile	36% Cu/MgO	<i>N</i> -propyl-1-methyl-3-phenylpropylamine	70	224, 225
	butyronitrile	36% Cu/MgO	<i>N</i> -butyl-1-methyl-3-phenylpropylamine	75	224, 225
	isobutyronitrile	15% Cu/Al ₂ O ₃ + 6% LiOH	<i>N</i> -isobutyl-1-methyl-3-phenylpropylamine	60	224, 225
	benzonitrile	36% Cu/MgO	<i>N</i> -benzyl-1-methyl-3-phenylpropylamine	70	224, 225
<i>p</i> -Methoxybenzylidenacetone	acetonitrile	15% Cu/Al ₂ O ₃ + 6% LiOH	<i>N</i> -ethyl-1-methyl-3-(<i>p</i> -methoxyphenyl)-propylamine	60	224
1-Phenylpent-1-en-3-one	"	15% Cu/Al ₂ O ₃ + 6% LiOH	<i>N</i> -ethyl-3-phenyl-1-ethylpropylamine	60	224
<i>T</i> = 220 °C, <i>p</i> H ₂ = 1.0 MPa, <i>v</i> = 0.30 h ^{−1}					
Acetone	phenylacetone	20% Cu/MgO	<i>N</i> -isopropyl-2-phenylethylamine	61	226
Diethyl ketone	"	20% Cu/Al ₂ O ₃	<i>N</i> -(pentan-3-yl)-2-phenylethylamine	36	226
Methyl propyl ketone	"	20% Cu/MgO	<i>N</i> -(pentan-2-yl)-2-phenylethylamine	50	226
Cyclohexanone	"	20% Cu/MgO	<i>N</i> -cyclohexyl-2-phenylethylamine	52	226



R = Me, Et, Prⁿ.

Systematic study of the reductive amination of carbonyl-containing compounds and secondary alcohols of the terpene series resulted in the development of preparative and selective methods for the synthesis of both unsaturated and completely hydrogenated amines with diverse structures (aliphatic; mono- bi- and tricyclic; containing three-, four, five- and six-membered rings)^{229–239} (Table 2).

A series of 3-(1-alkylaminoethyl)- and 3-(arylmethylaminoethyl)-pyridines have been synthesised in 50%–65% yields by hydroamination of 3-acetylpyridine **126** with aliphatic and aromatic nitriles.²⁴⁰



R = Me, Et, Prⁿ, Ar.

Hydroamination of an α,β -unsaturated heterocyclic ketone — 4-(2-furyl)but-3-en-2-one **127** — which has an additional reaction site, the oxygen atom of the furan ring, has been studied. This process can follow several alternative pathways depending on the catalyst used (Scheme 10). In the presence of a copper–magnesium catalyst, the reaction stops at the stage of formation of a

secondary amine of the furan series, namely, 2-(3-alkylaminobutyl)furan **128** (yield 45%–48%); the use of copper–alumina catalyst results in hydrogenolysis of the furan ring at the O(1)–C(5) bond and cyclisation of the intermediate amino ketone. In this case, *N*-alkyl-2-methyl-5-propylpyrrolidine **129** is the main product (yield 42%–46%).²⁴¹ In addition, the reaction products contain a small amount of pyrrole derivatives **130** (5%), which result from the direct replacement of the oxygen atom of the furan ring by an amino group accompanied by hydrogenation of the carbonyl group and the double bond in the side chain.

Scheme 10

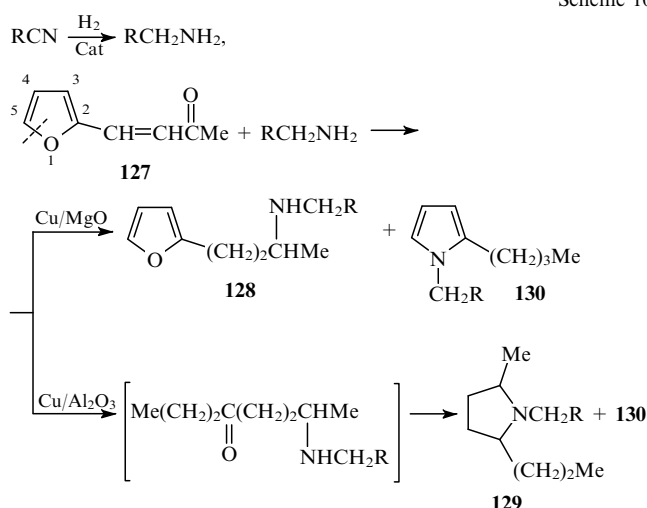
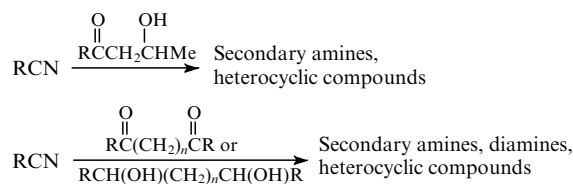


Table 2. Reductive amination of carbonyl-containing compounds and alcohols of the terpene series.

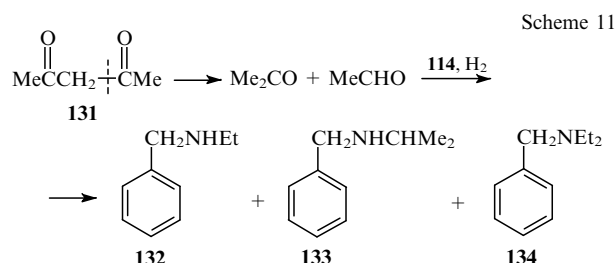
Ketone, alcohol	Nitrile, oxime	Catalyst	The resulting amine	Yield (%)	Ref.
$T = 220\text{ }^{\circ}\text{C}$, $p_{\text{H}_2} = 1.5\text{ MPa}$, $v = 0.25\text{ h}^{-1}$					
L-Camphor	acetonitrile	15% Cu/Al ₂ O ₃ + (2–6)% LiOH	<i>N</i> -ethylbornylamines (<i>exo</i> - and <i>endo</i> -isomers)	60 ^a	229
1,3,3-Trimethylbicyclo-[2.2.1]heptan-2-one	"	15% Cu/Al ₂ O ₃ + (2–6)% LiOH	the same	80	230
(+)- <i>S</i> -Carvone	"	15% Cu/Al ₂ O ₃ + (2–6)% LiOH	<i>N</i> -ethylcarvo-, isocarvo-, neocarvo- and neoisocarvomethylamines	60–70 ^a	231
Acetone	(+)- <i>S</i> -carvone oxime	15% Cu/Al ₂ O ₃ + (2–6)% LiOH	<i>N</i> -isopropyl-5-isopropyl-2-methylcyclohexylamine	60	232
L-Menthol	acetonitrile	15% Cu/Al ₂ O ₃ + (2–6)% LiOH; 36% Cu/MgO	<i>N</i> -ethylmenthyl-, neomenthyl-, isomenthyl- and neoisomenthylamines	70 ^a	233, 234
<i>cis</i> -3,7,7-Trimethylbicyclo-[4.1.0]heptan-2-ol	"	15% Cu/Al ₂ O ₃ + (2–6)% LiOH; 36% Cu/MgO	<i>N</i> -ethyl-5-isopropyl-2-methylcyclohexylamine	60	235
Hexahydropseudoionone	benzonitrile	15% Cu/Al ₂ O ₃ + (2–6)% LiOH	<i>N</i> -benzyl-1,5,9-trimethyldecylamine	85	236
1-Ethylbicyclo[2.2.1]-heptan-2-one	acetonitrile	15% Cu/Al ₂ O ₃ + (2–6)% LiOH	<i>N</i> -ethyl-1-ethylbicyclo[2.2.1]hept-2-ylamines (<i>exo</i> - and <i>endo</i> -isomers)	69 ^a	237
$T = 250\text{ }^{\circ}\text{C}$, $p_{\text{H}_2} = 1.5\text{ MPa}$, $v = 0.25\text{ h}^{-1}$					
Isocamphanone, isocamphanol	acetonitrile	15% Cu/Al ₂ O ₃ + (2–6)% LiOH	<i>N</i> -ethylisocamphylamines	80	238
Isufenchol	propionitrile	15% Cu/Al ₂ O ₃ + 6% LiOH	<i>N</i> -propylisofenchylamine	60	238
1-Ethyltricyclo-[2.2.1.0 ^{2,6}]heptan-3-one	acetonitrile	15% Cu/Al ₂ O ₃ + (2–6)% LiOH	<i>N</i> -ethyl-1-ethyltricyclo[2.2.1.0 ^{2,6}]hept-3-ylamine	75	238
Citronellal	propionitrile	15% Cu/Al ₂ O ₃ + (2–6)% LiOH	<i>N</i> -propyl-3,7-dimethyloctylamine, <i>N</i> -propyl-3,7-dimethyloct-6-enylamine	35 30	238
$T = 240\text{--}260\text{ }^{\circ}\text{C}$, $p_{\text{H}_2} = 1.5\text{ MPa}$, $v = 0.20\text{ h}^{-1}$					
2-Acetylbicyclo-[2.2.1]hept-5-ene	acetonitrile	36% Cu/MgO	2-(α -ethylaminoethyl)bicyclo-[2.2.1]heptane	70	239

^a The total yield is given.

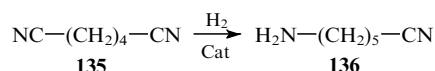
Several studies have been devoted to the interaction of nitriles with bifunctional oxygen-containing compounds in which both reaction sites can be involved in hydroamination. In particular, reactions of hydroxy ketones, diketones and diols were investigated.^{242–244}



α -Diketones and α -glycols react with nitriles according to similar patterns. Thus the reaction of diacetyl with nitriles yields the same products as the reaction of ethylene glycol, namely, mono- and diamines.^{243, 244} Acetylacetone (β -diketone) **131** is unstable under the reaction conditions, products of its decomposition being involved in reductive amination. The reaction of the diketone **131** and benzonitrile **114** over the 15% Cu/MgO catalyst at 240 °C and $p_{\text{H}_2} = 1.5$ MPa gives rise to *N*-ethylbenzylamine **132** (yield 29%), *N*-isopropylbenzylamine **133** (yield 19%) and *N,N*-diethylbenzylamine (yield 18%) (Scheme 11).

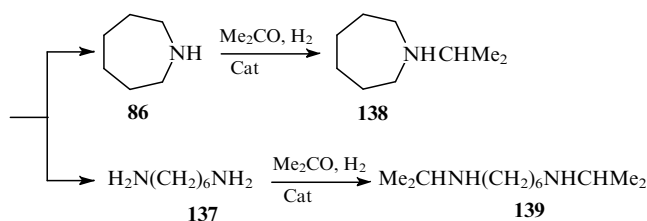
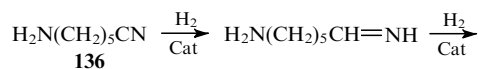


Reactions of dinitriles with carbonyl compounds have been studied. It was found²²¹ that hydroamination of acetone and butanal with adiponitrile **135** can follow two pathways, one yielding a heterocycle and one yielding aliphatic amines. The nitrile groups in the adiponitrile molecule behave under the hydrogenation conditions as if they possessed different reactivities. This fact has been explained by the formation of unstable cyclic systems.²⁴⁵ A pseudo-ring forms upon interaction of nitrogen of one nitrile group with the hydrogen located at the α -position relative to the second nitrile group. Therefore, reductive amination occurs as preferential reduction of one nitrile group rather than simultaneous reduction of both of them and yields 6-aminohexanenitrile **136**.



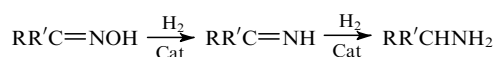
The amino nitrile **136** can undergo two types of transformation. The first of them is hydrogenation of the second CN group to give hexamethylenediamine **137** and subsequent hydroamination of a carbonyl compound, for example, acetone **29**. The second route includes hydrogenation of the amino nitrile **136** accompanied by cyclisation and gives rise to perhydroazepine **86**.

The crucial factor which determines the reaction route is temperature. Thus at 190 °C, the yields of *N*-isopropylperhydroazepine **138** and *N,N'*-diisopropylhexamethylenediamine **139** are 25% and 84%, respectively, whereas at 240 °C they are 22% and 3%.



The good results attained in hydroamination of oxygen-containing compounds, together with the theoretical fundamentals and the published data concerning reduction of oximes to primary amines under conditions similar to those used in hydroamination, permitted oximes to be employed for the first time for reductive amination of various ketones and aldehydes.^{246–249} Analysis of the ability of oximes to be reduced over heterogeneous catalysts led to the conclusion that, in addition to the traditional catalysts used to reduce oximes to primary amines (platinum Group metals and nickel), copper catalysts are also active in this process.

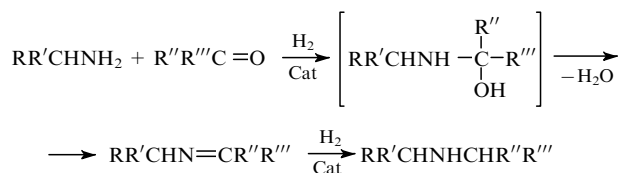
Hydroamination of carbonyl compounds with various oximes includes several consecutive coupled reactions, resembling those involved in hydroamination of carbonyl compounds with nitriles. The necessity of a high degree of coupling between separate stages becomes evident if one examines the processes occurring in the 'oxime-carbonyl compound-hydrogen' ternary systems over a heterogeneous catalyst. Initially, the oxime is reduced on the hydrogenating sites of the catalyst to give a primary amine (Scheme 12).^{247, 248}



R = Alk, Ar; R' = H, Alk, Ar.

Scheme 12

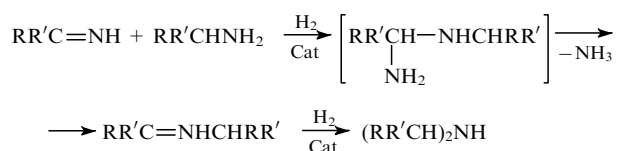
The resulting primary amine can participate in many thermodynamically allowed reactions. Within the scope of our review, condensation of the primary amine with the carbonyl compound is of interest (Scheme 13).^{247, 248}



R, R'' = Alk, Ar; R', R''' = H, Alk, Ar.

Scheme 13

The reaction of the primary amine with the imine, resulting from incomplete reduction of the oxime, is a competing process (Scheme 14).^{247, 248}



Scheme 14

Thus, when there is no coupling between the formation of primary amine and its condensation with the carbonyl compound (see Schemes 12 and 13), the overall process can be substantially influenced by the reaction of the primary amine with the nitrogen analogue of the carbonyl compound, *i.e.* imine (see Scheme 14). The formation of symmetrical secondary amines markedly decreases the selectivity of the main reaction.^{247, 248}

The attainment of coupling depends appreciably on the catalyst. The carbonyl compound should be activated towards condensation (see Scheme 13) to an extent that its reactivity in

Table 3. Reductive amination of ketones, aldehydes and alcohols with oximes.

Ketone, aldehyde, alcohol	Oxime	Catalyst	The resulting amine	Yield (%)	Ref.
$T = 210\text{ }^{\circ}\text{C}$, $p_{\text{H}_2} = 1.5\text{ MPa}$, $v = 0.25\text{ h}^{-1}$					
Pentan-2-one	cyclohexanone	36% Cu/MgO	<i>N</i> -(pentan-2-yl)cyclohexylamine	41	246
	cyclopentanone	36% Cu/MgO	<i>N</i> -(pental-2-yl)cyclopentylamine	52	246
Cyclohexanone	cyclohexanone	36% Cu/MgO	dicyclohexylamine	62	246
Acetaldehyde	"	15% Cu/Al ₂ O ₃ + 6% LiOH	<i>N</i> -ethylcyclohexylamine	55	247
Propanal	"	15% Cu/MgO	<i>N</i> -propylcyclohexylamine	67	247
Butanal	cyclopentanone	15% Cu/MgO	<i>N</i> -butylcyclopentylamine	74	247
2-Methylpropanal	"	15% Cu/MgO	<i>N</i> -isobutylcyclopentylamine	55	247
$T = 210\text{ }^{\circ}\text{C}$, $p_{\text{H}_2} = 1.0\text{ MPa}$, $v = 0.30\text{ h}^{-1}$					
Acetaldehyde	benzaldehyde	36% Cu/ZnO	<i>N</i> -ethylbenzylamine	44	248
Propanal	"	15% Cu/Al ₂ O ₃	<i>N</i> -propylbenzylamine	46	248
Pentanal	"	36% Cu/MgO	<i>N</i> -pentylbenzylamine	60	248
3-Methylbutanal	"	36% Cu/MgO	<i>N</i> -(pentan-2-yl)benzylamine	48	248
$T = 240\text{ }^{\circ}\text{C}$, $p_{\text{H}_2} = 1.5\text{ MPa}$, $v = 0.25\text{ h}^{-1}$					
Cyclohexylmethanol	3-methylbutanal	15% Cu/Al ₂ O ₃ + 6% LiOH	<i>N</i> -(pentan-2-yl)cyclohexylmethylamine	46	249
	"	36% Cu/ZnO	"	45	249

relation to the nucleophile be higher than that of the imine. This activation occurs on the acid sites of the catalyst.²⁴⁸ The condensation proceeds *via* intermediate formation of the addition product, which is converted into imine upon dehydration. This stage is followed by hydrogenation of the C=N double bond on the hydrogenating sites of the catalyst and by the formation of a secondary amine, which is the final reaction product. The data on the methods of synthesis of secondary amines from oximes, ketones, aldehydes and alcohols are presented in Table 3.

VI. Conclusion

The data considered in the review convincingly demonstrate the substantial progress achieved in the development of catalytic methods for the synthesis of amines based on reductive amination of various oxygen-containing organic compounds. The most significant achievements are the use of nitriles and oximes, which had not been used previously for these purposes, as aminating agents; elaboration and use of complex catalysts for reductive amination, which allow the processes to be conducted under mild conditions with high selectivity; and the use of reduced promoted fused iron catalysts in the synthesis of nitrogen-containing heterocycles.

The assimilation of new reactions of oxidative ammonolysis and oxo synthesis made it possible to synthesise numerous nitriles, carbonyl compounds and oximes, needed for the production of amines of various structures and compositions. Thus, there are strong grounds for believing that in the near future, the reaction in question would become one of the most significant methods for the preparation of amines.

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^a — *Dokl. Chem. Technol., Dokl. Chem. (Engl. Transl.)*

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

^c — *Kinet. Catal. (Engl. Transl.)*

^d — *Russ. J. Org. Chem. (Engl. Transl.)*

^e — *Russ. J. Appl. Chem. (Engl. Transl.)*

^f — *Russ. J. Phys. Chem. (Engl. Transl.)*

^g — *Chem. Nat. Compd. (Engl. Transl.)*

^h — *Russ. J. Gen. Chem. (Engl. Transl.)*

Levulinic acid in organic synthesis

B V Timokhin, V A Baransky, G D Eliseeva

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Abstract. Data concerning the methods of synthesis, chemical transformations and application of levulinic acid are analysed and generalised. The wide synthetic potential of levulinic acid, particularly as a key compound in the synthesis of various heterocyclic systems, saturated and unsaturated ketones and diketones, difficultly accessible acids and other compounds is demonstrated. The accessibility of levulinic acid from hexose-containing wood-processing and agricultural wastes is noted. The bibliography includes 260 references.

I. Introduction

At present, the use of organic synthesis on an industrial scale is so extensive that the problem of limited natural resources, such as petroleum and gas employed in this process comes to the foreground.¹ This generates a need for timely measures aimed at elaboration of alternative strategies of fine organic synthesis on the basis of alternative sources of raw materials. In this context, the synthesis of key compounds from wood processing products holds great promise. The most common cellulose-derived products include glucose, xylose, ethanol, polyhydric alcohols and furfural. Their use in industrial organic synthesis has been documented in numerous publications. Much less attention has been given to such cellulose hydrolysis products as organic acids, first of all, 4-oxopentanoic or levulinic acid (LA). The molecule of LA contains two highly reactive functional groups providing a great number of synthetic transformations. LA has been used to obtain various heterocyclic compounds, saturated and unsaturated ketones and diketones, difficultly accessible acids, alcohols and so on. We have analysed publications devoted to LA and found that despite the great number of these studies, their results have virtually not been generalised. Some reviews on the subject (see Refs 2 and 3) are not sufficiently comprehensive and outdated.

In our opinion, the synthetic potentialities of LA are far from being exhausted, although the attention of investigators has now switched to starting compounds from other natural sources. Our desire to fill the information gap in this field, on the one hand, and to attract the attention of investigators and practitioners in synthetic chemistry to the high synthetic potentialities of LA manufactured from wood-processing and agricultural wastes on an industrial scale, on the other hand, was the incentive to write this review.

II. Physicochemical characteristics

Under normal conditions, LA is a colourless crystalline compound with a melting point of 37 °C, its boiling point (with decomposition) is 246 °C. The main physical constants for LA are as follows: d_4^{20} 1.140, d_4^{25} 1.1447; n_D^{20} 1.4796, n_D^{25} 1.441; surface tension 39.7 dyne cm⁻¹ (25 °C); heat of vaporisation (150 °C) 0.58 kJ mol⁻¹ and heat of fusion 79.8 J mol⁻¹ (see Ref. 4).

Levulinic acid is readily soluble in water, ethanol, diethyl ether, acetone and many other organic solvents. The temperature dependence of solubility of LA in water has been studied in detail.⁵ In water, LA is fairly well dissociated, its pK_a (25 °C) is 4.59, see Ref. 6. In other words, the acidity of LA is comparable with that of the majority of lower alkane carboxylic acids. For comparison of gas-phase acidity of LA with those of other carboxylic acids, see Ref. 7.

The analysis of ¹H and ¹³C NMR spectra of LA allowed a correct assignment of signals,² which demonstrated that the protons of the β-methylene group at position 3 are more 'acidic': (δ = 2.71 ppm) than those of the α-methylene group (δ = 2.47 ppm).

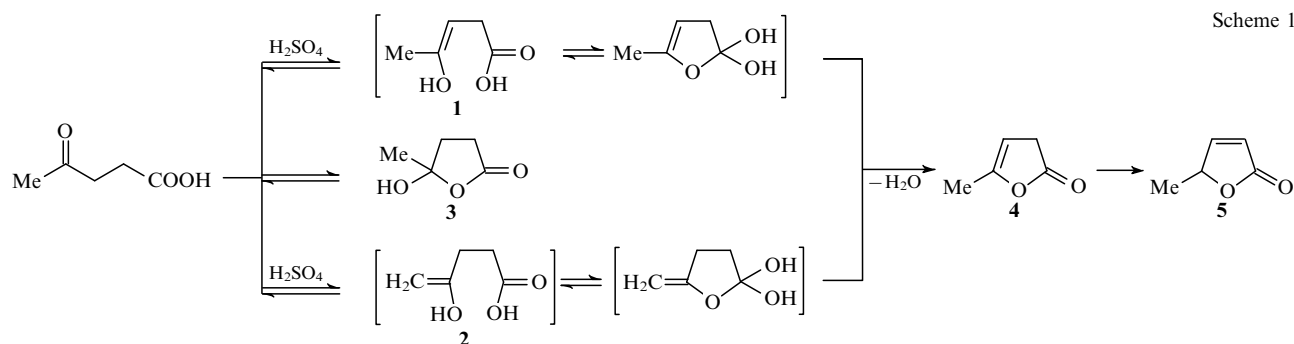
The rate of oxygen exchange of LA with water was studied using mass spectrometry. It was found⁸ that the exchange of the carbonyl group oxygen occurs 10 times faster than that of the carboxy group. The approximate values of the pseudo-first-order constants in excess of H₂¹⁸O are $k_{CO} = 7 \times 10^{-3}$ s⁻¹ and $k_{COOH} = 5 \times 10^{-4}$ s⁻¹, respectively. As expected, the carbon atom of the carbonyl group of LA is more susceptible to nucleophilic attack than that of the carboxy group.

The first ionisation potential of LA (9.7 eV according to photoelectron spectroscopic data⁸) corresponds to withdrawal of an electron from the orbital for which the main contribution is given by the unshared electron pair of the carbonyl oxygen atom.

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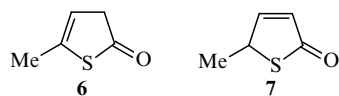
The knowledge of the specific characteristics of the keto–enol equilibrium of LA is substantial for the understanding of mechanisms of its reactions; for the equilibrium constants of LA derivatives see Refs 9 and 10. It was found¹⁰ that the content of the enolic forms of LA, *viz.*, 4-hydroxypent-3-enoic (**1**) and 4-hydroxypent-4-enoic acids (**2**), in diethyl ether is as low as $1.9 \times 10^{-2}\%$. The concentration of the LA enolic forms **1** and **2** in D₂O solutions is negligible, which followed from the absence of deuterium exchange at C(3) and C(4) (¹³C NMR spectral data). A similar conclusion was made from the analysis of UV spectra of aqueous solutions of LA.¹¹ Apparently, the ease of intramolecular transfer of the proton from the carboxy group to the carbonyl atom of oxygen is the reason for the predominant formation of 5-hydroxy-γ-valerolactone (**3**) rather than the enolic forms.

On the other hand, in acidic media (D₂O with addition of D₂SO₄) rapid H/D exchange occurred² resulting in the formation of C(3)D₂, C(5)D₃-pentadeuteriolevulinic acid. Thus under conditions of acid catalysis the concentration of the enolic forms **1** and **2** increases substantially. Apparently, the structures **1** and **2** are the intermediates in the cyclisation of LA into the lactones **4** and **5** (Scheme 1).⁸

Thus, the generally accepted viewpoint that LA is at equilibrium with the unsaturated lactones **4** and **5** (see, *e.g.*, Ref. 12) is not quite correct, since an appreciable concentration of these lactones is observed only in the presence of strong mineral acids. As expected, removal of water shifts the reaction towards the formation of the cyclic product. Thus the lactone **4** can be easily prepared by boiling LA in the presence of sulfuric or phosphoric acids using a Dean–Stark trap.¹³ It should be noted that the lactone **5** is thermodynamically more stable and is formed from the lactone **4** upon heating or treatment of the latter with a base.¹⁴

Enolisation of the lactone **4** into 2-hydroxy-5-methylfuran is theoretically possible. However, compound **4** does not manifest any enolic properties and its O-alkylation cannot be carried out despite the evolution of 0.3 equiv. of methane in the determination of mobile hydrogen according to the Tservitinov procedure.¹⁵ The chemical behaviour of furanones is rather specific and its consideration is beyond the scope of this review. Different aspects of furanone chemistry have been described in a comprehensive review.¹⁶

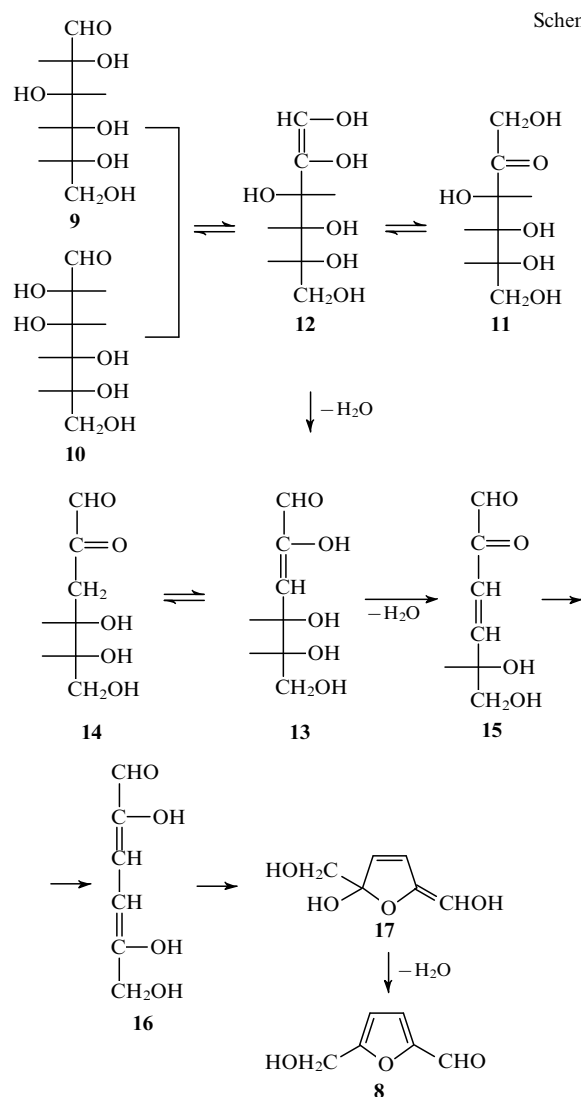
This derivatives of LA manifest an even greater trend for intramolecular cyclisation. Thus the reaction of LA with P₂S₅ or H₂S gives only cyclic products, such as the dihydrothiophenones **6** and **7** containing traces of 5-mercapto-5-methyltetrahydrothiophen-2-one.^{17,18}



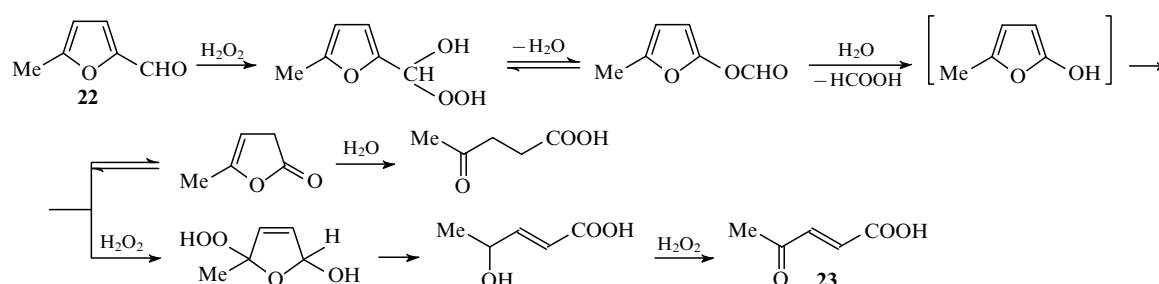
III. Preparation

On an industrial scale, LA is produced from wood-processing and agricultural wastes. The basis of industrial methods for the preparation of LA is transformation of hexoses in acidic media. This is usually considered as a combination of dehydration

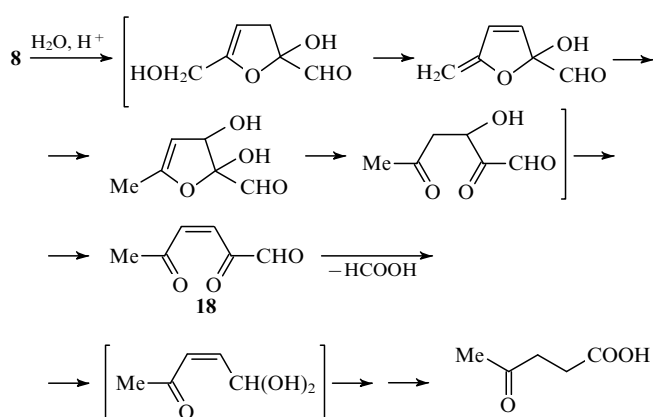
resulting in the formation of 5-hydroxymethylfurfural (**8**) and its subsequent hydration resulting in LA. The formation of 5-hydroxymethylfurfural **8** occurs through a series of consecutive reactions, which has been established by numerous studies aimed at identification of intermediate products and analysis of pathways of their further transformations (Scheme 2).^{19,20} The enediol **12** obtained upon enolisation of D-glucose (**9**), D-mannose (**10**) or D-fructose (**11**) in acidic media is the key compound in the formation of 5-hydroxymethylfurfural **8**. Its dehydration results in compound **13**, which represents the enol form of 3-deoxyhexosulose (**14**). Compound **13** yields 3,4-dideoxyglycosulose-3 (**15**). The latter is readily converted into the dienediol **16**, which eventually results in 5-hydroxymethylfurfural *via* the intermediate cyclic compound (**17**). Humin compounds are the side products of this reaction.²⁰



Scheme 3



The conversion of 5-hydroxymethylfurfural **8** into LA is a result of addition of a molecule of water to the $\text{C}(2)=\text{C}(3)$ bond of the furan ring.^{19, 20} This leads to ring opening with formation of an unstable tricarbonyl intermediate **18**. The latter is decomposed into the final products, viz., LA and formic acid.



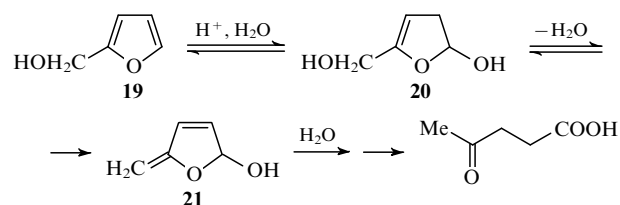
There are several assumptions about the nature of intermediates involved in the conversion of compound **8** into LA. The above scheme has been proposed in a recent study²¹ devoted to the analysis of this reaction (the formation of humin compounds is not shown). The sequence of transformations was proposed by Horvat *et al.*^{21, 22} on the basis of analysis of ^{13}C NMR spectra of the reaction mixture formed in the hydration of compound **8**.

Acid treatment of plant raw materials containing up to 75% of polysaccharides in the form of cellulose and hemicelluloses results in the hydrolysis of polysaccharides to monosaccharides.²³ The rate of wood pulp hydrolysis depends on the acid concentration, temperature, pressure and particle size.²⁴ Hydrolysis of cellulose to hexoses at atmospheric pressure is usually performed with strong acids (HCl , H_2SO_4) at 100°C . The resulting hydrolysate is heated up to 110°C with 20% HCl and kept at this temperature for 24–28 h. The reaction is accelerated by free halogens, transition metals, anion-exchange resins and other compounds.² After termination of the one-pot reaction, the reaction mixture is filtered to separate humin compounds and concentrated. LA is isolated from the mixture by distillation at reduced pressure or extraction with ether, ethyl acetate or ethyl methyl ketone. The yield of LA is about 40% with respect to the hexose content.² The reaction performed at 190°C under pressure gives a considerable gain in time.²⁵

Preparation of LA from hexoses in supercritical reactors (34.5 MPa, $200\text{--}385^\circ\text{C}$) has been described in many papers over the last decade.^{26, 27} In the absence of acidic or basic catalysts, the dehydration reaction is more selective. Currently, degradation of hexoses under hydrothermal conditions^{28, 29} or using alcohols in the presence of strong acids at $180\text{--}200^\circ\text{C}$ ³⁰ is being developed. This permits one to reduce the reaction time to several minutes at sufficiently high yields of LA. A search for new efficient catalysts is currently under way. Thus zeolites were found to

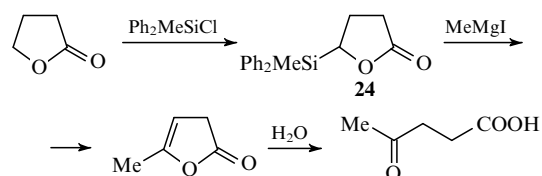
manifest high catalytic activity in the preparation of LA from glucose and fructose.³¹

Furfuryl alcohol (**19**), another product of wood pulp chemical processing, is an alternative source of LA. Its heating in aqueous organic acids ($K_a = 10^{-6}\text{--}10^{-4}$) in the presence of hydrochloric acid affords LA in more than 80% yield. When this reaction is performed in boiling ethyl methyl ketone in the presence of HCl , LA is formed in 90%–93% yield.^{33, 34} The hydroxy derivatives **20** and **21** were shown (^{13}C NMR) to be the key intermediates in this reaction.^{21, 22}

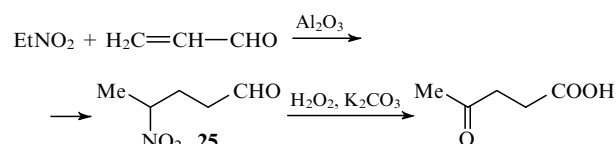


Levulinic acid is also formed upon oxidation of 5-methylfurfural (**22**) with 28% H_2O_2 at 60°C in the presence of HCOOH . This reaction gives a mixture of levulinic and 4-oxopent-2-enoic (**23**) acids (Scheme 3).^{35, 36}

It was shown³⁷ that LA is formed in high yield in the reaction of 4-(diphenylmethylsilyl)butyrolactone (**24**) with MeMgI .



LA can also be obtained in satisfactory yields³⁸ upon conjugate addition of nitroethane to acrolein in the presence of Al_2O_3 with subsequent oxidation of 4-nitropentanal (**25**) with an $\text{H}_2\text{O}_2\text{--K}_2\text{CO}_3$ system.



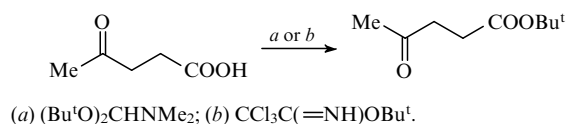
Despite the high yield of LA in the above reactions, they still cannot compete on an industrial scale with the simple and inexpensive procedures used in the preparation of LA from plant raw material.

IV. Reactions involving the carboxy group

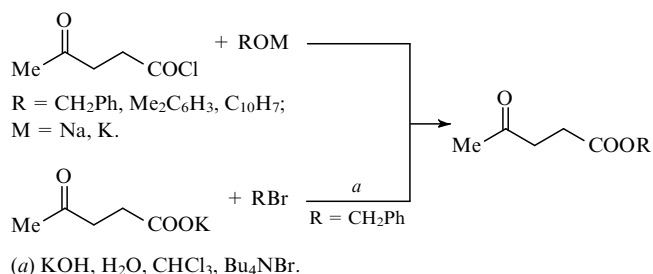
Of reactions involving the carboxy group of LA, special mention should be made of esterification which yields useful levulinates. The reaction of LA with primary alcohols, which is a first-order reaction with respect to both reactants,³⁹ occurs in solutions of LA in respective alcohols even at room temperature.⁴⁰ In order to

obtain esters in nearly quantitative yields, the reaction is carried out in the presence of typical dehydrating agents, such as sulfuric,^{41,42} polyphosphoric⁴³ or *p*-toluenesulfonic acid.^{44,45} The use of anion-exchange resins⁴⁶ or 2-halogenopyridinium salts⁴⁷ also gives good results. The increase in the size of the hydrocarbon fragment of the primary alcohol does not impede its esterification.⁴⁸ Since primary alcohols are easily and selectively acylated under these conditions, LA is used as a protective group in the synthesis of oligonucleotides⁴⁹ and oligosaccharides.^{50–52} Deprotection can be achieved using sodium borohydride⁵³ or sulfite anion donors.⁵⁴ However, hydrazinolysis is the most efficient method for deprotection.^{55,56} Under mild conditions, LA esters quantitatively react with hydrazine and its derivatives, which results in the regeneration of the original alcohol and the formation of the corresponding dihydropyridazinone, as a result of which the acid is completely eliminated from subsequent reaction. The formation of dihydropyridazinones and their reactivities are discussed in Section V.

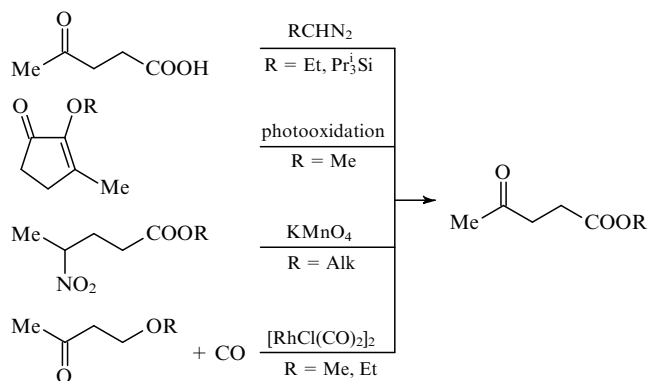
The synthesis of LA esters with tertiary alcohols in good yields usually involves other reactions than esterification. For example, *tert*-butyl levulinate is obtained by the reaction of LA with dimethylformamide *tert*-butyl acetal⁵⁷ or *tert*-butyltrichloroacetimidate.⁵⁸



Substituted benzyl and aryl esters of LA can be obtained using other classical methods for ester synthesis, e.g., acylation of alcoholates with levulinoyl chloride^{2,59–61} or alkylation of LA salts with alkyl halides under conditions of phase-transfer catalysis.⁶²

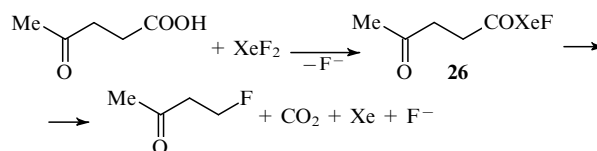


In addition to the methods described above, there are some other ways to obtain LA esters. Levulinates are formed by the reaction of LA with diazomethane derivatives,⁶³ upon photooxidation of cyclopentenone derivatives,⁶⁴ from the corresponding nitro compounds by the Nef reaction⁶⁵ or catalytic carbonylation of 4-alkoxybutan-2-one on rhodium catalysts.⁶⁶

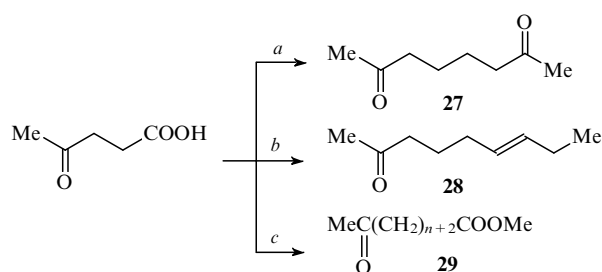


LA thio esters are obtained in high yields by the reaction of thiols with a pyridinium salt of LA formed *in situ* from the free acid and 2-fluoro-1-methylpyridinium tosylate.⁶⁷

Decarboxylation of LA in the gaseous phase occurs with difficulty.⁶⁸ Attempts to perform this reaction in a flow of hydrogen over Ni- and Pd-catalysts at 180–330 °C or over zeolites containing group I, II and VIII metals were more successful.⁶⁹ Thus heating of the lactone **4** up to 570 °C in the presence of SiO_2 gave up to 80% of ethyl methyl ketone.⁷⁰ A method for decarboxylation proposed recently using xenon fluoride was applied successfully to LA. Such fluorodecarboxylation occurs at room temperature⁷¹ via intermediate fluoroxenon esters **26**.

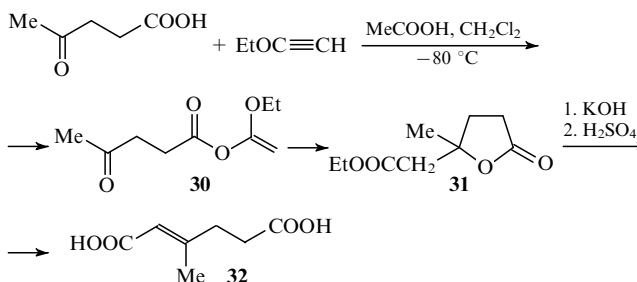


Studies of anodic electrolytic decarboxylation of LA under conditions of the Kolbe reaction have established interesting synthetic possibilities. In methanol, at a potential difference of 80–129 V and 2–3 A in the presence of sodium methoxide, LA was converted into octane-2,7-dione (**27**).⁷² Cross-decarboxylation in the presence of other carboxylic acids results in unsaturated ketones **28**⁷³ and higher aliphatic oxo acid esters **29**.^{74,75}



(a) $\text{MeOH}, \text{MeONa}$; (b) $\text{Me}-\text{CH}=\text{CH}-\text{COOH}$; (c) $\text{HOOC}(\text{CH}_2)_n\text{COOMe}$, $n = 4, 8, 12$.

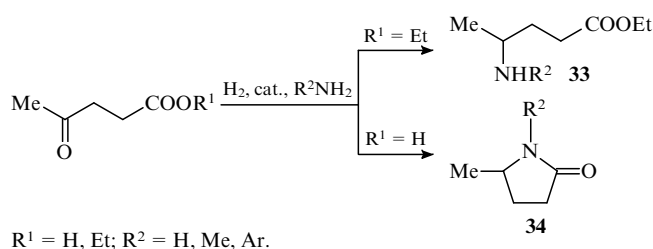
In addition to the above reactions involving the carboxy group of LA, of note is its nucleophilic addition to alkoxyacetylenes.⁷⁶ The addition product **30** is unstable and is easily rearranged into the lactone **31** which ultimately yields 3-methylhex-3-enedioic acid (**32**).



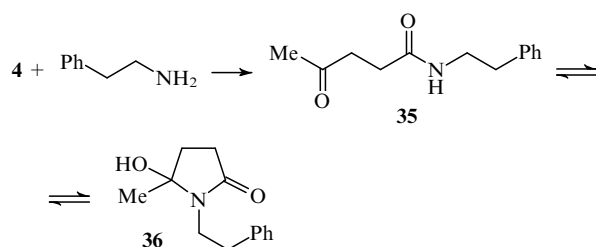
V. Reactions involving the carbonyl group

1. Reactions with N-nucleophiles

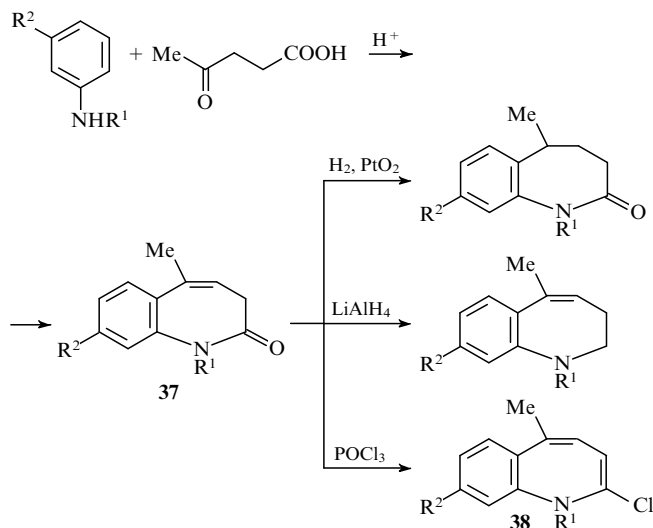
The presence of two highly reactive functional groups in the LA molecule determines its specific properties. Reactions of LA with nitrogen-containing nucleophiles provide an illustrative example. As a rule, reactions of LA with such nucleophiles are not terminated by their addition to the carbonyl group or the formation of the corresponding amide but result in heterocyclisation. For example, the carbonyl group of LA undergoes the Knoop–Oosterlin reductive amination.⁷⁷ This reaction is catalysed by Co, Ni and Pd and gives either the corresponding amino acids **33**,⁷⁸ or 5-methyl-2-pyrrolidone derivatives **34** as a result of cyclodehydration, depending on whether the carboxy group of LA is protected or not.^{79,80}



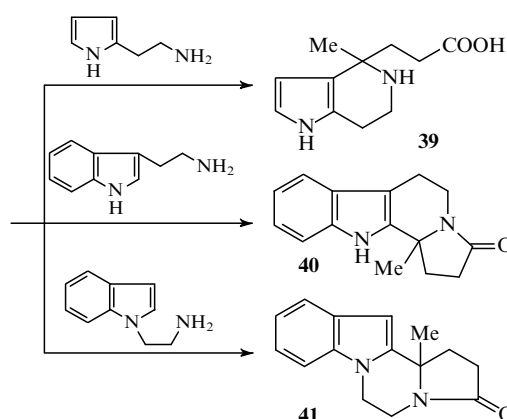
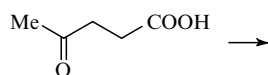
The amides formed by the reaction of LA with various amines are attractive not only because of their biological activity,⁸¹ but also because of their ability for cyclisation. Thus the amide **35** formed in the reaction of phenethylamine with α -angelicalactone (**4**) is unstable and is at equilibrium with the corresponding pyrrolidone **36** (the **35**:**36** ratio is 1:2).^{82, 83}



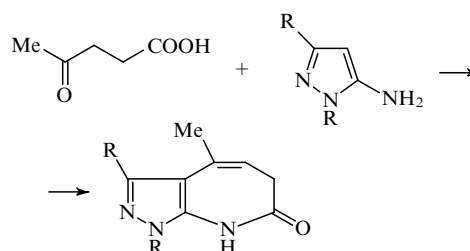
Reactions of anilines with LA or the lactone **4** in acidic media yield reactive benzoazepinone derivatives **37** rather than anilides.^{84, 85} The direction of their hydrogenation depends on the nature of the reagent used. Thus hydrogenation with hydrogen over PtO_2 results in saturation of the C(4)=C(5) bond of the azepine ring, whereas treatment of the benzoazepinones **37** with LiAlH_4 results in the reduction of the oxo group to the methylene group. Treatment of compound **37** with POCl_3 gives the chloro-substituted benzoazepine **38**.



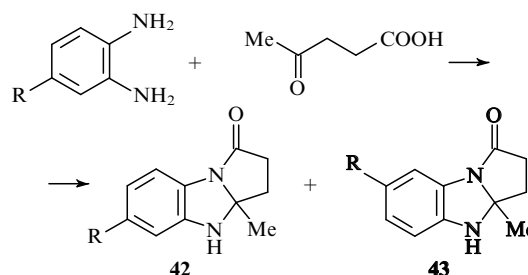
The result of the reaction of LA with pyrrole derivatives containing the 2-aminoethyl group depends on its position in the ring. Thus the reaction of LA with 2-(2-aminoethyl)pyrrole gives the 1*H*-pyrrolo[3,2-*c*]pyridine derivatives **39**.⁸⁶ A similar reaction of LA with 3-(2-aminoethyl)indole (tryptamine) or *N*-(2-aminoethyl)indole leads to the formation of fused heterocyclic systems **40** and **41**, respectively.^{87, 88}



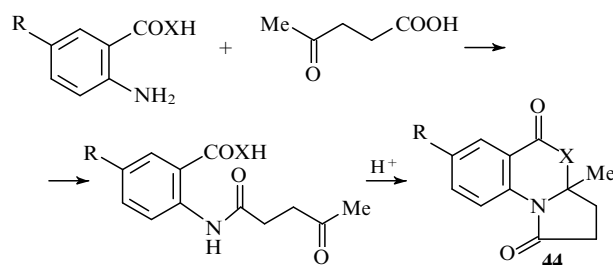
The reaction of LA with 5-aminopyrazoles gives substituted 4-methyl-6*H*-7,8-dihydropyrazole[3,4-*b*]azepin-7-ones.⁸⁹



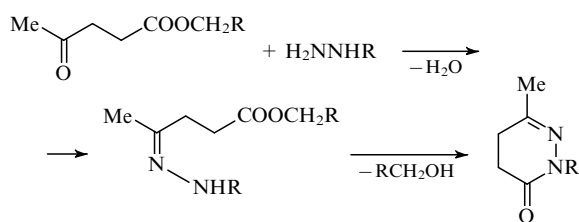
The reaction of LA with *o*-phenylenediamine derivatives results in the formation of the benzoimidazole ring and yields isomeric pyrrolobenzoimidazolones **42** and **43**.⁹⁰



Substitution of an amide group for an amino group in the aromatic component of this reaction affords other types of heterocyclic derivatives. Thus anthranilic acid and its amides react with LA to give fused heterocyclic systems, *e.g.*, 2,3,3*a*,4-tetrahydropyrrole[1,2-*a*]quinazoline-1,5-diones **44** from anthranilamides.^{91, 92}

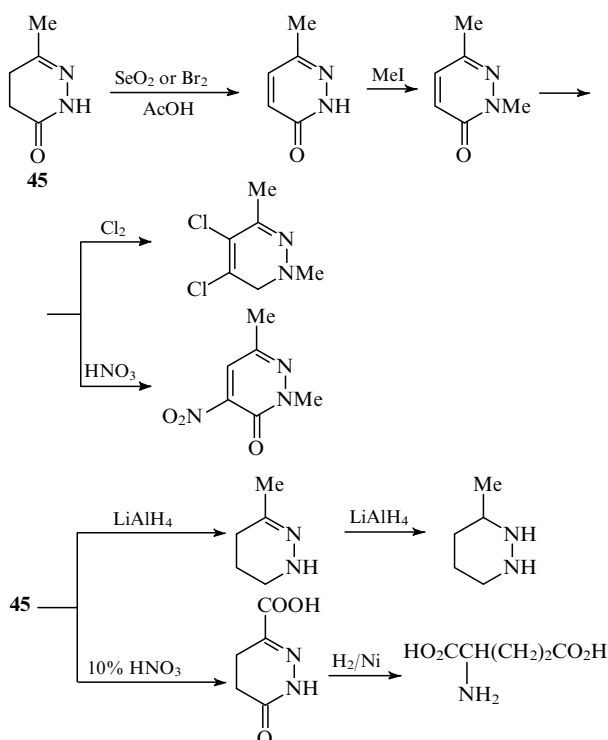


As noted above, LA and its esters readily react with hydrazine and its derivatives to give the corresponding hydrazones. Dihydropyridazinones^{93–96} possessing analgesic and diuretic activities are formed from hydrazine and its monosubstituted hydrazones upon cyclodehydration.⁹⁷

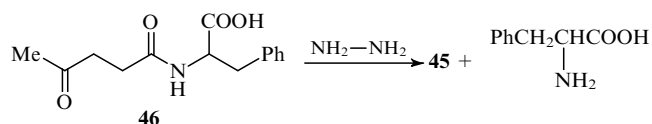


R = H, Alk, Ph, *p*-MeC₆H₄, *p*-EtOC₆H₄.

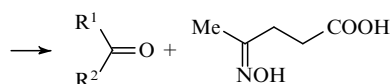
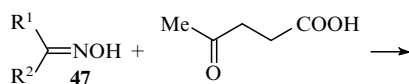
Dihydropyridazinones are highly reactive compounds and can be used in organic synthesis. Using compound **45** as an example, it was demonstrated that dihydropyridazinones are easily oxidised with bromine or SeO₂ to the corresponding pyridazinones^{93,94} and reduced with LiAlH₄ first to tetrahydropyridazines⁹⁵ and then to hexahydro derivatives.⁹⁸ Pyridazinones undergo alkylation, nitration and chlorination.⁹⁹ Compound **45** was also used to obtain glutamic acid *via* the intermediate pyridazinone-3-carboxylic acid.¹⁰⁰



The formation of the dihydropyridazinone ring upon treatment of levulinamide with hydrazine illustrates the possibility of nonenzymic hydrolysis of the peptide bond. This is exemplified by reaction of *N*-levulinoyl-L-phenylalanine (**46**) with hydrazine.¹⁰¹

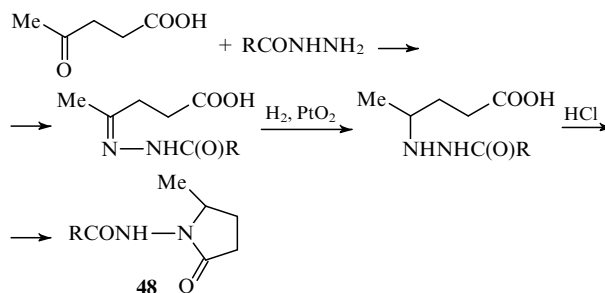


LA reacts very easily with 2,4-dinitrophenylhydrazine. This circumstance was used in the development of a semi-quantitative colorimetric procedure for determination of hydrazones. This method is based on the ability of LA to serve as an acceptor of 2,4-dinitrophenylhydrazine and to regenerate the ketone from the corresponding hydrazone as a result of the exchange reaction.¹⁰² It was noted also that treatment of the oximes **47** with LA recovers carbonyl derivatives.¹⁰³



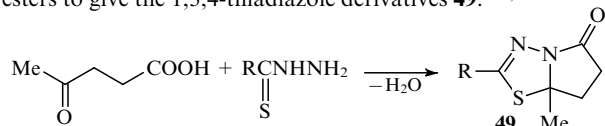
R¹ = Me, R² = Ph; R¹ = Ph, R² = H; R¹ = R² = Ph.

LA hydrazones manifest noticeable antibacterial activity.^{104–106} They also serve as a source of *N*-substituted pyrrolidones. The reaction between LA and hydrazides of nicotinic or isonicotinic acids demonstrates an approach to the synthesis of *N*-acyl pyrrolidones **48**.¹⁰⁷

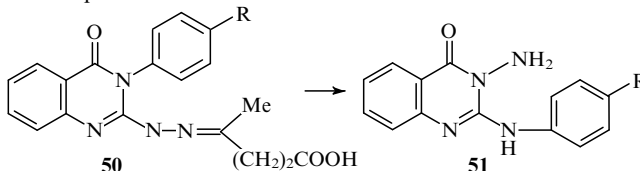


R = 3-pyridyl, 4-pyridyl.

Unlike acylhydrazines, their thio analogues react with LA or its esters to give the 1,3,4-thiadiazole derivatives **49**.^{107, 108}

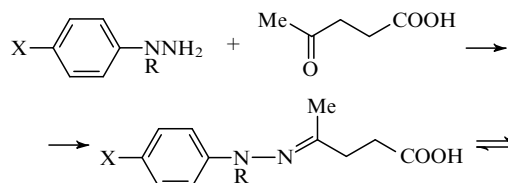


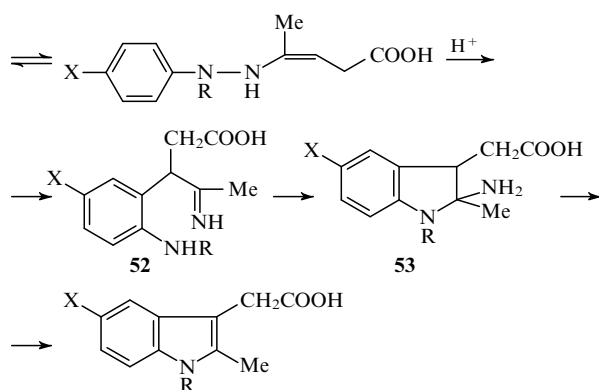
The hydrazones **50** prepared from LA and 3-aryl-2-hydrazinoquinazolinones are thermally unstable and undergo the Dimroth rearrangement at melting temperature with simultaneous cleavage of the imine bond, eventually resulting in 3-amino-2-anilinoquinazolinones **51**.¹⁰⁹



The role of LA arylhydrazones in the Fischer indole synthesis has been studied in most detail, since this reaction gives an access to not only heteroauxin analogues manifesting growth-regulating activity¹¹⁰ but also to a broad range of antiinflammatory drugs, such as indometacin [1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-ylacetic acid].¹¹¹ Halogen-, alkyl- and alkoxy-substituted arylhydrazines,^{112,113} 1-naphthylhydrazine¹¹⁴ and various *N*-acyl-*N*-arylhydrazines enter into this reaction.^{115–120} Sodium arylhydrazinesulfonate can be used instead of phenylhydrazine hydrochloride which is unstable on storage.^{121, 122}

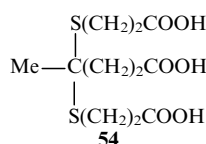
The mechanism of this reaction was studied with LA as an example. It was found that hydrazone rearrangement, which is probably similar to the Claisen rearrangement of allyl phenyl ethers, is the key stage. The key intermediate of the imine type, *viz.*, compound **52**, which gives the intermediate **53** upon heterocyclisation, was studied by ¹³C NMR spectroscopy.¹²³



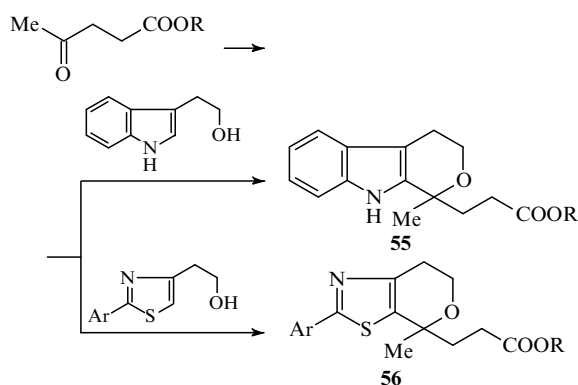


2. Reactions with O- and S-nucleophiles

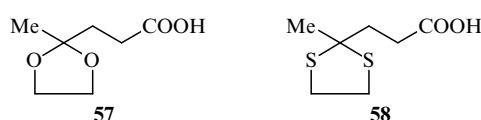
Under conditions of acid catalysis, LA esters react easily with alcohols and thiols to give the corresponding dialkylacetals and dialkyldithioacetals in more than 90% yields.¹²⁴ Special mention should be made of compound **54** formed in the reaction of LA with 3-mercaptopropionic acid, which can selectively extract some metal cations.¹²⁵



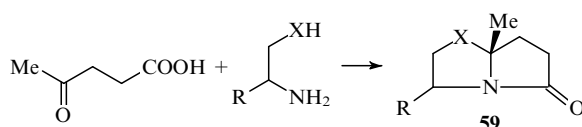
The reaction of LA with thiazolyl- and indolyethanols gives the fused tetrahydropyrans **55** and **56**.^{126, 127}



The reaction of LA or its esters with 1,2-diols or dithiols gives dioxolanes and dithiolanes.^{128, 129} As is known, the formation of such structures is often used to protect the carbonyl group. This approach is also used in multistage syntheses involving LA. Thus the 1,2-dioxolane (**57**) and 1,3-dioxolane (**58**) derivatives of LA were used to protect its carbonyl group in the syntheses of a natural pheromone,¹³⁰ Z-jasmone and dihydrojasmone.^{131–133}



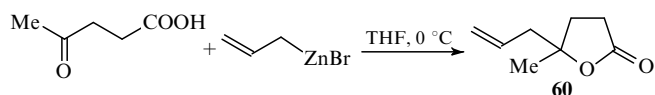
The presence of an amino group in the α -position with respect to the hydroxy or the mercapto group in amino alcohols or amino thiols makes it possible to carry out heterocyclisation on their reactions with LA^{134, 135} to give the bicyclic lactams **59**.



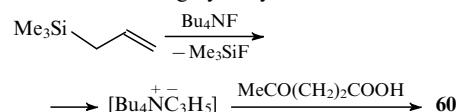
R = COOH, CHMe₂; X = O, S.

3. Reactions with organoelement compounds

The carbonyl group is capable of nucleophilic addition of organometallic compounds. However, this reaction is often complicated due to involvement of the carboxy group. γ -Valerolactone derivatives^{136–140} are formed instead of the expected hydroxy acid derivatives even in reactions of organometallic derivatives of group I and II elements with levulinates with the protected carboxy group. Thus the reaction of LA with allylzinc bromide gives 5-allyl- γ -valerolactone (**60**) in 80% yield.¹³⁹

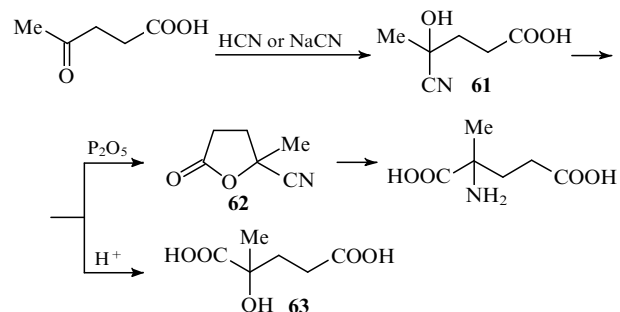


The allyl carbanion formed *in situ* as a result of hydrolysis and scission of the Si–C bond in allyltrimethylsilane under the action of tetrabutylammonium fluoride adds to LA to give the γ -valerolactone **60** following hydrolysis of the intermediate product.¹⁴¹

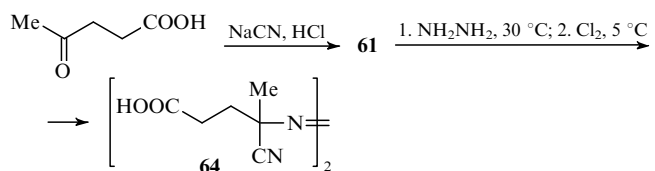


Nevertheless, allylation of LA and its esters to the corresponding derivatives of 4-hydroxyvaleric acid can be achieved with allyl bromide in the presence of metallic Zn, Sn and Al^{142, 143} as well as alkyl complexes of transition metals.¹⁴⁴ The pseudo-Barbier reaction involving ethyl levulinate and alkyl halides in the presence of samarium cyclopentadienyl complexes is also possible.¹⁴⁵

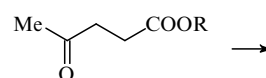
The reaction of LA with metal cyanides and hydrocyanic acid gives the cyanohydrin **61**.¹⁴⁶ The latter yields 5-cyano- γ -valerolactone (**62**) under the action of dehydrating reagents; its hydrolysis gives 2-hydroxy-2-methylglutaric acid (**63**). The lactone **62** can also be converted into 2-methylglutamic acid.¹⁴⁷

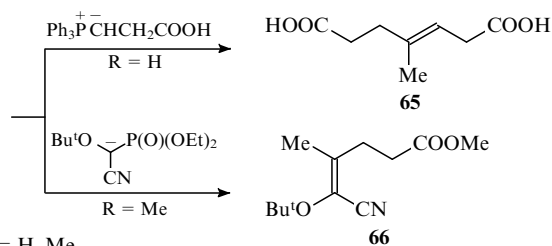


The reaction of the cyanohydrin **61** with hydrazine followed by oxidation gave the azo compound **64**, which is an initiator of radical reactions.^{148, 149}

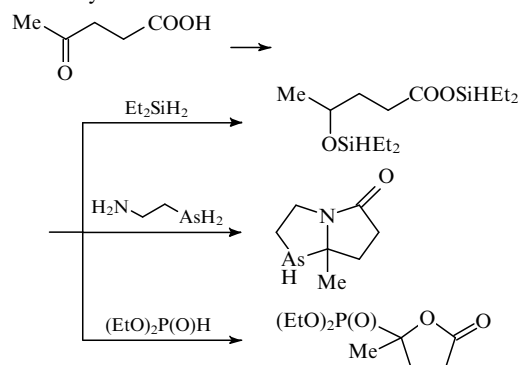


The carbonyl group of LA or its esters reacts with phosphorus-substituted carbanions^{150, 151} in the Wittig and Horner–Emmons reactions to give compounds **65** and **66**.

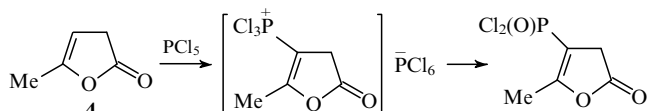




Hydrides of group IV and V elements also easily add to the carbonyl group of LA. Hydrosilylation in the presence of rhodium complexes with chiral ligands occurs as enantioselective reduction.^{152, 153} However, unlike diethylsilane, which gives a stable silylation product,¹⁵⁴ hydride derivatives of arsenic and phosphorus yield unstable addition products that easily undergo intramolecular cyclisation.^{155, 156}

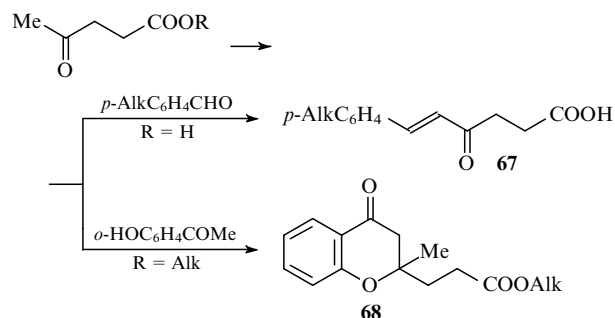


The result of the reaction of halides of group V elements with LA depends on the nature of the halide. As would be expected, bismuth and antimony halides yield predominantly acyl derivatives,^{157, 158} whereas the reaction with MeNbCl₄ results in the chlorination of the carbonyl group of LA.¹⁵⁹ The same result is observed in the interaction of LA with phosphorus pentachloride.¹⁶⁰ However, the reaction of PCl₅ with α -angelicalactone (4) leads to phosphorylation of the multiple bond.¹⁶¹



4. Condensation reactions

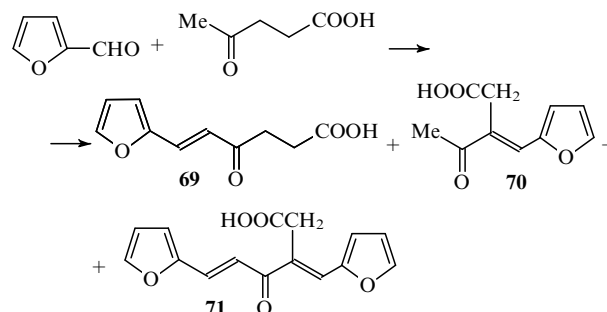
Aldol condensation of LA with aromatic and heterocyclic aldehydes under conditions of the Claisen reaction gives α,β -unsaturated carbonyl compounds and their derivatives. Benzaldehyde and its analogues easily enter into the condensation reaction to give 6-aryl-4-oxohex-5-enoic acid (67),^{162–164} while the reaction of LA esters with 2-hydroxyacetophenone yields the 2-substituted chromone 68.^{165–167} It is believed¹⁶⁸ that this reaction proceeds *via* the lactone intermediate by the Stobbe condensation.



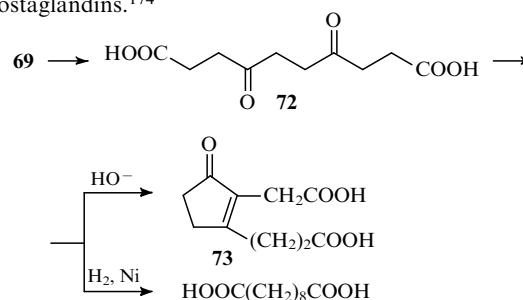
Since the unsaturated acids 67 thus formed are γ -oxo acids, they retain ability to form pyridazinones on reaction with hydra-

zine. Pyridazinones can undergo bromination and yield pyridazines.¹⁶⁹

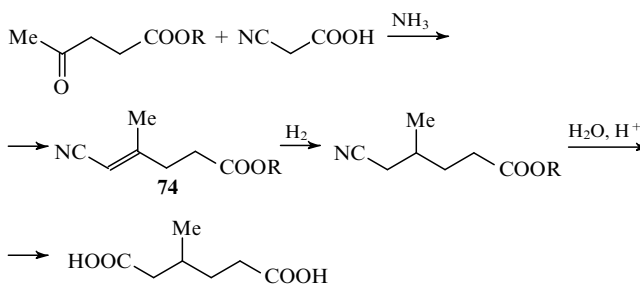
Condensation of LA with furfural offered even broader possibilities for the synthesis.^{170–175} This reaction can yield diverse furancarboxylic acids. 5-Furfurylidenelevulinic acid (69) is the main reaction product at room temperature. However, at a temperature above 50 °C, the proportion of 3-furfurylidene- (70) and 3,5-difurfurylidenelevulinic acids (71) increases.¹⁷³



Acid treatment of the acid 69, *i.e.*, the main reaction product, gives dilevulinic acid 72; its reduction on a Raney nickel catalyst yields sebacic acid,¹⁷¹ and its cyclisation results in the dicarboxylic acid 73, which served as the starting compound in the synthesis of prostaglandins.¹⁷⁴

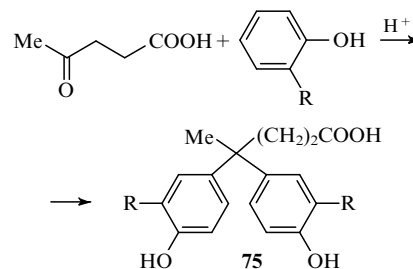


Condensation of LA or its esters with cyanoacetic acid under conditions of the Knoevenagel reaction yields the nitriles 74. The latter were used to obtain 3-methyladipic acid by reduction of the double bond and acid hydrolysis.¹⁷⁶



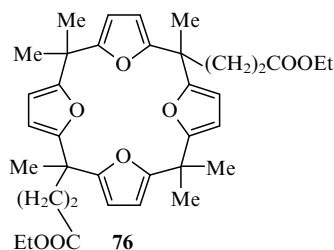
$\text{R} = \text{H, Me, Et, CH}_2\text{Ph.}$

Like aldehydes and ketones, LA undergoes acid-catalysed condensation with phenols and naphthols to give the 4,4-diaryl-substituted valeric acids 75.^{177–180}

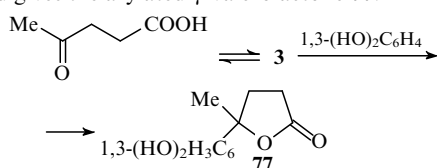


$\text{R} = \text{H, Me.}$

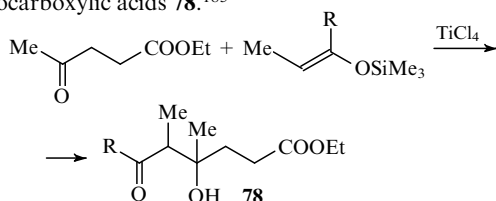
Furan and its derivatives react analogously.^{181–183} Conjugate condensation of furan with acetone and LA or its esters makes it possible to obtain macrocycles of the type **76**, which can selectively extract metal ions similarly to crown ethers.



The reaction of LA with resorcinol occurs in a different way and gives the arylated γ -valerolactone **77**.¹⁸⁴



In the reaction of LA esters with enol silyl ethers in the presence of equivalent quantities of TiCl_4 , cross-aldol condensation occurs smoothly to yield esters of 4-hydroxy-4,5-dimethyl-6-oxocarboxylic acids **78**.¹⁸⁵



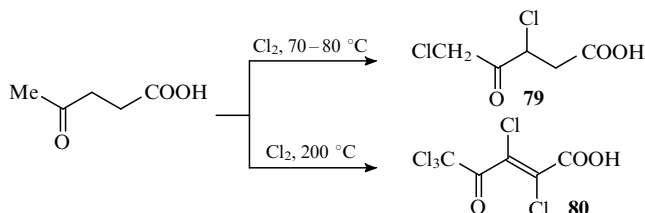
R = Alk.

A similar reaction takes place in the condensation of LA with chlorodifluoromethyl ketones.¹⁸⁶

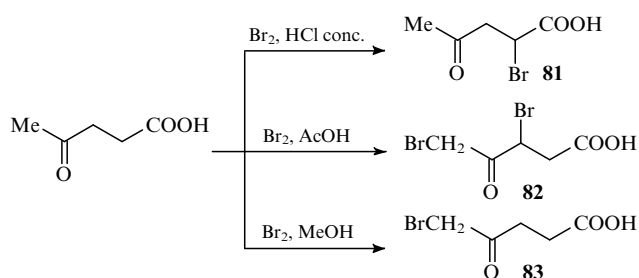
VI. Reactions involving the methyl and the methylene groups

The carbonyl and the carboxy groups of LA activate the neighbouring carbon atoms. Therefore, LA undergoes easy chlorination and bromination. These reactions yield organic halides which represent valuable 'building blocks'.

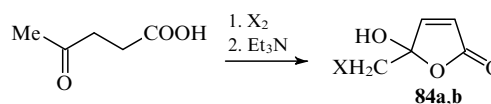
Chlorination of LA with chlorine at moderate temperatures results in 3,5-dichlorolevulinic acid (**79**).¹⁸⁷ With a rise in temperature or in the presence of Lewis acids, more profound chlorination takes place to give 2,3,5,5,5-pentachloro-4-oxopentenoic acid (**80**),^{188–191} which can be used as defoliant.



The result of bromination of LA strongly depends on the medium in which the reaction is performed. By varying the solvent, one can obtain different bromo derivatives of LA with sufficiently high selectivity. Thus bromination in the presence of concentrated HCl gives predominantly 2-bromolevulinic acid (**81**),¹⁹¹ whereas in acetic acid 3,5-dibromo-derivative **82** is obtained.¹⁹² In methanol, the reaction results in regioselective bromination of LA at the methyl group to give 5-bromolevulinic acid (**83**).¹⁹³

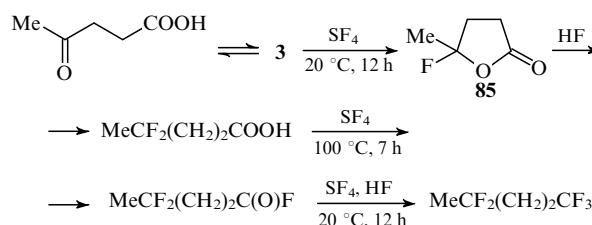


Combination of halogenation and dehydrohalogenation of LA affords halogen-containing hydroxyfuranones **84a,b**.^{194, 195}



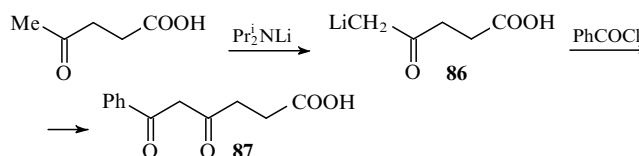
X = Cl (**a**), Br (**b**).

Sulfur tetrafluoride^{196–198} and its derivatives¹⁹⁹ are the most effective fluorinating agents for LA. However, this does not involve the methyl and the methylene groups. It was shown that the lactone **3**, which is always present in a solution of LA, is the first to undergo fluorination. The latter is converted into 1,1,1,4,4-pentafluoropentane through the intermediate **85**.



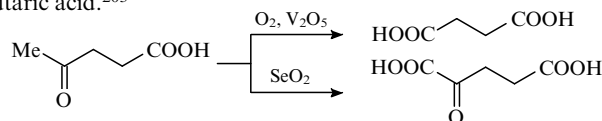
Ethyl levulinate undergoes fluorination only at the carbon atom of the carbonyl group under these conditions.²⁰⁰

The methyl group of LA is active in the metallation reaction. Thus treatment of LA with lithium diisopropylamide gives the organolithium compound **86** which, in turn, yields 6-phenyl-4,6-dioxohexanoic acid (**87**) in the reaction with benzoyl chloride.²⁰¹

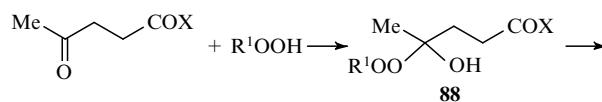


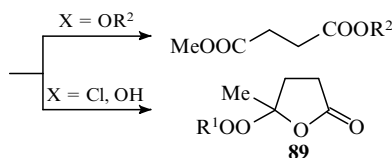
VII. Oxidation and reduction reactions

The result of oxidation of LA strongly depends on the type of the oxidant. High-temperature oxidation of LA with oxygen over V_2O_5 gives succinic acid²⁰² and oxidation of LA with selenium dioxide under conditions of the Riley reaction results in 2-oxoglutaric acid.²⁰³



Oxidation of LA and its derivatives with peroxy compounds in the Baeyer–Williger reaction has been studied.^{204–207} The first step of this reaction yields hydroxyperoxyvaleric acid derivatives **88**, which rapidly cyclise to peroxyvalero- γ -lactones **89**. If the carboxy group is protected, succinates are formed.

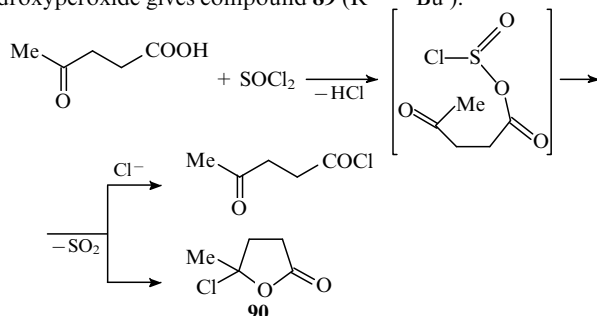




Reduction of LA can be carried out by various methods. First, mention should be made of catalytic hydrogenation of LA and its esters on Raney nickel. The free acid is quantitatively converted into γ -valerolactone,²⁰⁸ while its esters are reduced to 4-hydroxyvaleroates.²⁰⁹ Analogous products are obtained upon hydrogenation of LA and its esters on a copper–chromium catalyst (CuO, 80%; Cr₂O₃, 20%).²¹⁰ Modification of hydrogenation catalysts with optically active substances (L-alanine, L-phenylalanine, L-glutamic acid, D-tartaric acid) allowed one to accomplish asymmetric synthesis of γ -valerolactone from LA.^{211–213}

Under conditions of reductive cyclisation, LA and its esters serve as starting compounds in the synthesis of different saturated lactones, e.g., 5-substituted butyrolactones.^{214–216} Thus the optically active γ -valerolactone is obtained in good yield by reduction of LA with silanes in the presence of rhodium catalysts with chiral ligands.²¹⁷

The reaction of LA with SOCl₂ gives the saturated lactone **90** in addition to levulinoyl chloride. This reaction is believed to occur according to the mechanism depicted in the scheme given below.²¹⁸ The yield of compound **90** can reach 100%.²¹⁹ Apparently, the formation of 5-methoxy- γ -valerolactone in the reaction of LA with methyl chloroformate occurs in a similar way.²²⁰ The halogen atom in compound **90** is rather mobile. Thus the reaction of the lactone **90** with equimolar amount of 90% *tert*-butyl hydroxypoxide gives compound **89** (R¹ = Bu¹).²²¹



The reaction of LA with sodium dithionite in boiling aqueous dioxane also gives γ -valerolactone. It is believed²²² that this reaction occurs through the formation of α -hydroxysulfonates. For catalytic hydrogenation of the oxo group of LA catalysed by ruthenium and rhodium complexes see Refs 223 and 224.

More profound reduction of LA derivatives to diol or valeric acid is also possible. Thus reduction of LA with lithium aluminium hydride gives racemic pentane-1,4-diol,²²⁵ while electrochemical reduction of LA under conditions of catholyte recirculation and membrane separation of anolyte gives valeric acid.²²⁶ Bakers yeast reduce LA esters to 4-hydroxyvalerates in good yields and then to (*R*)- γ -valerolactone and (*S*)-pentane-1,4-diol.²²⁷

VIII. Conclusion

Thus, easy access to LA from natural renewable raw materials makes this acid a readily available starting compound for the synthesis of 1,4-dicarbonyl systems the synthetic approaches to which are limited.²²⁸

On the one hand, LA enter into miscellaneous reactions of nucleophilic addition of N-, O-, S- and C-centred nucleophiles at the oxo group; on the other hand, it undergoes classical transformations characteristic of carboxylic acids. Moreover, LA as a typical representative of γ -oxo carboxylic acids reacts with involvement of both functional groups at once. This permits the

synthesis of various types of heterocyclic compounds on the basis of LA, e.g., pyrrolidone, benzoazepinone, indole and chromone derivatives.

It is noteworthy that the presence of an electron-acceptor carbonyl group in the LA molecule strongly increases the acidity of the protons at C(3). Their mobility favours the alkylation and halogenation of the LA molecule as well as its lactonisation.

Owing to the accessibility of LA, the methods for synthesis of various compounds based on it efficiently compete with alternative synthetic approaches.

In addition, both LA and its derivatives possess various useful properties which significantly expand the range of their ever increasing synthetic applications. Thus levulinic acid is used to control plant growth.²²⁹ Being an inhibitor of choline photolysis,²³⁰ LA can inhibit or stimulate chlorophyll synthesis.²³¹ It is used as a modifying additive to resins based on furfuryl alcohol,²³² modifies the surface of aminoaerosols,²³³ confers radiation-protective properties to polymers²³⁴ and is used for scheelite flotation.²³⁵ Its esters and salts are used in the food industry^{236–240} as preservatives, stabilising and flavouring agents as well as in the manufacture of cosmetics^{241–246} and in medicinal practice.^{247–250} LA esters as additives increase thermal stability of poly(vinyl chloride)²⁵¹ and improve the characteristics of motor fuels,²⁵² while glycol esters are perfect plasticisers.^{41, 61, 253} Compounds synthesised from LA are used as corrosion inhibitors,²⁵⁴ initiators of radical polymerisation,^{148, 149, 255–257} cross-linking reagents²⁵⁸ and components of liquid crystals.^{259, 260}

There is no doubt that LA may be used as one of the components in the elaboration of an alternative source of raw materials in organic synthesis.

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Chemistry on the border of two centuries — achievements and prospects[†]

A L Buchachenko

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Abstract. Chemistry is on the threshold of a new flight; new ideas and lines of research are originating now; new directions arise, which form a new face of chemistry. The bibliography includes 79 references.

I. Introduction

Chemistry ultimately formed as a fundamental science only in the early XXth century when it got a reliable and solid physical basis made of three main concepts of quantum mechanics, namely

- the Schrödinger equation, which is the quantum successor of the classical mechanics equations (Hamilton–Jacobi equations);
- Pauli's exclusion principle, which governs the distribution of electrons among spin states and energy levels and
- wave function, which carries information on the charge and spin distribution.

It is these concepts that have imparted physical meaning to the D. I. Mendeleev Periodic Table, an outstanding discovery of the XIX century the significance of which goes far beyond chemistry. From the viewpoint of these three concepts, a chemical reaction should be regarded as a physical process involving rearrangement of electron shells and nuclei.

The understanding and realisation of the significance of these quantum-mechanics principles for chemistry makes chemical science clear and predictable as regards its main features; they give rise to the diversity and richness as well as to the elegant logic and beauty of chemistry.

In the XX century chemistry became an exact science; many quantitative regularities and precise laws have been established (including the 'electron periodicity' of the Mendeleev law); a very high metrological level of determination of atomic, molecular,

thermodynamic and kinetic constants, characterising both substances and chemical processes, has been attained.

During this century, chemistry has developed into a branched science. Nowadays, many fields of chemistry exist as separate branches of science — inorganic, organic and physical chemistry; radiochemistry, biochemistry, analytical chemistry, geochemistry, *etc.* Each of them has its own subject and the scope of investigations as well as its own problems and experimental techniques. However, by the 80s, the professional separation of the chemistry branches has started to be replaced by attempts to tackle jointly the general fundamental problems of chemical science.

The first attempt to identify the most important 'integration' lines in chemistry was made in a paper by Legasov and Buchachenko,¹ in which chemistry was classified at a new level. The chemical science was structured according to the targets and problems rather than according to the names of various 'chemistries,' which now number more than four dozen. This classification follows the logic inherent in chemistry, which does not separate chemistry into 'chemical counties' but instead organises it as a unified science and also unites chemists as a community.

Nowadays, at the end of the XXth century, the classification proposed in the publication mentioned above¹ has not changed much, and the hierarchy of general problems of chemistry can be presented as follows.

- the art of chemical synthesis;
- chemical structure and function;
- control of chemical processes;
- chemical materials science;
- chemical technology;
- chemical energetics;
- chemical analytics and diagnostics;
- chemistry of living matter.

These are the main 'arterial roads' which direct the development of modern chemistry and reflect its achievements and progress.

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[†] This paper is an extended version of the report presented by the author at the General Meeting of the Division of General and Technical Chemistry of the Russian Academy of Sciences and at the XVIth Mendeleev Congress on General and Applied Chemistry (St. Petersburg, 1998).

Chemical synthesis is the key direction in the development of chemistry and the source of all its treasures. This route makes chemistry the most constructive branch of science. Chemistry provides other branches of science and industry with materials; in this sense, one can say that it stands in the middle of natural sciences. It is especially intriguing that, despite the existence of theoretical principles of chemical synthesis, there still remains scope for the freak of imagination and intuition. This brings chemical synthesis closer to an art.

The atomic and molecular architecture and the electronic structures of newly synthesised compounds are infinitely diverse, so are their physical and chemical properties and, therefore, functions. The relationship between the structure and functional behaviour of a substance is the subject of the second line of research.

The control of chemical processes and their molecular mechanisms and the use of chemical factors (complex formation, solvation, molecular organisation, catalysis) and physical treatment (ranging from light to mechanical treatment) for controlling chemical processes constitute the essence of the third line.

A substance is not a material yet but only the precursor of a material. People have to 'teach' substances to work as materials and to estimate their operation characteristics and ranges of applicability. These are the tasks of the *chemical materials science*.

The aim of *chemical technology* is to design, optimise and scale a technological process as well as to ensure its low energy expenditures and safety and to make it environmentally clean.

The development of efficient ways of transformation of chemical energy into other kinds of energy, accumulation of energy in energy-storing substances and materials (including lasers with chemical and solar pumping), transformation of solar energy, chemical cells and coupling of energy-producing and energy-consuming processes constitute the subject of *chemical energetics*.

The progress in chemical materials science and chemical technology would be impossible without reliable *chemical analytics and diagnostics*. This is a vigorously developing line of research (which includes chemical sensors and the chemistry of odour) having links to lots of branches, ranging from technical monitoring systems to medicine or ecology.

There is no question that all these lines of research are related not only logically. They are intrinsically connected by the methodology of chemical research itself — elements of several lines can be found in a good scientific article. The remarkable combination of differentiation and integration makes up the efficient and creative style of modern chemistry.

Finally, the *chemistry of living matter* is an enormous chemical galaxy, which is still to be explored. It assimilates the results of biochemistry, chemistry of natural products, phytochemistry, enzyme science, medical and pharmaceutical chemistry, genetic engineering, biotechnology and many other fields of chemistry. This line of research is associated with great expectations; it undoubtedly possesses an exceptionally high potential, indisputable prospects and a highly promising future. Even today, its outlines and significance can be traced by looking at the transgene technology.

II. Novel chemical structures and materials

Each arterial road of chemistry has its own events and discoveries, which can be both regular and unexpected. However, the most significant events still occur in the first, key arterial road. Development of methods for the synthesis and design of new substances and materials are the main goals of chemistry. It should be noted that the number of compounds that have been created chemically (artificially and skilfully) is permanently increasing. The molecular architecture of newly formed compounds is infinitely variable and fabulously abundant. For example, the following unusual structures have been obtained: rhombic molecules — structural units of one-dimensional metals; proton

'sponges' and 'tubes' (molecularly organised proton-carrying reservoirs and channels); toroidal molecules; polymetal rotaxanes; catenanes; crowns and anticrowns, capable of separating cations and anions; hypervalent radicals such as NH_4 , CH_5 , H_3O , some of which are long-lived species, for example, $(\text{CH}_3)_2\text{NH}_2$ (lifetime $\sim 3 \mu\text{s}$);² high-spin molecules containing tens of unpaired electrons within a single species [for example, the complex $\text{Mn}_6^{2+}(\text{R}_2\text{NO})_6$ has 36 unpaired electrons]; multi-deck polyaromatic molecules; molecules with large numbers of chiral centres, etc. Some of the compounds obtained artificially may remain exotic species for good, but some others would trigger new lines of research.

The adoption of new principles of radial synthesis in which molecules unite according to the fractal pattern to give an enormous molecule, *dendrimer*, has been an important event in chemistry. Nature has used this principle to produce glycogen, amylopectin and some other polysaccharides and proteins. Many remarkable discoveries have been made in the chemistry of dendrimers, especially in the polymer chemistry.³ The architectures of dendrimer structures are virtually infinite; the same is true for their functions and applications. In particular, it has been predicted that dendrimers based on polyconjugated molecules could serve as energetic antennas collecting the energy of optical (including solar) excitation and transforming it into photoelectric current.

Impressive results have been attained in the synthesis of organometallic polymers. The preparation of ladder, tape and rod-like organometallic polymers can be formally classified as 'one-dimensional' or 'two-dimensional' radial synthesis. Thus Fig. 1 shows two projections of an unusual organometallic ladder polymer $[(\text{CuL}_2)\text{PF}_6]_\infty$, prepared by polymerisation of 2,7-diazapyrene (L) and $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ in the MeCN–PhCN system.⁴ It can be seen from the Figure that a monomer unit of this polymer is

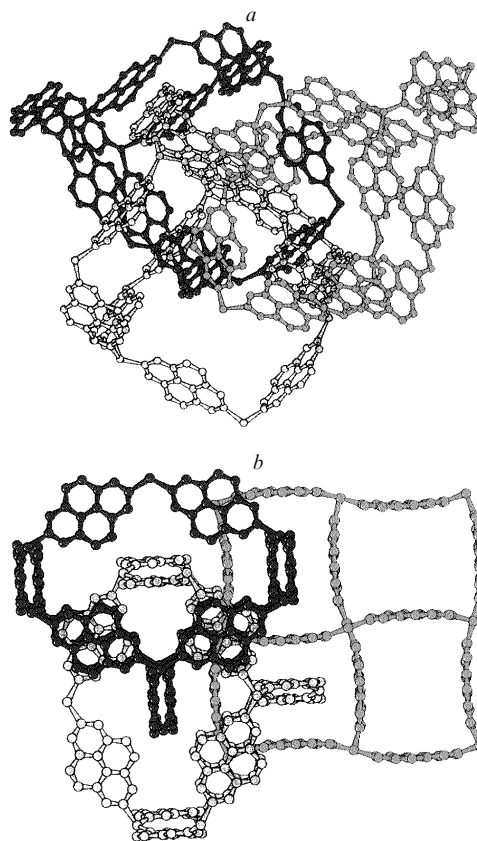


Figure 1. Two projections of the organometallic ladder-type polymer $[(\text{CuL}_2)\text{PF}_6]_\infty$ (L = 2,7-pyrene) with polycatenane and adamantane structural units.⁴

formed by three interpenetrating adamantane networks arranged at angles of 90° relative to one another. Examples of three-dimensional organometallic dendrimers have been reported (see below).

The discovery of *superconducting ceramics* has stirred up not only physicists and engineers but also chemists. These compounds had been prepared well before their superconducting properties were discovered, but it was this intriguing and unexpected feature of ceramics that aroused most enthusiasm and hope. The achievements in this field proved to be modest compared to the expectations; although the progress along this line has now substantially slowed, some pleasant surprises are still possible (note the startling publication⁵ dealing with superconductivity of inorganic compounds at room temperature, the value of which is still unclear). It is about this type of situation that Niels Bohr said that problems are more important than solutions. In fact, solutions can become obsolete to leave the problems, which stimulate the search for new solutions.

After a great number of paramagnetic organic compounds (stable radicals and high-spin molecules) had been synthesised, attempts to prepare *molecular ferromagnets* were undertaken. The principle of design of organic ferromagnets had been formulated long before they were discovered in 1989.^{6,7} The exchange interaction of the unpaired electrons in paramagnetic organic molecules is known to be negative; it accounts for the antiparallel arrangement of the magnetic moments of the electrons. It has been suggested that macroscopic ferromagnetism in ferromagnets is attained *via* pairwise antiferromagnetic interactions. This hypothesis immediately received experimental support.⁸

Figure 2 shows the crystal structure of 2-(4-nitrophenyl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazolyl-*N'*-oxyl *N*-oxide.

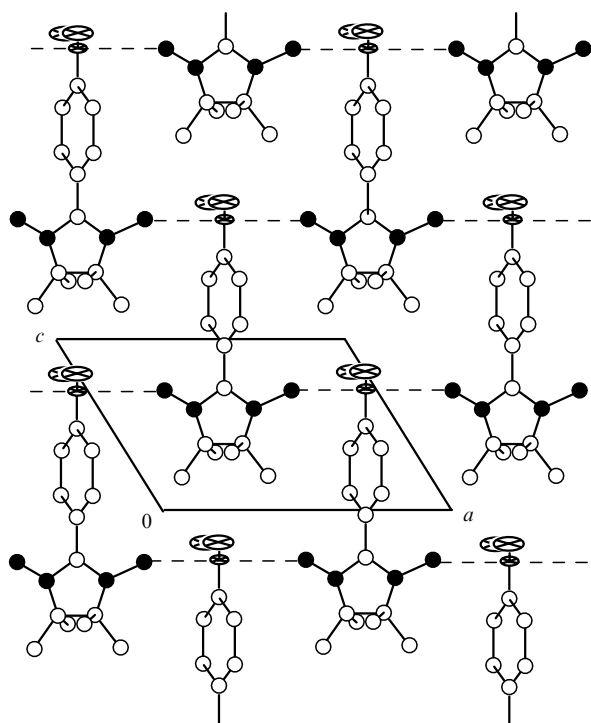
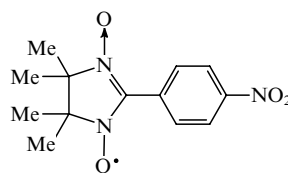


Figure 2. Two-dimensional representation of the crystal lattice of 2-(4-nitrophenyl)-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazolyl-*N'*-oxyl *N*-oxide.

The NO[•] groups (areas with high spin density) are coloured black, while the NO₂ groups (areas with small negative spin density) are designated by crosses.⁸



It can be seen that the nitroxides are arranged in the crystal in such a way that fragments with high spin density (NO[•] groups) are located close to fragments where the spin density is low and negative (NO₂ groups). Owing to the pairwise exchange interaction of the neighbouring spins with positive and negative electron density, spins with positive density align in one direction, while those with negative density align in the opposite direction; this creates macroscopic ferromagnetism in the crystal. This is only one of the numerous examples of organic ferromagnets.⁹

One should not, however, create illusions about this class of compound. The specific spin density and the degree of magnetisation in these substances are very low; correspondingly, the temperatures of ferromagnetic phase transitions are also very low (~ 1 K). Mixed organometallic ferromagnets are more promising (and therefore more attractive). Figure 3 presents the structure of an organometallic ferromagnet, $\{[\text{FeCr}(\text{ox})_3] \cdot (\text{NBu}_4)\}_\infty$ (ox is oxalate anion). The structure consists of the Cr(ox)₃ fragments being joined together by the Fe ions to form a huge ferromagnetic molecule. In the crystal, the compound $\{[\text{FeCr}(\text{ox})_3](\text{NBu}_4)\}_\infty$ has a layered structure.^{10,11}

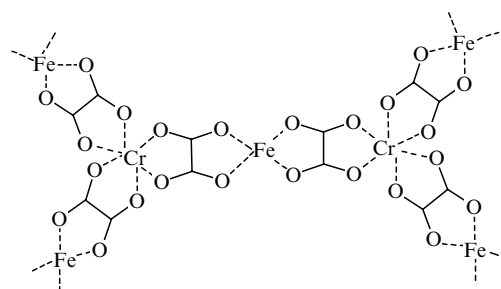


Figure 3. Structure of the organometallic ferromagnet $\{[\text{FeCr}(\text{ox})_3](\text{NBu}_4)\}_\infty$ ($T_c = 12$ K). For the sake of simplicity, the tetra-butylammonium cation is not shown.¹⁰

Fullerenes have become a real treasure for chemistry. The most daring and optimistic forecasts are associated with fullerenes. Fullerenes C₆₀, C₇₀, etc. can be prepared in macroscopic quantities by the arc method. However, the mechanism of their formation still remains obscure. The perception of this fact stimulates experimental and theoretical (molecular dynamics) studies of the formation of fullerenes from atoms, pairs of atoms and clusters under the conditions of gas discharge, plasma, electric arc, etc. The main goal of these studies is to understand the mechanism of polyhedral clustering and the arrangement of atoms to give a fullerene structure (see, for example, Ref. 12). The search for catalysts of this process is also perfectly reasonable. It is beyond doubt that this route would bring both predicted discoveries and godsend.

At present, in addition to traditional chemistry, targeted chemistry of these compounds is in progress. In particular, it is of interest to perform polymerisation of fullerenes with retention of the spherical cage units (*via* cross-linking). According to predictions, these polymers would possess high electron 'capacity,' which would permit them to be used in chemical and storage cells. Thermal polymerisation of the most readily available C₆₀ fullerene is known to be forbidden from the symmetry viewpoint. Therefore, it requires some sort of treatment which would stimulate distortion of the icosahedral symmetry of C₆₀ and

eliminate the prohibition (high pressure,[‡] shear deformations, shock waves, *etc.*). This is a key problem.

Among other lines of research in the targeted chemistry of fullerenes, mention should be made of fullerene modification aimed at producing materials for microelectronics (the easy construction of integral circuits, simple and clean nano-technologies and other advantages) and synthesis of fullerene-based organometallic and organic complexes to be used as superconductors.

Thus it was found that M_3C_{60} and $M_2M'C_{60}$ fullerides ($M, M' = K, Na, Rb, Cs$) exhibit superconducting properties. The compound $RbCs_2C_{60}$ still remains the record holder, $T_c = 33$ K. A remarkable feature of the superconducting fullerides is the dependence of the temperature of superconductivity transition T_c on the crystal lattice parameter (Fig. 4).¹³ This dependence proved to be opposite to that observed for organic superconductors based on tetrathiafulvalene and its derivatives, which were famous in the 60s–70s (for details, see Ref. 1). In the latter case, compression of the crystal lattice by external pressure results in higher T_c values; conversely, in the case of fullerides, compression decreases T_c . This unusual behaviour has stimulated the search for new superconducting fullerides based on the expansion of the fullerene crystal lattice (by intercalation by NaN_3 and NaH , introduction of NH_3 , *etc.*). In particular, the compound $(NaH)_4C_{60}$ obtained by intercalation of C_{60} by NaH exists as two crystal phases, cubic and orthorhombic. The cubic β -phase conducts electricity, while the orthorhombic α -phase does not.¹⁴ Within the framework of the same idea (crystal lattice expansion), synthesis of charge transfer complexes based of fullerenes and tetrathiafulvalene and its derivatives (the latter served as 'bricks' in the construction of organic superconductors) is being developed.

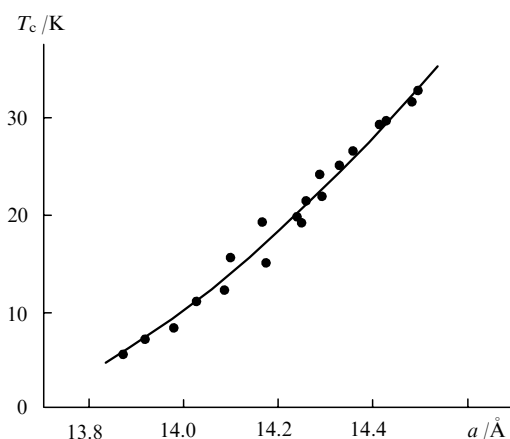


Figure 4. Dependence of the superconductivity transition temperature T_c on the crystal lattice parameter a in the series of fullerides M_3C_{60} with a face-centered cubic structure.¹³

The mechanism of superconductivity still remains an intriguing question. Does the consideration of this problem go beyond the canonical electron pair theory, according to which the movement of electron pairs is governed by the lattice phonon spectrum (the Bardeen, Cooper, Shrieffer — BCS — theory)? This question has stimulated the synthesis of $^{13}C_{60}$ fullerene (with 99% replacement of ^{12}C by ^{13}C) and the corresponding fullerides, $K_3^{12}C_{60}$ and $K_3^{13}C_{60}$.¹⁵ In qualitative agreement with the BCS theory, the superconduction point decreased from 19.2 to 18.8 K on passing from $K_3^{12}C_{60}$ to $K_3^{13}C_{60}$. This important result confirms partic-

ipation of phonons in the formation and movement of the Cooper pairs.

According to the canonical BCS theory, the superconduction point $T_c \propto M^{-\alpha}$, where M is the mass of the particle responsible for the phonon spectrum (in this particular case, $^{12}C_{60}$ and $^{13}C_{60}$), and α is a characteristic parameter, equal to 0.5. Taking account of the isotope effect and proceeding from the value $T_c = 18.8$ K, one can easily find that $\alpha = 0.3$ (rather than 0.5 as predicted by the BCS theory) for the fulleride $K_3^{12}C_{60}$. This could prompt the conclusion that the BCS theory requires modification. However, this conclusion is not ultimate. In particular, there are no grounds for claiming that the phonons responsible for the Cooper pairing are generated by vibrations of C_{60} as a whole; the pairing might be due to the part of the phonon spectrum created by internal vibrations of C_{60} (for example, the breathing vibration of the sphere). In this case, a mass smaller than the mass of C_{60} should be substituted into the expression $T_c \propto M^{-\alpha}$ and thus the resulting α would move towards 0.5. These conclusions are consistent with the results obtained for Rb_3C_{60} with partial substitution of ^{13}C atoms for ^{12}C . The α value found for this fullerene (0.37) is closer to 0.5.

Endofullerenes constitute one of the most exotic and remarkable classes of chemical compounds created by chemistry. They are formed upon insertion and capture of atoms or ions inside the fullerene sphere. However, it is not the insertion into the fullerene sphere itself that makes these compounds unique but rather the fact that capture of these species by fullerenes is a virtually irreversible process (unlike, for example, the capture of species by cyclodextrins, which is reversible).

A great number of endofullerenes have already been synthesised: $T@C_{60}$ (tritium atoms are formed from ^6Li ions on irradiation with neutrons in the presence of C_{60}), $(^3He, ^4He)@C_{60}$, $K@C_{59}B$, $La@(C_{60}, C_{70}, C_{74}, C_{82})$, *etc.*; endofullerenes with two or even three captured atoms have been obtained, for example, $He_2@C_{70}$, $La_2@(C_{72}, C_{74}, C_{80})$, $(Gd_2, Y_2)@C_{90}$, $(Sc_2, Er_2)@C_{82}$, $Sc_3@C_{82}$, *etc.*¹⁶ It should be noted that in the synthesis of $La_2@(C_{72}, C_{74})$ in the arc of graphite implanted with La_2O_3 , only endofullerenes $La_2@C_{72}$ and $La_2@C_{74}$ are intensively formed, no 'empty' C_{72} and C_{74} being observed. This fact may prove significant from the viewpoint of catalysis of fullerene synthesis.

Some answers to the question of what is the mechanism of the endofullerene synthesis have already been found. As was to be expected, the early idea that the carbon shell is permeable for high-energy atoms proved to be naive. This idea might (although not for sure) be valid in the case of hydrogen atoms; however, even for He direct insertion into C_{60} (without violation of the cage structure) would require ~ 10 eV, and He^+ would be able to penetrate through a six-membered ring upon an orthogonal collision only if it has an energy of 35–45 eV. This is much larger than the energy required for dissociation of the C–C bonds in the fullerene shell (70–80 kcal mol^{−1}). It is clear that rupture of the C–C bonds to open a 'window' in the shell followed by insertion of the guest atom and closure of the 'window' upon restoration of the C–C bonds is energetically much cheaper than direct insertion.

This mechanism is not at variance with the experimental results. Thus helium slowly (over a period of several weeks) enters the C_{60} sphere at a pressure of ~ 3000 atm and a temperature of 600–650 °C.¹⁷ The endofullerene $Ne_2@C_{70}$ is obtained by heating C_{70} under a high pressure of neon, the $C_{70} : Ne@C_{70} : Ne_2@C_{70}$ ratio being dependent on the number of the synthesis cycles and reaching a limiting value of 1000 : 1 : 0.02.¹⁸ These findings led to the important conclusion that there exists a promoter or catalyst which facilitates the insertion of He atoms into C_{70} . This might be a radical, which adds to fullerene and thus weakens the adjacent chemical bonds and promotes the opening of a 'window'. Certainly, discovery of a catalyst able to reversibly open and close a 'window' in the fullerene sphere would ensure a breakthrough into this new class of compound.

[‡] The report that at high pressures and temperatures the hardness of the fullerene polymerisation product exceeds that of diamond has not been supported.

Probably, a reversibly appearing 'window' as a capture mechanism is important for small neutral atoms (such as He and Ne). In the case of large atoms (*e.g.*, lanthanides), trapping of atoms (or ions) during the formation of the carbon sphere is apparently more significant. The search for appropriate catalysts which would facilitate this process is also worth efforts.

Both mechanisms can act simultaneously; apparently, this is the case for trapping of an N atom by C_{60} (when C_{60} is heated in a nitrogen plasma).¹⁹ In the $N@C_{60}$ molecule, the nitrogen atom with three unpaired electrons (one electron in each *p* orbital) is chemically inert (this is also true for hydrogen in $H@C_{60}$ and for phosphorus in $P@C_{60}$). The unique chemical inertness of an inner π -electron shell in fullerenes is in sharp contrast with the high reactivity of the outer π shell. Thus reactions involving the outer shell (Fig. 5) barely affect the inner nitrogen atom; only slight distortion of its EPR spectrum is observed, which is manifested as weak satellite lines, indicating that the spherical symmetry of C_{60} has been somewhat distorted. This makes the nitrogen *p* orbitals energetically slightly non-equivalent (by ~ 0.003 eV) and stimulates dipole spin splitting of the Zeeman levels.

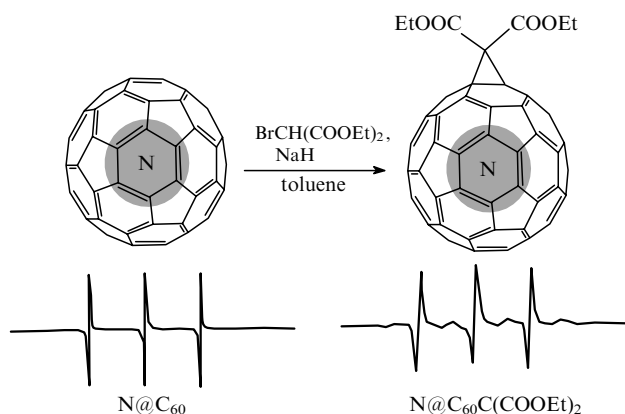


Figure 5. Scheme of the $N@C_{60}$ molecule and the product of its cyclopropanation. The corresponding EPR spectra are shown below.

Yet another feature of endofullerenes, which is of fundamental importance, is noteworthy, namely, contraction of the electron shell inside the fullerene sphere. The constant of hyperfine (electron–nucleus) coupling in a free N atom is 3.7 G, that in the KN_3 crystal is 5.0 G and the same value for $N@C_{60}$ is 5.7 G. This indicates that atoms inside the fullerene sphere experience substantial pressure, which results in contraction of the *p* orbitals of valence electrons. In terms of quantum chemistry, this means perturbation of the wave function resulting in an increase in the contribution of the *s* orbital to the superposition of atomic orbitals. Contraction of the electron shell of the inner atom has also been found in the endofullerenes (Sc,La,Y) $@C_{60}$. In these compounds, anisotropy of the *g*-factor of the unpaired electron was observed,²⁰ which points unambiguously to hindered rotation of the atoms inside the sphere.

It is not difficult to find a relationship between the electron shell contraction and the behaviour of 'onion' fullerenes such as $C_{60}@C_{240}@C_{540}$..., which consist of several spherical molecules arranged one inside the other, the distance between the sphere surfaces being ≥ 0.34 nm. This is a new class of endofullerenes. The inner spheres experience enormous pressure of the outer spheres, and this accounts for the fact that the inner spheres are converted into diamond even upon weak photo or radiation treatment.

Synthesis of *cylindrical carbon nanotubes* (~ 100 Å in diameter), which are formed according to the same principle as fullerenes, has become a prominent event in modern chemistry. They can be doped with metals (both on the inside and on the outside)

and are characterised by high solubility of hydrogen (owing to capillary condensation); therefore, they can be used in chemical cells. Young's moduli of carbon nanotubes are close to that of graphite (in one plane). The first experimental data on the use of nanotubes as probing tips in scanning force tunnelling microscopy were reported. Development of methods for the preparation of oriented nanotubes on thin metallic films using laser etching is in progress. Polymerisation of nanotubes opens up ways to new porous materials such as organic zeolites. Multilayer nanotubes consisting of molecular cylinders enclosed one into another have been obtained.

Technologies that enable manipulation of nanotubes by virtue of atomic force tunnelling microscopy are being developed.²¹ One can lay, bend, cut, straighten, cross and move nanotubes thus arranging molecular electronic devices. Thus, it becomes possible to pass from fine words to impressive deeds.

Preparation of *metallic hydrogen* represents one more important achievement of recent years. It can be debated whether it was done by chemists or physicists; however, the transformation of hydrogen into metallic hydrogen is undoubtedly a chemical process, resulting in a rearrangement of the electron shells of hydrogen molecules. Metallic hydrogen is obtained by shock compression of a 0.5-mm thick liquid film of molecular hydrogen placed between single-crystal Al_2O_3 anvils at a pressure of 2 Mbar.²² The electrical conductivity of this material ($\sim 2000 \Omega^{-1} \text{ cm}^{-1}$) is close to those of molten cesium and rubidium; in this sense, metallic hydrogen resembles liquid alkali metals. The mechanism of its formation is unknown; it involves either immediate complete release of the electrons from a hydrogen molecule or dissociation of the molecule into atoms followed by the discharge of electrons to the conduction band. In order to decide between these variants, non-stationary reaction regimes need to be studied.

III. Chemistry in micro- and macro-reactors

It should be admitted that the chemistry created by the mind and hands of Man is only a minor fraction of chemistry created by Nature. The vast majority of reactions implemented by humans are 'non-organised' reactions in which species (molecules, ions, atoms or radicals) react when they meet by chance (in space and time). Meanwhile, the 'natural' chemistry is highly organised, *i.e.* almost all the chemical transformations occur in systems with molecular or supermolecular order. Large sets of biochemical reactions are organised both in space and in time. Thus, during photoreception each light quantum absorbed by the retina of an eye triggers a cascade of reactions yielding ultimately cyclic guanosine monophosphate (quantum yield 10^4), which induces an electric potential on the membrane. This signal is then recorded in the brain as the signal for light reception (other examples can be found in a review¹). It is owing to the high degree of organisation that the selectivity and productivity of biochemical reactions reach very high levels, which are yet inaccessible in conventional chemistry.

The realisation of this fact and the turning of chemistry as a science to molecular and supermolecular organisation of reactants started in the second half of this century; now this is a leading line in the intrinsic self-organisation of chemistry directed towards the future.

The simplest microreactor in which reactants can be organised in space is a van der Waals molecule. A large number of micro-reactors of various natures and sizes and various degrees of molecular ordering exist. They include complexes, crystal solvates, gas (for example, methane) hydrates, inclusion compounds (in which 'hosts', represented by cyclodextrins, semispherands, calixarenes, *etc.*, organise reactions of 'guest' molecules), macromolecules, (helices or rigid zigzag-like rods), the cavities of zeolites and other porous media, micelles and vesicles. Microreactors change the molecular dynamics of reactants, mechanisms and rates of chemical transformations, the *pK* values of acids and

bases, local charges and charge distributions, ionisation potentials, electron affinities, conformations and reactivities. Reactions in microreactors follow new 'forced' pathways, and other anomalous features can also be observed.

Two-dimensional microreactors are represented by the electric double layer, monomolecular layers (of the Langmuir–Blodgett type), membranes (both biological and artificial), interfaces (they are used in phase transfer catalysis, especially in reactions involving ordered and directed exchange by substances and electric charges between the phases), adsorption layers of reactants on solids ('two-dimensional' zone reactions) and so on.

A classical two-dimensional microreactor — electric double layer — has now a new lease on life, associated with high time resolution regimes ($\sim 10^{-12}$ – 10^{-9} s), which are brought about by the laser-induced chemistry at solid–liquid interfaces. The main character in such a microreactor is an electron, either solvated or free. Its chemical behaviour is the subject of special interest regarding generation of electric potentials and modelling of the potentials existing in 'natural' chemistry. Potentials at a liquid–liquid interface also deserve attention.

The interest in 2D monolayers on solids is due not only to their use as heterogeneous catalysts (this topic is already out of date) but also to the new opportunities offered by synthetic chemistry on the surface. For example, 1,5-cyclooctadiene, which binds to the surface of an Si(001) single crystal upon rupture of one C=C bond, forms a two-dimensional molecular lattice.²³ The highly ordered monolayer consisting of grafted molecules exhibits high reactivity and can participate in further chemical functionalisation leading to any chemical architecture.

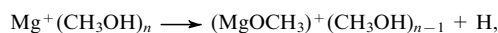
Cluster microreactors are highly diverse. They can be atomic, molecular, ionic, ion-molecular and organometallic, either charged or neutral. Clusters are formed in gases (for example, in expanding supersonic atomic-molecular beams), in zeolite channels (for example, the In_8 clusters), in liquids, on solid surfaces, in solid matrices (such as solid argon or xenon), *etc.* They play an important role in the chemical materials science (cluster materials with unusual physics and mechanics), in chemical analytics and diagnostics (detectors and sensors) and in other fields of applied chemistry.

The main, fundamental problem in the chemistry of clusters is associated with dimension effects. This is an intriguing question — how do the properties of separate species evolve on their combination into the properties of a new phase; how are the bridges between the world of a separate molecule and the world of macroscopic matter being built? The dimension effects are so diverse and unexpected that no general solution of this problem exists. Quantum chemistry and molecular dynamics methods provide partial answers only to some questions.

Clusters still remain enigmatic objects (for unusual properties of clusters, see for example, Ref. 24). Thus Re atom is inert towards CH_4 , whereas the Re_3 cluster is active; the linear clusters Cu_3 and Ni_3 do not react with H_2 or CH_4 , whereas triangular clusters react readily and rapidly; the Co_n clusters are reactive towards H_2 at $n = 3, 10$ and 12 and are inert at any other n ; the Nb_n clusters with $n = 3, 4$ and 5 react with H_2 , whereas other Nb clusters are relatively inert; Nb clusters with $n = 5, 6$ and 11 are active in dehydrogenation of benzene; the Ag_n clusters exhibit metallic properties starting from $n = 6$, whereas Na_n do not exhibit any signs of a metal phase even at $n = 14$. The $\text{I}_2(\text{C}_6\text{H}_6)_m$ cluster is polyhedral and $\text{V}_n(\text{C}_6\text{H}_6)_m$ has a multi-deck sandwich structure.

The MoO^+ cation does not react with NH_3 , whereas the Mo_3O_8^+ and Mo_3O_9^+ clusters dehydrogenate NH_3 to give complexes with the nitrogen formed upon dehydrogenation. The same clusters oxidise CO to CO_2 . The V_3O_7^+ and $\text{V}_3\text{O}_{12}^+$ clusters are efficient in dehydrogenation of butadiene and destruction of butane, while V_3O_6^+ and $\text{V}_3\text{O}_{11}^+$ are inert in these reactions but they are active in the addition and oxidative cyclisation reactions.²⁵

In the cluster of α -naphthol with $(\text{H}_2\text{O})_n$ (these compounds are called crystal hydrates), proton transfer from excited α -naphthol to water has been detected only for $n \geq 20$; in the case of α -naphthol clusters with $(\text{NH}_3)_n$ this process occurs even at $n \geq 4$. In the clusters of univalent magnesium (or calcium) with $(\text{H}_2\text{O})_n$ and $(\text{CH}_3\text{OH})_n$, the electron transfer and hydrogen reduction



occur for $6 \leq n \leq 15$; at any other n the reaction does not occur, and hydrogen elimination is not observed.²⁶

The rate of photoinduced isomerisation of *trans*-stilbene placed in the $(\text{hexane})_n$ cluster was measured in molecular beams by picosecond spectroscopy.²⁷ The rate constant for this process decreases in the sequence 9.7×10^9 ($n = 0$, free molecule), 3×10^9 ($n = 1$), 1×10^9 ($n = 2$), 0.8×10^9 ($n = 3$), $0.5 \times 10^9 \text{ s}^{-1}$ ($n = 4$). Unexpectedly, all these constants proved to be smaller than the observed isomerisation constant of *trans*-stilbene in pure liquid hexane at the same temperatures and energies ($11.5 \times 10^9 \text{ s}^{-1}$); *i.e.* immersion of *trans*-stilbene into the $(\text{hexane})_n$ cluster decreases its reactivity. The cluster shell fixes the molecule even more strongly than a 'liquid-phase' shell; it abnormally increases the kinetic (Kramers) friction, which accompanies the movement of the reacting molecule along the reaction coordinate.

Special interest is aroused by the dimension effects in semi-conducting nanocrystals the size of which is smaller than the Bohr radius of an exciton. Quantum capture of an electron and a hole (generated by photochemical or radiation-chemical treatment) in the confined space of these nanoclusters (called quantum dots) results in an increase of the band gap following a decrease in the cluster size; hence, recombination luminescence shifts to the blue region (to higher energies). A striking example is provided by nanocrystals of CdSe 'coated' by one or two ZnS monolayers. When the diameter of the inner CdSe nucleus increases stepwise from 23 to 55 Å, the bright blue luminescence passes into green, yellow, orange and, finally, bright red luminescence.²⁸

In addition, cluster chemistry opens up the way to a new strategy in heterogeneous catalysis, especially when combined with scanning tunnelling microscopy. The tip of the microscope is able to apply any number of any atoms on the faces, edges or terraces of any crystal, thus creating diverse catalytic microreactors and providing conditions for testing various reactions on them. This is a new wind in the fundamental science of catalysis and its future.

Clusters are much more widespread and, hence, much more significant than it has been believed until recently. Thus it has been found experimentally (by cold-neutron and X-ray scattering) that liquid ammonia is clustered — it consists of the $(\text{NH}_3)_7$ clusters containing one molecule in the centre and six molecules at the periphery.²⁹ The cluster structure of liquid water is well known: water molecules are united into hexa-, penta- and tetramers, having close energies and forming prismatic, cage, 'open-book' and adamantane structures, and also into dodecahedra and other big clusters. Liquid aqueous solutions of ethanol are also non-uniform; they consist of water and ethanol clusters.³⁰ It is noteworthy that when the content of the alcohol in water is $\sim 40\%$, the proportions of ethanol and water clusters are equal. Perhaps, this accounts for the special receptive-gustatory properties of the well-known and popular water-ethanolic drink. Indications of clustering have also been found in liquid benzene. This might prove to be a general phenomenon; if this is really so, all liquid-phase reactions should be interpreted as occurring in microreactors.

Furthermore, a chemical reaction can itself stimulate molecular organisation of a microreactor. Thus a colourless molecule of spiropyran having a long hydrocarbon 'tail' is converted upon photochemical treatment into a coloured bipolar form with separated charges; it is in this form that spiropyran molecules

unite to form micelles. Here photochemical reaction acts as the trigger for micelle formation.

Brain is a macroreactor of enormous complexity. There occur a tremendous number of chemical reactions, responsible for the synthesis of the memorising molecular structures, which form memory and the whole control system of a living organism. Brain is of key importance in the entire chemistry of living matter; chemistry of brain is the chemistry of the XXI century.

The main purpose of brain is to transform chemical energy into electric energy; this task is accomplished by neuromediators. They stimulate enzymic synthesis in synaptic membranes and ensure communication between neurons, formation of electric potentials and transfer of electric signals *via* recharge of the membrane. They control a cobweb of impulses and potentials, which govern all functions of a living organism. Neuroprotectors act *via* chemical mechanisms.

Many neuromediators have long been known. Thus dopamine and its chemical functions have been studied comprehensively; however, only recently it has been found that its deficiency in an organism is responsible for dotage. One reason for the reduction of the dopamine level with advance in age is that it is destroyed under the action of the enzyme monoamino oxidase B. Another reason is that the number of dopamine-receiving neurons in an organism decreases with time (a low level of these neurons is also characteristic of those who suffer from parkinsonism). In addition, it has been found that some narcotics trap neurons and remove them from the functioning of brain. It is clear that the understanding of the chemical mechanisms of the operation of neuromediators opens up ways for eliminating disorders in the work of the brain macroreactor.

Other neuromediators are also known; among these, mention should be made of versatile nitrogen oxide with a broad spectrum of chemical and physiological action and Semaks – a neuropeptide consisting of seven amino acids.

Study of a macroreactor such as the human brain requires delicacy, which sharply restricts the range of possible direct experiments. Nevertheless, these studies are carried out within the framework of neurophysiology in combination with medicine and clinical surgery. The studies widely use microelectrode equipment, which permits estimation of the behaviour of the electric potentials formed and their response to chemotherapy and physiological treatment. Enormous opportunities are also provided by positron-emission tomography, in which the ^{11}C isotope and ^{11}C -labelled chemical compounds being tested are used as the positron sources. At present, researchers have realised that wide use of experimental modelling of brain elements can help in the understanding of the operation of this macroreactor. The main goal of modelling is to answer the question how does the brain perform its primary task, *i.e.* how does it transform chemical energy into electric energy. By the way, as a 'side result' of this modelling, one could expect design of molecular devices characterised by high coefficients of conversion of chemical energy into electric energy (within the framework of chemical energetics).

The Earth is a huge *geochemical macroreactor*. This mechanochemical reactor is the source of earthquakes. It covers the whole of mechanochemistry and its consequences: chemical bond rupture induced by mechanical treatment, formation and migration of dislocations, generation and multiplication of cracks, shears and shear waves, generation of electric potentials and their gradients, radio waves, magnetic fields and chemical emission. Now scientists have understood that the key to the diagnostics and prediction of earthquakes lies in mechanochemistry. All events that take place in the geochemical macroreactor echo in the ionosphere as electric field gradients and are detected there as forerunners of earthquakes. Mechanochemistry, a field of science in which chemistry occupies a prominent place, is directed towards the XXI century.

IV. Coherent chemistry

Coherent chemistry is a 'new face' of chemistry. Coherence is the ability of chemical systems to generate oscillation regimes of reactions. The coherence (time synchronisation) of a chemical reaction is manifested as cyclic variations of the reaction rate and can be detected as oscillating product yields, luminescence emission, electrochemical currents or potentials, *etc.*

Chemical coherence exists at two levels, quantum and macroscopic levels. In the former case, the coherence refers to the reactivity of an assembly of reacting particles generated by a laser pulse. Such an assembly oscillates between states with different reactivities, these oscillations modulating the yields of the reaction products. The vibrational and spin types of coherence are of the quantum origin. In the case of macroscopic coherence, the concentrations of active reagents (or intermediates) periodically change. The best known example of macroscopic coherence is the Belousov–Zhabotinsky reaction.

The coherence introduces new notions into chemistry, such as wave packet, phase, loss of phase coherence (dephasing), interference, bifurcation and bifurcation diagrams, phase portrait, strange attractor and phase turbulence. This is not simply a new language of chemistry; this reflects a new level of thinking and a new level of chemical research practice. In the coherent chemistry, the random, statistical behaviour of molecules is replaced by organised, ordered and synchronous behaviour; thus, chaos turns into order.

A short (10^{-14} – 10^{-13} s) laser pulse (with a duration shorter than the period of vibrations of atoms) 'excites' a molecule and 'throws' it onto a new potential. In this new potential, an assembly of molecules prepared by the laser pulse behaves coherently, *i.e.* vibrations of atoms of all of the members of the assembly are synchronised, the whole assembly being a wave packet.

When moving on the potential surface, a wave packet can disperse into several smaller packets (with different vibration amplitudes and phases); some of them can go out of phase (lose the coherence) and disappear, while some other can interfere to restore partially the initial packet, *etc.*

A classical illustration of the coherent behaviour of a wave packet is provided by an assembly of NaI molecules (Fig. 6).³¹ Molecules of NaI excited by a short (~ 50 fs) pulse are 'transferred' from the surface of the ground (ionic) state to the surface of an excited 'covalent' state; this creates a wave packet localised on a potential surface. This wave packet slides in an adiabatic potential (Fig. 6a, the upper curve), in which it oscillates between the covalent and ionic states and crosses at some intervals the point of intersection of the ionic and covalent terms (when the interatomic distance is 6.93 Å). Due to the non-adiabatic connection of these two terms, there is a finite probability of penetration of the packet from the upper curve to the lower one. As this takes place, a part of the penetrated packet dissipates to generate Na atoms (they can be detected experimentally) and the rest becomes a new wave packet, which moves coherently in the lower valley.

The point of intersection of the ionic and covalent terms (where the upper and the lower potential curves contact with each other) is the bifurcation point in which the wave packet splits into two packets, one of which is partially irreversibly destroyed. In principle, it is clear that the packet situated in the lower potential curve can return to the upper potential curve *via* the same bifurcation point and restore the initial packet (interference), although in this particular case, the probability of this event is low. For other systems characterised by a different configuration of the potential energy surface, this probability can be substantial and the packet interference can be manifested fairly clearly.

These qualitative considerations can be converted into a quantitative picture by calculating the probabilities of dissipation of the packet at the bifurcation point (according to Landau–Zener). Fig. 6b shows the pattern of the packet movement on the time and space coordinates. It can be readily seen that the coherent movement of the packet in the upper valley generates a stream of

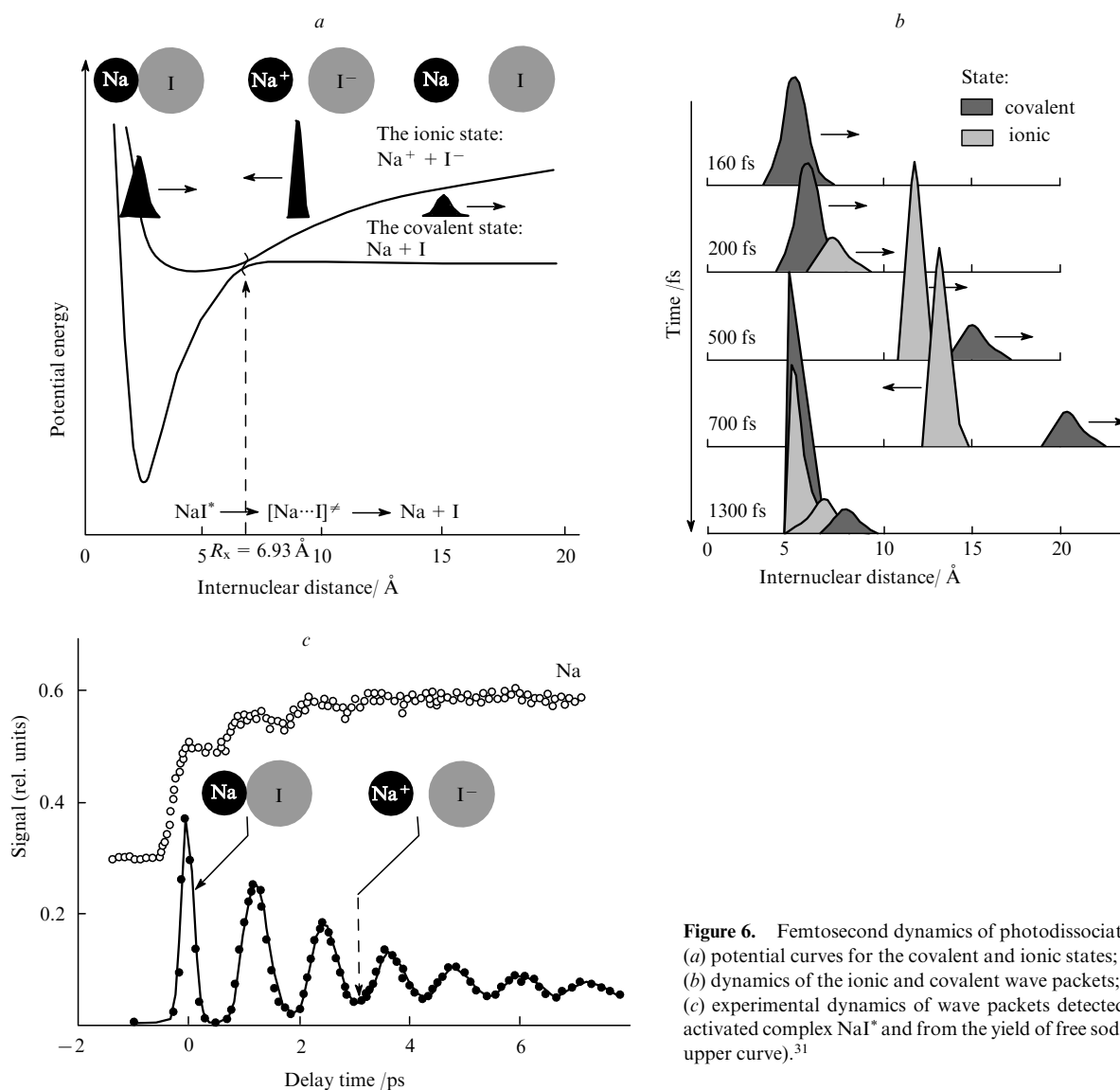


Figure 6. Femtosecond dynamics of photodissociation of NaI; (a) potential curves for the covalent and ionic states; (b) dynamics of the ionic and covalent wave packets; (c) experimental dynamics of wave packets detected based on the activated complex NaI^* and from the yield of free sodium atoms (the upper curve).³¹

Na atoms (reaction product) at the bifurcation point. The density of this stream oscillates with time, the oscillation frequency being equal to the frequency of packet oscillation in the upper valley; the density amplitude attenuates due to the packet dissipation, dephasing and falling into the deep lower valley (Fig. 6c).

The coherence created initially is retained during the reactions and is transferred to the products. This indicates that the molecular assembly undergoes a collective, synchronous and phase coherent chemical transformation.

This coherence can be found not only in simple reactions such as dissociation of the NaI, I_2 , HgI_2 , etc. molecules but also in complex systems. Thus phototransformation of rhodopsin and its analogues occurs in parallel *via* a coherent and a non-coherent[§] channel over a wide spectral range (400–1100 nm).³² The key process in the phototransformation of rhodopsin — a molecular system consisting of an apoprotein (opsin) and 11-*cis*-retinene attached to it — is the *cis*–*trans*-isomerisation of retinene around the C(11)=C(12) bond. The direct coherent formation of the first intermediate (bathorhodopsin from rhodopsin and hR_K from halorhodopsin hR) occurs over a period of ~200 fs, the coherence being retained in the reaction product. The fact that even in a complex molecular system such as rhodopsin, the degree of

coherence remains remarkably high (~20%) merits attention. When the hydrogen atoms at C(11) and C(12) are replaced by deuterium, the isotope effect is not observed over a short period of time (up to 110 fs); it appears only in the range 110–170 fs, when rocking around the C(11)=C(12) bond is characterised by a large amplitude and leads to full rotation. This means that the coherence of the whole process (it takes ~200 fs) is a stable characteristic, which is retained at any amplitude along the coordinate of isomerisation.³³

Vibrational coherence can also be detected in the chemical transformations of such a bulky molecular system as the bacterial photosynthetic centre.³⁴ Moreover, coherence has been found in the antennae of photosynthesising centres, its degree and ‘length’ (*i.e.* the length of the ‘coherent’ accumulation of energy) being dependent on the molecular order and spatial arrangement of the light-collecting complexes near the the energy-collecting photosynthesising centre.

It is not the coherence itself that is the most remarkable feature of the coherent chemistry but rather new and non-traditional methods for controlling chemical reactivity. When the first pulse throws a wave packet onto a potential surface, the second pulse can influence its evolution: either throw it further onto a new surface or bring it back onto the initial surface (the Raman process). This can be done either before or after the wave packet has passed the bifurcation point by changing the delay between the first (pump) pulse and the second (probe) control pulse. In

[§]Phototransformation *via* a non-coherent channel implies statistical thermalisation of the excited state followed by slow (2–4 ps) statistical formation of the product.

other words, the dynamics of wave packets and their chemical fate can be controlled; the ratio of the channels of their transformation and the yields of the reaction products can be altered. Thus a new tool for controlling a chemical reaction appears, *i.e.* the phase of a coherent assembly. By affecting a wave packet in various phases of its evolution, one can change its chemistry.

For example, in the electronically coherent assembly of HD^+ molecules, prepared from HD by a short ionising laser pulse (pump pulse), the electron oscillates between the H and D atoms. Using the second (control) pulse, one can attain the coherent control of the HD^+ dissociation, which gives either $\text{H} + \text{D}^+$ or $\text{H}^+ + \text{D}$, depending on the instant when the second pulse acts. To induce the former dissociation pathway, the second pulse should be switched on when the electron resides on the hydrogen atom, whereas for the latter pathway, it should occur when the electron is on deuterium. This is the highest level of coherence in chemistry, the prospects of which are being discussed even now.³⁵

An even finer and a more elegant way of controlling the chemical fate of a wave packet is embodied in the phase relationship between the packet and the probe pulse. The current state of optics makes it possible to control the frequency-dependent phase of laser pulses. The delay $\tau(\omega)$ of the group velocity of a particular frequency component of the optical spectrum is known to depend on the phase of this component Φ by the relation $\tau(\omega) = \partial\Phi(\omega)/\partial\omega$. For a pulse with a given spectrum, all the frequency components should be in phase and should arrive simultaneously at the destination point, *i.e.* $\tau(\omega)$ does not depend on frequency. In this case, $\Phi(\omega)$ includes no frequency-dependent quadratic terms (or terms with higher exponents). However, one can change $\Phi(\omega)$ in a specified way (by virtue of optical grids and prisms) in order to introduce frequency-dependent quadratic terms (they are called chirps). In these chirped pulses, phase velocities become frequency dependent. Thus when the chirps are negative, the red component of the pulse lags behind and arrives at the destination point (*e.g.*, at a wave packet) later than the high-energy blue component. Conversely, in the case of positive chirps, the red light is ahead of the blue one. It is clear that by changing the chirp of an optical pulse, one can control the relationship between the phases of the wave packet and the control pulse and thus 'catch' the packet in various positions on the potential surface by either red, or blue, or another appropriate light.

Certainly, this is a simplified picture illustrating in a clear form the main principles and chemical effects of the vibrational quantum coherence. The main idea is that the coherent chemistry brings about a new factor controlling chemical reactions, namely, the phase. By changing the phase (this can be attained by delaying the control pulse relative to the generating pulse or by chirping), one can manipulate the chemical behaviour of assemblies of reacting species without changing the energy or angular momentum.

The next level of coherence is quantum periodicity in a system consisting of two species, each carrying an electron spin (for example, a pair of radicals). Such a spin pair can exist in two states — singlet (reactive) and triplet (chemically inert). An assembly of these pairs, prepared by a pulsed method (photolysis or radiolysis) in a specified spin state (*e.g.*, in the triplet state), oscillates synchronously between the two states. The driving force of this oscillation is the difference between the Zeeman energies of the two partner spins or the hyperfine electron – nuclear coupling (if the radicals contain magnetic nuclei). The magnitude of these interactions is of the order of several megahertz (it is with this frequency that the assembly oscillates between the singlet and triplet states). It is clear that the yield of the products of a chemical reaction (which are formed only when the species occur in the singlet state) is time-modulated at the same frequency (Fig. 7). The periodicity in the product formation is a consequence of the coherence of the behaviour of spin pairs; this is an example of electron-spin quantum beats in chemical reactions (as opposed to the vibrational quantum beats, considered in the previous Section).

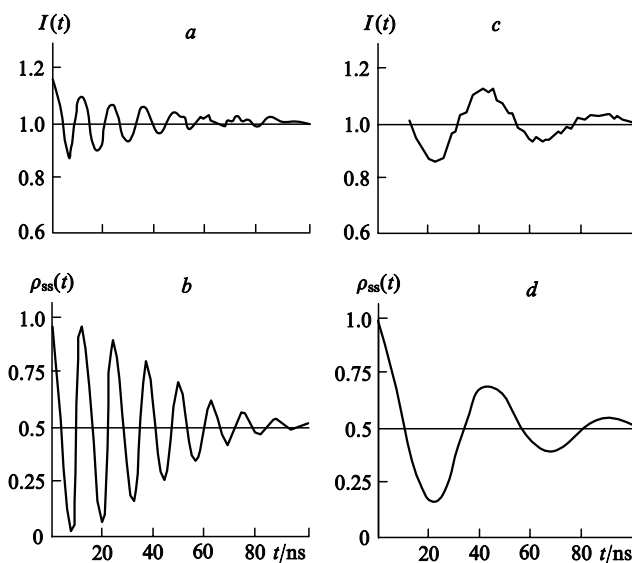


Figure 7. Quantum beats in the recombination of the (diphenyl sulfide)⁺/(*p*-terphenyl-*d*₁₄)[−] radical-ion pair in *cis*-decalin at $H = 1200$ (a, b) and 3000 G (c, d). The product of recombination of *p*-terphenyl-*d*₁₄ was detected by fluorescence.

(a, c) Experimental data, (b, d) theoretical calculations; $I(t)$ is the fluorescence intensity, $\rho_{ss}(t)$ is the content of the singlet state in the radical-ion pair.

The electron-spin coherence has been found in photochemical and radiation-induced chemical reactions of radical pairs³⁶ and in the primary photochemical event of charge (and electron spin) separation in the photosynthetic reaction centres. In these systems coherence originates due to the synchronous oscillation of spin pairs between the singlet and triplet states. Moreover, in addition to the electron-spin coherence, nuclear-spin coherence has been found in these systems (ordered in-phase precession of the system of polarised nuclei occurs).³⁷

The advantage of spin coherence is that it provides new methods of investigation and identification of fine and accurate details of the structure and dynamics of chemically generated spin systems. Furthermore, even when the chemical reaction producing spin systems occurs statistically (non-coherently), spin coherence exists in these systems, which opens up a way to the new field of science, chemical radiophysics (see Section V).

The oscillating regimes of chemical reactions were first observed rather long ago. At that time, oscillations were considered to be an exotic rather than a regular feature. Nowadays the Belousov–Zhabotinsky reaction and oscillations of pH and electrochemical potentials in heterogeneous systems such as oil–water systems, Liesegang rings and wave combustion, have become classical examples. However, the fact that macroscopic coherence is a fundamental property has been realised only recently. The science of chemical oscillators has been revived owing to two important facts.

Firstly, it became clear that coherent regimes could increase the yields of reaction products and the process selectivity and could lead to self-cleaning of surfaces from catalytic poisons, *etc.* These expectations have been confirmed, especially for chemical oscillators with forced oscillations.³⁸

Secondly, the interest in chemical oscillators has been aroused again owing to biochemical oscillating processes occurring in nerve cells, muscles, and mitochondria. This resulted in active assimilation of new systems of oscillators, *i.e.* in combination of several chemical oscillators into a common unified system. It is believed that such a system would be a prototype (although yet primitive) of the future models of neuron networks.³⁹ However, even now, studies are in progress on the oscillator excitation thresholds in such a combined system and on the influence of the

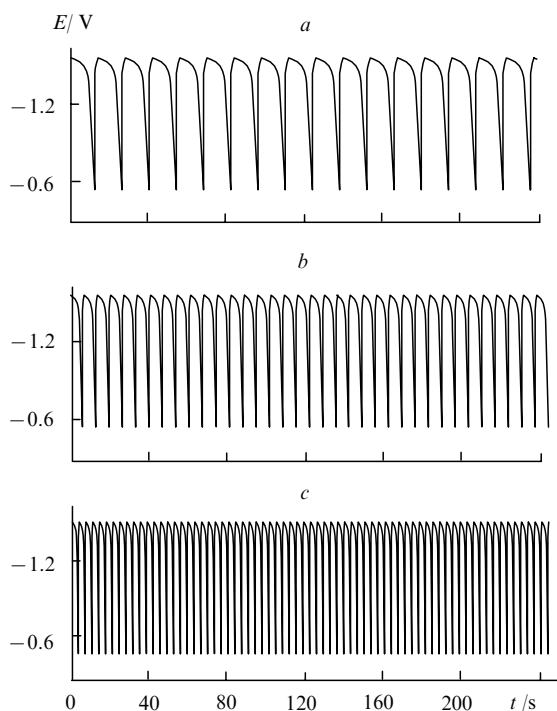


Figure 8. Periodic potential oscillations during the reduction of bromate ions in a solution of NaOH at a silver electrode and at the current 1.5 (a), 2.5 (b) and 3.0 mA (c).⁴²

number of oscillators, the way of their connection (a linear or a circulating system) and the connection parameters (mass exchange, control of electrochemical potential and currents) on the excitation of collective oscillations, *etc.*

New chemical oscillators have been discovered. Thus the potential of a platinum electrode in the $\text{ClO}_2\text{--I}_2\text{--CH}_3\text{C(O)CH}_3$ system varies as a periodic function of time. When formaldehyde and methanol are oxidised under galvanostatic conditions, the oscillation frequency repeatedly doubles, resulting in the break-down to chaos at the bifurcation points.⁴⁰ This type of behaviour resembles that observed in some enzymic reactions and biological systems.⁴¹ Oxidation of bromate ions in alkaline solutions is also an oscillating process (Fig. 8). Oscillations are due to the concentration effects at the electrode surface and, therefore, they vary as a function of the surface geometry (roughness, presence of islets, *etc.*).⁴² Another bromate oscillator catalysed by tris(bipyridine)-ruthenium is, in addition, a photo-controlled system displaying different bifurcation diagrams in the light and in the dark. A strange bifurcation behaviour of the order and chaos regimes and doubling of frequency are also observed in the peroxidase-catalysed oxidation of dihydro(nicotinamide)adenine dinucleotide (NADN).⁴³

In heterogeneous catalytic oscillators, oscillations may arise due to a non-linear relationship between the rates of chemical reaction and heat exchange, concentration gradients, periodic modulations of the composition of a 'two-dimensional' reactant, 'breathing' of the surface (when atoms go down and up, similarly to waves in a two-dimensional lattice), *etc.* Examples of chemically oscillating processes are provided by the reduction of NO with hydrogen (when the pressure of H_2 decreases, the period of oscillations repeatedly doubles until break-down to chaos occurs), oxidation of CO with oxygen on platinum, accompanied by generation of time-and-space helical waves (Fig. 9)⁴⁴ and some other processes.

The brain is a striking and a unique example of a system self-organised in space and time. The chemical activity of enzymes and, as a consequence, the electric potentials in the system of synaptic membranes and neurons in brain are remarkably

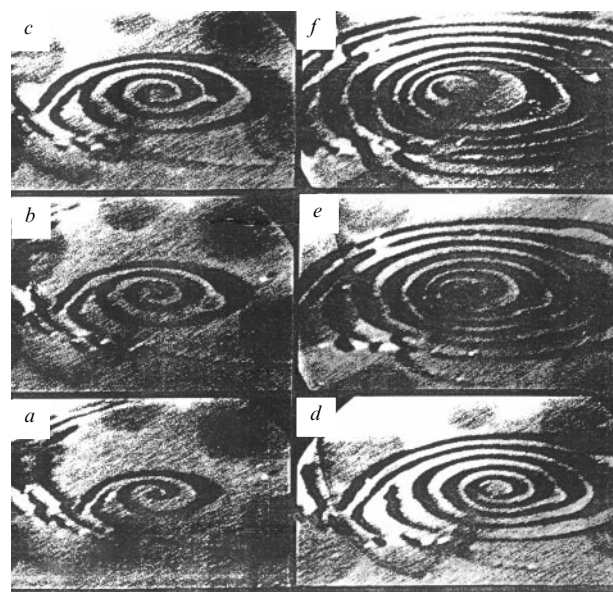


Figure 9. Helical wave on the Pt(110) surface which develops during oxidation of CO with oxygen (434 K). The light sections are areas occupied by CO; the dark sections are areas occupied by oxygen. The photographs were taken consecutively at times 0 (a), 10 (b), 21 (c), 39 (d), 56 (e) and 74 s (f) on a $0.2 \times 0.2 \text{ mm}^2$ area.⁴⁴

synchronised (coherent). It is also clear that the scales of coherence (*i.e.* the sizes of synchronised areas in brain) are different for different levels of brain functioning. In other words, the brain consists of biochemical oscillators of various sizes connected to one another and combined into a unified control system.

Order is the normal state of this system, while chaos implies severe pathologies (such as Alzheimer's disease). Perfect order is the property of a brilliant genius brain (this idea is only hypothetical but looks like being true).

V. Spin chemistry and chemical radiophysics

Yet another new field of modern chemistry is spin chemistry concerned with the behaviour of angular momenta (spins) of electrons and nuclei during chemical reactions. Spin chemistry is based on the fundamental law: in adiabatic chemical reactions the electron and nuclear spins are strictly retained. Only those reactions are allowed which do not require spin change. In other words, all the chemical reactions are spin-selective, *i.e.* they are allowed only for those spin states of reactants the total spin of which is equal to the total spin of products, and they are completely forbidden when the reactant spin is not equal to the product spin.

A simple example is provided by a radical pair comprising methyl and hydroxyl radicals. Recombination of these radicals to give methanol occurs only in the singlet state, because this ensures that the electron spin of the pair ($S = 0$) is identical to that of CH_3OH . However, disproportionation of the same radicals in the singlet state to yield H_2O and triplet methylene (the total spin of the products $S = 1$) is forbidden for spin reasons. For the triplet radical pair ($S = 1$), on the contrary, recombination is forbidden, whereas disproportionation is allowed, although its activation energy is relatively high, $\sim 6 \text{ kcal mol}^{-1}$.

One should be conscious of the fact that chemistry is governed by two fundamental factors — energy and spin (as shown in the previous Section, one more factor, phase, appears in the coherent chemistry).

Unlike the prohibition for energy reasons (it appears when the energy of reactants is lower than the energy barrier to the

reaction), which can be overcome *via* tunnelling under the barrier, the spin prohibition is insurmountable.

Spin can be changed upon non-chemical magnetic interactions; only they can transform spin-forbidden (non-reactive) states of reactants (*e.g.*, radical pairs) into spin-allowed (reactive) states. Magnetic interactions, the energy of which is negligibly small, switch reaction channels — they can open closed channels and, conversely, close the open (allowed) ones, depending on the initial state of the reactants. Actually, they write a new, magnetic script of a chemical reaction.

The spin selectivity and, hence, the magnetic sensitivity of chemical reactions has served as the source of three generations of magnetic effects discovered during the last two decades.⁴⁵ Fig. 10 illustrates the origin of these effects in relation to a particular example, which is, however, frequently encountered in chemistry, namely, a radical pair able to exist in either the singlet or the triplet spin state. In the case where triplet–singlet transitions are induced by static magnetic fields (external fields or internal fields of magnetic nuclei), first-generation magnetic effects arise. Magnetic effects of the second generation appear when the spin conversion of pairs occurs on exposure to microwave fields. Finally, when the conversion is induced by the influence of a third paramagnetic species, a remarkable phenomenon, spin catalysis, can be observed, which represents the third generation of magnetic effects. The third species (a radical or a paramagnetic ion) acts as a spin catalyst.

First-generation magnetic effects. An external magnetic field exerts two types of influence on the spin conversion of radical pairs and, hence, on the chemical reactivity. Firstly, the field switches off two of the three channels of spin conversion, namely, $S-T_+$ and $S-T_-$, so that only the $S-T_0$ channel is left (T_+ , T_0 and T_- are triplet states which differ in the projection of the total spin). Secondly, it accelerates the $S-T_0$ conversion if the partners of the pair have different Zeeman energies. Depending on the initial spin state and magnetic parameters (hyperfine coupling energy, *g*-factors, dipole interaction) of the reactants, chemical reactions can be accelerated or decelerated by an external magnetic field.

Magnetic field effects have been found in a great number of chemical and biochemical reactions, their range constantly extending. A reliable theory capable of predicting the significance

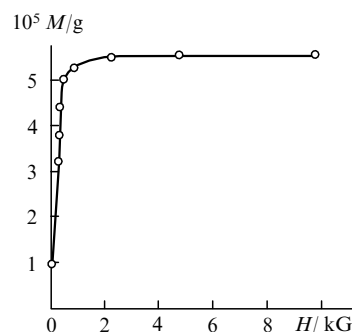


Figure 11. Molecular mass of the polymer obtained by emulsion polymerisation of styrene (dibenzyl ketone as a photoinitiator; sodium dodecyl-sulfate as an emulsifier; constant polymerisation time) *vs* magnetic field intensity.⁴⁶

and behaviour of magnetic effects has been developed. The magnitudes of these effects are often quite large. Thus the rate of photoinduced aqueous-emulsion polymerisation of styrene and the molecular mass of the resulting polymer increase 6–8-fold even in weak magnetic fields, ~ 100 G (Fig. 11).⁴⁶ An even more pronounced effect (20–25-fold increase) is attained in the light scattering by colloidal particles subjected to photochemical cross-linking.⁴⁷ This strong effect can be used for visualisation of magnetic fields and their gradients.

Being selective regarding the electron spin, chemical reactions between spin carriers (radicals, paramagnetic ions and molecules, carbenes, *etc.*) are also selective as regards the nuclear spin. If the two spin subsystems (electronic and nuclear) are related by the Fermi hyperfine coupling (FHC), the nuclear subsystem can affect the behaviour of the electronic subsystem *via* the FHC and thus modify the chemical reactivity of spin carriers. The nuclear-spin selectivity is manifested as different rates of spin-selective reactions of radicals (or other spin carriers) with magnetic and non-magnetic nuclei. This is a new phenomenon referred to as magnetic isotope effect (MIE), which differs fundamentally from the classical isotope effect (CIE), resulting from nuclear-mass selectivity of reactions. Both effects sort the isotope nuclei: the CIE selects nuclei according to their weights, while the MIE selects them according to their spins and magnetic moments.

The discovery of the magnetic isotope effect is a prominent event of the last quarter of the XX century, its significance being comparable with that of the discovery of the classical isotope effect. In addition, the magnitude of this effect substantially exceeds that of the CIE (Fig. 12) and, unlike the magnitude of the CIE, it depends on the magnetic field, temperature, molecular and chemical dynamics and the spin state of the reactants. The magnetic isotope effect results in fractionation of magnetic and non-magnetic isotopes in chemical, biochemical, geochemical and interstellar processes.⁴⁸

The third effect belonging to the group of first-generation magnetic effects is chemically induced dynamic nuclear polarisation (CIDNP). Unlike the MIE, in this case the nuclei are sorted not only according to their magnetic moments but also according to their orientations. During a chemical reaction, nuclei with different orientations are sent into different products and this creates non-equilibrium populations of the Zeeman nuclear levels in these products. An excessive population of the lower Zeeman level corresponds to the positive nuclear polarisation, whereas overpopulation of the upper level implies negative polarisation. The latter case is especially remarkable: when the overpopulation of the upper level exceeds some permissible limit, the populations are inverted; this provides the basis for chemical radiophysics.

An assembly of product molecules with inverted populations accumulates energy in the Zeeman storage reservoir; the energy can either be consumed as heat (*via* spin–lattice magnetic relaxation) or be converted into stimulated emission at a Zeeman

SPIN CHEMISTRY

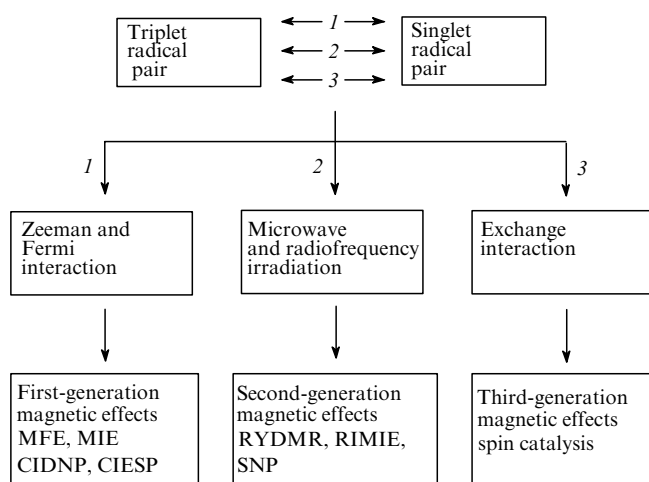


Figure 10. Spin evolution of radical pairs. The following designations are used: MFE is magnetic-field effect, MIE is magnetic isotope effect, CIDNP and CIESP are chemically induced dynamic nuclear polarisation and electron spin polarisation, RYDMR is reaction yield detected magnetic resonance, RIMIE is radio-induced magnetic isotope effect and SNP is stimulated nuclear polarisation.

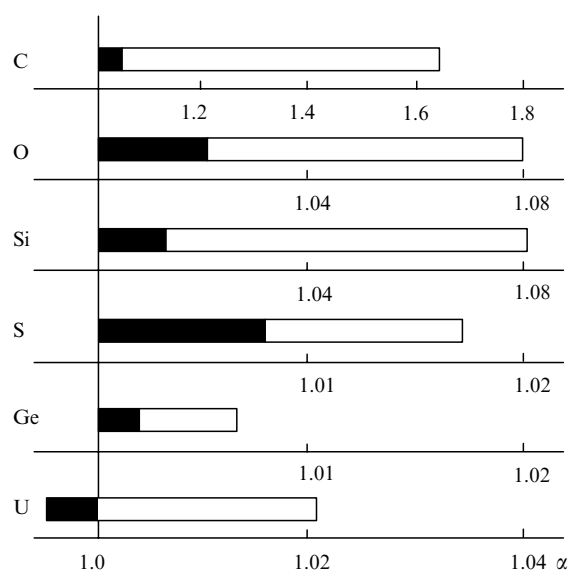


Figure 12. Comparison of the magnitudes of the magnetic (white areas) and classical isotope effects (black areas) in the separation of the $^{13}\text{C}/^{12}\text{C}$, $^{17}\text{O}/^{16}\text{O}$, $^{29}\text{Si}/^{28}\text{Si}$, $^{33}\text{S}/^{32}\text{S}$, $^{73}\text{Ge}/^{72}\text{Ge}$ and $^{235}\text{U}/^{238}\text{U}$ isotope pairs. The coefficient α of one-stage isotope separation (a universal measure of isotope effect) is plotted as the abscissa.

nuclear frequency. In this case, the reaction becomes a radio-frequency emitter, *i.e.* a quantum generator with chemical pumping (similar to chemical lasers). This new phenomenon — radio-frequency emission of chemical reactions — was first predicted theoretically and later found experimentally.⁴⁹ It appears when the energy stored in the Zeeman storage reservoir exceeds the generation threshold, the movement of nuclear spins spontaneously becomes coherent, and this coherent set of nuclei functions as a quantum generator.

Chemically induced electron spin polarisation (CIESP) is the fourth effect. It arises due to the electron-spin selection during the reaction and results in non-equilibrium population of the Zeeman electron levels in radicals and paramagnetic molecules (in this respect, CIESP resembles CIDNP).

The two latter effects are widely used in chemistry and biochemistry as new investigation methods (diagnostics of reaction mechanisms, detection of radicals, and chemical kinetics and chemical physics techniques).

Second-generation magnetic effects. The microwave emission of chemical reactions is only one aspect of chemical radiophysics. A chemical reaction can be not only a generator but also a receiver of microwaves. The reception at the chemical level follows from the principles of spin chemistry: the resonance microwave radiation stimulates the triplet–singlet conversion of radical pairs (or pairs of other spin carriers) and changes the yields of chemical products, which can be detected by chromatography, luminescence, electrical conductivity, *etc.* Thus, owing to the second-generation magnetic-spin effects, a reaction becomes a chemical receiver of microwave radiation.⁵⁰ Moreover, this expedient can be performed selectively. If the microwave pumping affects all the radical pairs, the final outcome reduces to the change in the product yield at resonance frequencies. This effect has been called reaction yield detected magnetic resonance (RYDMR). Selective pumping involving only radical pairs with magnetic nuclei brings about a remarkable phenomenon, radio-induced magnetic isotope effect (RIMIE). Finally, when the microwave pumping is also selective regarding the orientation of nuclear spins (involves only assemblies of radical pairs with selected orientations of nuclear spins), stimulated nuclear polarisation (SNP) appears.

Third-generation magnetic effects. Spin catalysis is the first example of purely physical catalysis.⁴¹ This phenomenon is notable because the spin conversion of reactants is induced by a

paramagnetic species, a spin catalyst. Conversion occurs as a result of exchange interaction of the catalyst with the reactants. Spin catalysis accelerates radical recombination, *cis–trans* isomerisation of compounds with double bonds (by seven to eight orders of magnitude), recombination of spin-polarised atoms, *etc.* Spin catalysis might also be effective in biochemical processes.

The spin chemistry and the chemical radiophysics are based on electron- and nuclear-spin manipulation. When manipulation is accomplished by the chemical reaction itself, interesting first-generation magnetic-spin effects arise; they include microwave generation, which transforms a chemical reaction into a molecular radio station. When spin manipulation is induced by microwaves, even more elegant second-generation magnetic effects originate. They serve as an indicator of microwave reception.

The spin chemistry and the chemical radiophysics are tightly connected; nevertheless, each of them solves independent problems. The former develops new principles of the control of chemical reactions (including that by virtue of microwaves), while the latter is significant practically for biomedical purposes.

VI. Chemistry under extreme and exotic conditions

Nowadays, the scope of chemistry is expanding, modern chemistry is actively encroaching upon fields that have not been of interest or have been inaccessible for classical chemistry. Transition from the ‘explored’ reaction conditions to extreme, non-classical and even exotic conditions occurs more and more swiftly. These conditions include intense electric and magnetic fields, superhigh pressures, shear deformations, light fields with intensities comparable with those of the electric fields inside the molecules, supercritical conditions, powerful gravitation, sonic and microwave fields, *etc.*⁵²

Ultrashort laser pulses (duration 10 fs or shorter) carry enormously powerful optical radiation and electric fields. This immediately gave impetus to the search for new possible effects. In fact, the interaction of optical and electric fields with the electron shells of molecules gives rise to lots of unusual effects.

Picosecond pulses with a power of up to 10^9 W cm^{-2} induce ‘orbital’ excitations in molecules, which lead mainly to the molecule fragmentation. However, when the power is higher (about $10^{14}–10^{15} \text{ W cm}^{-2}$), multielectron ionisation of molecules occurs, which is followed by Coulomb explosion of the atomic-nuclear core. This type of behaviour is observed, for example, for clusters: an intense laser pulse (120 fs, $10^{15} \text{ W cm}^{-2}$) induces efficient ionisation of the NH_3 molecular clusters, which is accompanied by Coulomb explosion, yielding charged nitrogen atoms (N^{2+} , N^{3+} , N^{4+}).⁵³ Fullerene C_{60} is also ionised by an intense laser beam (100 fs, $10^{16} \text{ W cm}^{-2}$) to give C_{60}^{4+} , which is split into fragment ions *via* Coulomb explosion.⁵⁴

The Lorentz forces, which accompany the passage of a laser pulse through a substance, induce several other effects. Thus they ensure the formation of microparticles in polymer solutions. The photon pressure of the Lorentz forces in a concentrated beam captures polymer chains and condenses them into microparticles with diameters of $\sim 10 \text{ nm}$ or larger.⁵⁵ In addition, laser beams cause ablation of atoms and atomic-molecular clusters from solid surfaces, thus performing molecular etching. Each of these effects can provide the basis for not only new chemical research methods but also new high-end chemical technologies.

High-power laser pulses are an excellent means for generating powerful short shock waves (in particular, they are used in physics for laser compression of deuterium aimed at attaining controlled nuclear fusion). In chemistry, laser shock waves are employed to study the behaviour of substances under extreme conditions (high temperatures, high pressures, shear deformations). Thus laser-induced shock waves ensure a pressure of up to 5 GPa in the front; the duration of the leading front can reach several hundred picoseconds for reversible compression and $\sim 20–25 \text{ ps}$ for irreversible compression. The temperature drop behind the shock front occurs at enormous rates (about 10^{11} K s^{-1}).

Laser-stimulated shock waves provide great scope for ‘extreme’ chemistry; they actually give rise to a ‘new wave’ in the use of shock waves. Onion fullerenes and the transformation of fullerene spheres into diamond have been already mentioned. The same occurs with multilayer nanotubes: at pressures of ~ 50 GPa, their outer shells are torn and twisted to give graphite structures (diamond nanocrystals have also been detected).⁵⁷ The synthesis of diamond according to the known explosion technology might occur (at least, partly) *via* onion fullerenes and nanotubes, which are then converted into diamond under the action of a shock wave.

The supercritical state of matter is a source of unexpected and, hence, ‘anomalous’ effects. For example, near the critical point, highly developed density fluctuations are observed, which implies fast reversible clustering of the substance. Perhaps, it is this feature that accounts for the considerable technological advantages of the supercritical state for extraction and other processes.⁵⁸

Synthesis of metallic hydrogen (which has been mentioned above) and the reaction of tritium with hydrogen and deuterium in normal liquid helium and in superfluid quantum helium should be noted as the latest achievements of the ‘extreme’ chemistry.⁵⁹ It was found that the exceptionally large isotope effects observed in this reaction (this is predictable) are different for normal and quantum helium (this is unexpected). If this finding is confirmed, new and unusual evidence for chemical coherence will be thus obtained.

Magnetic-field effects in chemistry have been already discussed within the framework of spin chemistry. All the effects observed in spin chemistry arise as a response of the electron and nuclear magnetic moments to magnetic treatment (a magneto-static field or the magnetic component of a microwave field). In a system of moving electric charges (solvated electrons or ions), the magnetic fields create Lorentz forces, which, in turn, induce a number of other effects. Therefore, the range of magnetic-field effects may prove to be even broader than predicted by pure spin chemistry.

Magnetic fields have considerable influence on the rate of migration of dislocations in ionic and atomic crystals such as NaCl and Si (the rate increases 3–6-fold in 4–5 T magnetic fields),⁶⁰ on the plastic deformation rate and on the strength of ionic crystals⁶¹ (Fig. 13). These effects are of interest for chemistry and solid-state mechanics. Despite the fact that they can find a reasonable and non-contradictory explanation in terms of the concepts of spin chemistry (spin-dependent recombination of dislocations on paramagnetic stoppers, affecting the rate of migration of dislocations), a contribution of Lorentz forces also

cannot be ruled out, even more so because the effects themselves depend on low-frequency (about hundreds of hertz) electric fields.

The influence of magnetic fields on the electrodeposition of silver on copper is apparently also associated with Lorentz forces (the yield of the reaction in a ~ 80 T field at a field gradient of 4×10^3 kT m⁻¹ increases to 45%; in addition the density of the dendrites of the deposited metal increases and their quality improves).⁶² In this case, the magnetic field influences the microdynamics and microturbulence of the electric double layer at the electrode–solution interface *via* the Lorentz force. (It would be pertinent to evaluate the prospects of this new phenomenon).

Unlike chemical radiophysics, based on the magnetic component of a microwave field, *microwave chemistry* utilises the electric component of this field. In microheterogeneous systems with localised polar and non-polar regions (*e.g.* when polar reagents are concentrated in microreactors), microwaves are absorbed by polar and polarisable areas. Actually, these areas function as miniature microwave ovens with addressed supply of heating energy; therefore, reactions which occur in these reactors are highly selective.⁶³

Chemical reactions initiated by ultrasound also occur in microreactors (cavitations). Although the chemical effects in them are specific, they largely resemble those induced by low-temperature plasma and shock waves. Both microwave and ultrasound chemistry are regarded (for good reason) as providing new means for synthetic chemistry.

Finally, the chemistry in intense gravitation fields (as well as the chemistry in the state of weightlessness) undoubtedly belongs to the ‘extreme’ chemistry. A sharp increase in the gravitational force of molecules, clusters and associates in these fields should generate new effects; the magnitudes and signs of the concentration gradients change, equilibria shift, the arrangement of phases in accordance with density is inverted and the rates and competition of processes alter.⁶⁴ The opportunities provided by these effects are virtually unlimited; the problem lies only in the availability of technical means needed to implement them in practice. Of course, this would be possible only for high-end technology rather than for large-scale chemical production.

The *low-temperature region* (near 4 K) was assimilated by chemistry relatively long ago. The most outstanding result is the discovery of the quantum mechanism of chemical reactions, *i.e.* tunnelling through the barrier, and its consequences (enormous isotope effects, temperature-independent limiting rates of reactions). Certainly, this also can be classified as ‘extreme’ chemistry.

The chemistry dealing with temperatures of 10^{-4} – 10^{-6} K should be regarded as ‘exotic’. The preparation of ultracold atoms is based on the fact that the velocity of their movement changes upon the absorption of an optical quantum (laser cooling of atoms). If atoms and laser photons are selected in such a way that the absorption occurs in the low-frequency region of the spectrum (‘red’ edge), then the resonance absorption by an atom moving towards the photons shifts to the line centre and is enhanced, due to the Doppler shift. In the case of ‘accompanying’ atoms, the Doppler effect shifts the resonance away from the centre and attenuates the absorption; consequently, the atoms experience a decelerating force directed along the photon stream. Atoms placed in orthogonal laser beams are decelerated in all the three directions; this creates an optically viscous medium in which the movement of atoms stops, their kinetic temperature being 10^{-4} – 10^{-6} K (even temperatures of 10^{-10} K can be attained).

From ultracold ⁸⁵Rb atoms, a crystal lattice has been constructed (it proved to be a body-centred cubic lattice), the lattice parameters were measured by optical diffraction and the frequencies of collective lattice vibrations were determined.⁶⁵ In other words, scientists succeeded in creating a new state of matter — crystalline gas.

Ultracold atoms, devoid of kinetic energy, are of interest for precise spectroscopy and metrology, for probing the atom – atom and atom – surface potentials, for experimental verification of the postulates of quantum electrodynamics of a single-atomic maser.

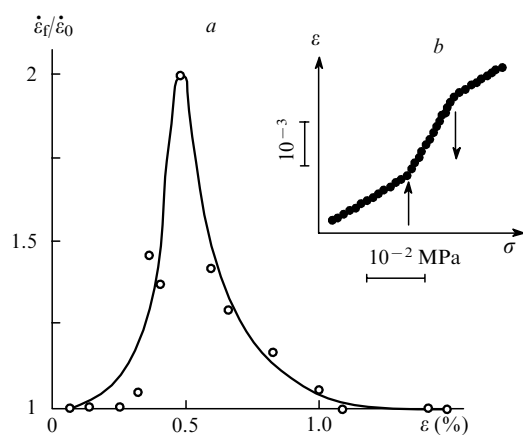


Figure 13. Rate of plastic deformation of a single crystal of NaCl $\dot{\epsilon}_f$ in a 0.7 T magnetic field (in relation to the rate of deformation $\dot{\epsilon}_0$ in a zero field) as a function of deformation ϵ (a), and deformation ϵ as a function of stress σ (b) (the up arrow shows the instant when the magnetic field is switched on, and the down arrow shows the instant of switching off the field).

Optical excitation of atoms in the crystalline gas affords electronically excited atoms, which react with other atoms to give excimer molecules implanted into the crystalline gas. The first steps in the chemistry of the energy-free cold atoms and molecules have already been made; its future starts today. Furthermore, the possibility of laser cooling of molecules in liquids is being discussed.⁶⁶

VII. Once again about cold fusion

In the late 80s of the outgoing century, the scientific world was overwrought by a dramatic event — discovery of nuclear reactions accompanying electrochemical synthesis. The brilliant horizons of the cold nuclear fusion immediately became visible; indirect evidence supporting this finding (neutrons, γ -radiation, excess thermal effects) was even obtained. However, the euphoria has soon come to an end; experimental mistakes and non-reproducibility of the observed effects were found. Consequently, ‘cold fusion’ was wittily renamed to ‘confusion’. At present, both experimental research and debates concerning cold nuclear fusion have transformed into sluggish processes continued by a small group of enthusiasts.

However, the curiosity of this ‘discovery’ has not disappeared. The questions of whether a chemical reaction can induce nuclear fusion and whether transformations of the electron shell can stimulate nuclear transformations still remain open.

Probably, the answer is that generation of neutrons can accompany a chemical process; however, neutrons do not result directly from this process but are formed as a secondary product. They can arise upon nuclear decay induced by γ - and X-radiation emitted by the electron shell, *i.e.* they have a chemical nature.

Although direct chemonuclear fusion was not accomplished, it has given rise to a new strategy of chemical energetics — coupling of a mechanochemical reaction with a non-branched (or slightly branched) chain photonuclear reaction.

This strategy is based on the following idea: mechanically stimulated reactions result in excited electron shells and give rise to γ - and X-rays, which are captured by nuclei (photonuclear reaction); the nuclei excited in this way decay to generate new γ -quanta and/or neutrons. A chain (or partially branched) chemonuclear reaction with energy evolution can occur. The problem is that the mechanical treatment must excite inner electrons; only in this case, conversion of outer electrons to inner vacancies (such as the Auger process) would generate hard X-rays or γ -rays. It is clear that shock waves would be the most suitable type of mechanochemical treatment for this purpose. It is also necessary to elucidate theoretically the appropriate type of electron shell compression (this has already been mentioned in relation to endofullerenes and diamond synthesis) that would enable excitation of high-lying electronic levels of inner electrons (excitation of the outer electrons followed by ionisation would imply escape and inefficient consumption of the mechanical energy).

Another problem is to choose an atomic composition of molecules (or mixtures of molecules) that would permit complete capture of γ - and X-rays by the nuclei. The capture cross-section in photonuclear reactions is known to be relatively large, its spectrum being fairly broad. This provides grounds for believing that the second problem could be solved more easily than the first one (effective mechanochemical generation of hard radiation).

Obviously, this is a strategic goal; on the way to its solution, one can face insurmountable and yet unpredictable obstacles. However, the aim deserves development (at least theoretically, to start with).

VIII. Physics of chemical reactions

Chemistry, like any other highly developed branch of science, has become a high-risk science. This means that the problems of chemistry are complicated and it is not always possible to solve

them by existing methods; therefore, the probability of failures and wasted labour, time and resources becomes fairly high. The risks can be reduced only on the basis of deep insight into the physical aspect of chemical reactions, which is the most important and elitist part of chemical physics.

The physics of chemical reactions is based on four types of dynamics:

- molecular dynamics and molecular organisation;
- energy dynamics (energy dynamics in gases, energy migration in clusters, energy transformation in liquids, energy relaxation in solids);
- chemical dynamics (potential energy surfaces, energetics in the chemical dynamics, theory of chemical reactions);
- angular momentum dynamics and spin dynamics.

The physics of chemical reactions is a field of science involving both experimental and theoretical research; its advances are natural and the problems are traditionally clear (they are analysed in Ref. 24). The main point in this field of science is chemical dynamics, the most important aspect of which is the theory of chemical reactions.

Chemical dynamics have grown out of chemical kinetics; the latter include a general knowledge that has penetrated into all the branches of chemistry and has promoted the development of universal chemical criteria for reaction mechanisms.

However, chemical kinetics deal with the number of chemical events (*i.e.* the interval between the events), whereas chemical dynamics are concerned with the course of the events themselves (movement of the reactants over the potential energy surface). This is the central event in the circle of which the whole chemistry moves and which lies at the heart of a chemical reaction. Chemical dynamics are the ‘cardiogram’ of this ‘chemical’ heart.

The advances in the theory of chemical reactions constitute an individual and broad subject.^{67,68} Actually, two large problems need to be solved: the construction of potential energy surfaces and the calculation of the movement of the reactant nucleus in the calculated potential fields (the proper dynamics of a chemical event).

Both problems can be solved in various modifications, with several levels of approximation and with different degrees to which the quantum nature of the movement is taken into account. In principle, it is now possible to construct a potential surface for any reaction with any degree of accuracy (taking account of the capabilities of modern computers, one has to be able to reduce a reaction of any desired complexity to a simple one without losing its physical or chemical contents). Reliable methods for the calculation of the dynamic trajectories of the reactant movement over the potential surfaces have now been developed. They include methods of classical trajectories (based on the Hamilton–Newton–Lagrange laws of classical mechanics), semiclassical trajectories (taking account of quantum effects *via* superposition of the initial quantum states of the reactants) and purely quantum trajectories (based on the solution of the Schrödinger equation, which presents the probabilities of reactant transformations *via* all reaction channels as an *S*-matrix or scattering matrix). The resulting set of trajectories is used to calculate the canonical $k(T)$ and microcanonical $k(E)$ rate constants (T and E are temperature and energy). Two examples of such calculations are presented in Figs 14 and 15.

General methods for the solution of the dynamic problem have been developed: the method of the reaction path Hamiltonian, the method of the trajectory curvature, multidimensional quantum dynamics and quantum transition state theory. The main idea of the dynamical methods is to distinguish the movement of the reactants along the reaction coordinate and to take into account the influence of all the other types of movement (both ‘assisting’ and retarding). The interaction of all the types of movement (both those directed along the coordinate and others) is considered to be ‘dynamic friction’ and, among other tasks, the modern theory should provide calculation of its value.

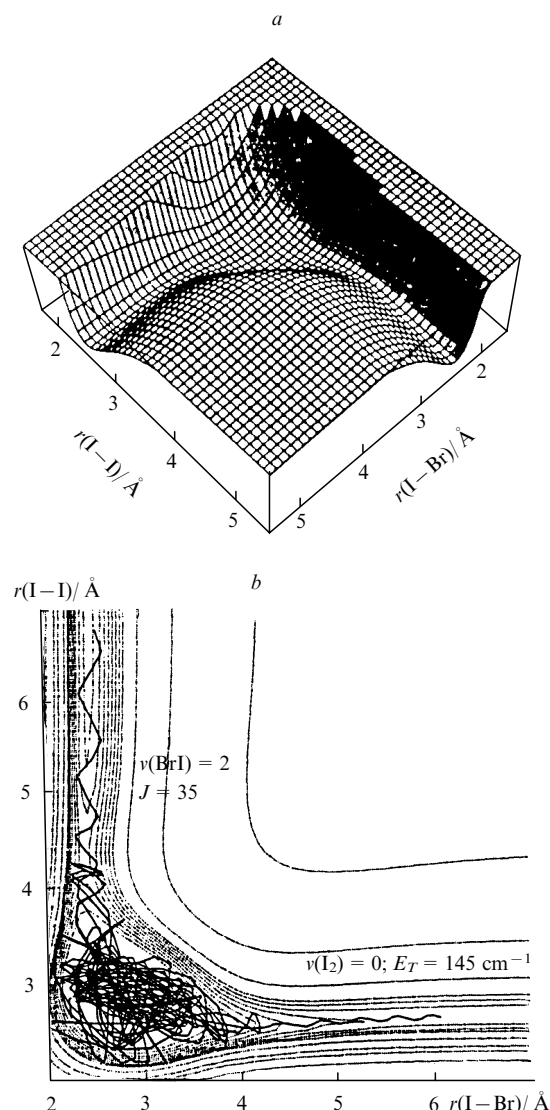


Figure 14. Potential energy surface for the reaction $\text{Br} + \text{I}_2 \rightarrow \text{BrI} + \text{I}$ (a) and one of the trajectories on this surface (b) with a duration of 17.6 ps; v are vibrational states, J is the rotation moment and E_T is the kinetic energy.

However, the great theoretical power of chemistry has an unpleasant aspect. Owing to the broad and successful application of quantum chemistry and molecular dynamics methods, researchers tend to avoid science-dependent and expensive experiments, this tendency becoming more and more pronounced. This is objective reality and the general trend of development of world's chemistry (perhaps, not only chemistry).

The theory of chemical reactions is closely related to the theory of nuclear reactions (this is true not only for the diffusion regime in which the kinetic equations and their solutions are absolutely identical). A system that undergoes a chemical reaction in a liquid or in a solid is similar to the reacting nucleons surrounded by the medium, *i.e.* other nucleons in a nucleus. In this case, too, chemistry occupies an advantageous position: it is simple in the sense that only one type of interaction operates, namely, the Coulomb interaction with a known energy–distance relationship. This is a fundamental statement, which follows from quantum mechanics (the accuracy of its laws is beyond controversy, like that of the laws of classical mechanics). However, there is also direct experimental evidence supporting this statement. The case in point is the experimental probing of atomic wave functions, which are the basis for the entire chemistry.

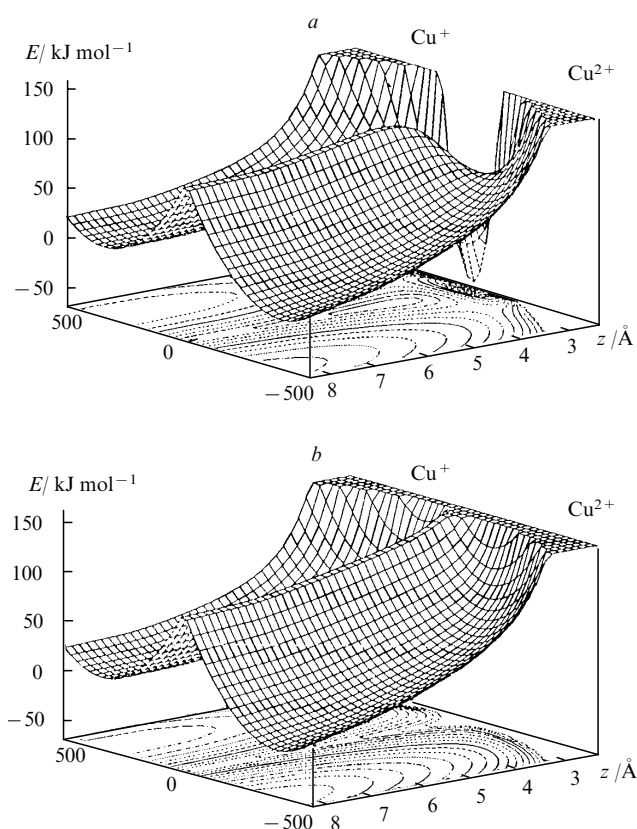


Figure 15. Free energy surfaces for the reaction $\text{Cu}^{2+} \rightarrow \text{Cu}^+$ at an electrode for adiabatic (a) and nonadiabatic (b) transformation; z is the distance of the ion from the electrode, E is the energy of solvent reorganisation.

This experiment is very simple: an atomic (Ca or Cu) beam is excited by polarised light to the p_z or d_{z^2} state; after that, this beam with spatially oriented p_z or d_{z^2} orbitals is exposed to a crossed beam of He atoms; scattering of the He beam is detected, the scattering pattern being used to reconstruct the scattering potential. The result proved to be very vivid: the scattering profile exactly reproduced the shapes of the atomic orbitals.

One can argue that this result is trivial (in the sense that no other result was to be expected); however, it leads to the understanding of the fact that only the Coulomb potential operates in chemistry (a part of it, the exchange interaction, is spin-dependent). Moreover, if we recall the fact that the atomic wave functions have originated on the tip of a pen from the quantum-mechanics postulates and the Schrödinger equation with a centrosymmetrical Coulomb potential, we can feel the triumph of the human mind.

The magic and fascination of chemistry are due to the fact that the Coulomb potential gives rise to a variety of chemical bonds (ionic, covalent, donor–acceptor, dative, hydrogen and van der Waals bonds), chemical species (atoms, carbenes, ions, molecules, exciplexes, Rydbergs, excimers, van der Waals molecules, complexes, radicals, *etc.*), states (ground, excited, charge, spin, orbital, differing in symmetry, *etc.*), mechanisms of chemical transformations and controlling factors (energy, spin, phase, orbital symmetry). With this diversity and wealth, chemistry is always new. The discovery of new states of hydrogen molecules can serve as an example (Fig. 16). They are matched by adiabatic potential minima located in the vicinity of the points of intersection of the binding term $\text{H}^+ + \text{H}^-(1s^2)$ and the repulsive terms $\text{H}(1s) + \text{H}(np)$, where $n = 1, 2, 3, \dots$. These species are not Rydberg molecules having ‘plump’ electron shells with principal quantum numbers reaching hundreds but ‘normal’ molecules with

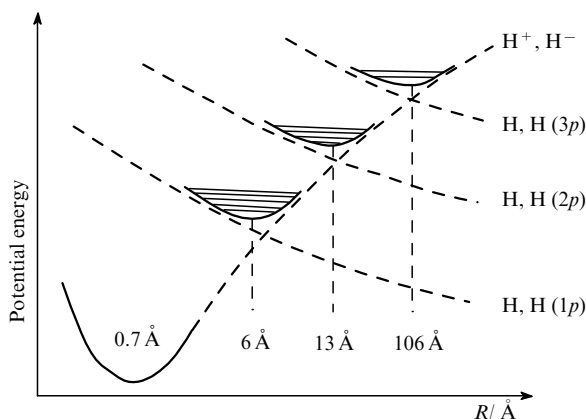


Figure 16. Terms of metastable hydrogen molecules with interatomic distances 6, 13 and 106 Å. They are located in adiabatic valleys at the intersection of the ionic term (H^+ , H) with the terms corresponding to the orbitally excited states $H(1p)$, $H(2p)$ and $H(3p)$.

equilibrium interatomic distances of 6, 13, 106 Å, *etc.* characterised by their own vibrational-rotational spectra. Similar molecules can also exist for other atoms. They can be detected in low-temperature or rarefied plasma or in the huge interstellar chemical reactor.

IX. Atomic-resolution spectroscopy and chemistry

This field of modern chemistry is being vigorously developed; it assumes detection of chemical reactions with high time resolution (about ≤ 10 fs, which is shorter than the period of vibrations of an atom in a molecule) or with high space resolution (~ 1 –5 Å, which is about the size of a single atom or a molecule). Both values correspond to atomic resolution.

The adoption of short laser pulses has extended the scope of chemistry and introduced into chemistry new ideas, which have been embodied in *femtochemistry*.⁶⁹

Firstly, the time periods of 10–100 fs are so short in relation to the period of nuclear vibrations that the nuclei remain virtually fixed at their positions during this period. For example, the interatomic distances in a iodine molecule in the ground state oscillate between 2.5 Å (contracted bond) and 5 Å (stretched bond). A femtosecond pulse ‘catches’ a molecular assembly with a particular interatomic distance and a particular motion phase and throws it almost instantly onto a new potential surface. On this potential, atoms start a new movement, which is now synchronous (coherent). Thus the femtosecond pulse has created a wave packet — an assembly of molecular oscillators with a fixed vibration phase, a given interatomic distance and a definite energy. In other words, femtochemistry opens up the way for production of coherent wave packets.

Secondly, a time resolution of 1–100 fs corresponds to a coordinate resolution of 0.1–0.01 Å. This means that the movement of the nuclei over the potential surface, including that on the top of the barrier and near it, is monitored with this coordinate resolution. It is clear that we are dealing with spectroscopy and chemistry of the transition state, which has always been an object for investigation by theorists but now has become the subject of experimental research. Femtochemistry deals with the time of movement of reaction systems on the potential surface and introduces into chemistry the experimental chemical dynamics.

Thirdly, by monitoring the movement of nuclei over the potential surface, one can interfere in the dynamics of the transition state by its energy or phase pumping and thus change the transformation pathways of the transition state itself. In this sense, one can say that femtochemistry is the chemistry of the transition state.

As an example of the control of chemical reaction channels, let us consider decomposition of a chlorine dioxide molecule $OCIO$. When the pumping energy is $\sim 0.3 \times 10^{12} \text{ W cm}^{-2}$, decomposition follows predominantly the $O + ClO$ pathway; when the energy exceeds $0.8 \times 10^{12} \text{ W cm}^{-2}$, the second channel leading to $O_2 + Cl$, starts to predominate and at an energy of $1.4 \times 10^{12} \text{ W cm}^{-2}$, the rate of decomposition *via* the second channel is 12 times greater than that according to the first channel.⁷⁰ Chemical approaches also permit complete switching of the reaction from the first channel to the second one, for example, this can be attained by adding a water molecule to chlorine dioxide or by placing chlorine dioxide in an $(H_2O)_n$ cluster.⁷¹ Although the chemical method leads to the same result as femtochemistry, this result is achieved by an absolutely different mechanism. In fact, when the initial state of the reactants changes, the reaction switches to a new potential surface; thus, the chemical approaches represent a classical example of changing the reactivity upon complex formation or solvation.

Fourthly, femtochemistry has opened a new chapter in the structural analysis of short-lived species including transition states. Instruments which permit ultrafast diffraction of electrons on these species have been designed. The first femtosecond pulse from a photocathode generates an ultrashort electron beam accelerated by an intense electric field ($\sim 30 \text{ kW cm}^{-1}$). After that, the second femtosecond pulse (with a controlled delay) generates a wave packet or a transition state for a chemical system under study. After that, electron beam diffraction on the transition state or on the reaction product is recorded.

In the future, this remarkable equipment would permit probing of the transition state geometry.⁷² A resolving power of ~ 1 ps with respect to the electron beam (which is the factor limiting the capability of the instruments) has already been attained, and this limit can undoubtedly be overcome. This would enable not only time (spectroscopic) but also geometrical monitoring of the transition state (based on the electron diffraction).

Finally, fifthly, femtochemistry provides great possibilities for investigating ultrafast reactions such as proton (electron) transfer in acid–base (donor–acceptor) pairs; tautomerisation; *cis–trans*-isomerisation with detection of *twist*-conformations; photo-generation and relaxation of an electron–hole pair in semiconductors; elementary steps of photosynthesis; decomposition of molecules (*e.g.*, decomposition of iodine in clusters near the gas–liquid phase transition or under supercritical conditions, *etc.*).

Femtochemistry reveals important new facts concerning heterogeneous processes, in particular, desorption of molecules and desorption mechanism. A femtosecond pulse heats an electron gas to a temperature of several thousand degrees but leaves phonons in metal almost cold (heated to a temperature of only several hundred degrees). The low phonon temperature cannot account for either the high rates of desorption or the high vibrational temperature ($\sim 2000 \text{ K}$) of diatomic molecules. It is clear that the fast desorption of molecules (not more than 10 vibrations on the surface after a femtosecond pulse) is stimulated by the hot electron gas (apparently, *via* generation of an electron–hole pair followed by its fast annihilation at the adsorption site).⁷³ Independent experiments with generation of a surface electromagnetic wave, which probes the surface and its adsorption coverage, has confirmed that, after a femtosecond pulse has been initiated, a molecule remains on the surface only for 3–5 vibrations.

Apparently, femtochemistry would enable detection of fast electronic events such as electron exchange between the protons in the H_2^+ cation (these events take ~ 2 fs), π -electron migration in the Kekule structures of benzene, electron revolution round the nucleus, electron transfer to upper orbitals upon excitation, *etc.* However, this would require lasers of the next generation with a resolving power in the attosecond range (1 attosecond = 10^{-18} s).

The progress in the design of photodetectors and scanning optical microscopes has given access to *observation of single*

molecules (such as rhodamine 6G, and terrylenediimine). By exciting and monitoring stationary luminescence of single molecules (molecular ‘fireflies’), one can study lateral diffusion of molecules on solid surfaces and bulk diffusion in solids (such as polymers). When polarised light is used for excitation and polarised luminescence is recorded, it becomes possible to measure reorientation of molecules and monitor their trajectories. The first wonderful phenomena have already been discovered. Thus an unusual type of behaviour of rhodamine 6G molecules deposited on glass was found; some of the molecules remain still, some other move without rotating and some other rotate without moving.⁷⁴ The behaviour of terrylenediimine on an SiO₂ surface proved to be even more surprising: luminescence of some molecules was found twice modulated by a low frequency (10 and 100 Hz), the luminescence bands of ‘modulated’ molecules being shifted to higher frequency.⁷⁵ Even these two examples demonstrate that probing of a surface by molecular ‘fireflies’ promises a lot of new discoveries.

The capability of optical detection using single molecules is not limited to investigations of molecular dynamics. A ‘flickering’ (non-statistical) behaviour of single molecules associated with spectral diffusion has been found; it is also possible to measure directly the rate of energy transfer to neighbouring molecules and to elucidate the dependence of the energy on the distance (by changing the number of ‘fireflies’ per unit surface; normally several molecules are located on one square micron).⁷⁶

It is obvious that the potentialities of detection using single molecules are substantially increased by using pulse excitation. This brings about new opportunities in the investigation of ergodicity and new methods for direct measurement of quantum yields in the photodecay of single molecules, etc.

The discovery of *tunnelling vibrational spectroscopy* of single molecules is a new great breakthrough in chemistry.⁷⁷ The tunnelling current, which flows between the tip of a tunnelling scanning microscope and a solid surface on which an adsorbed molecule ‘sits’ under the tip, has a clear-cut resonance character. The resonance always occurs in the case where the tip potential (and, hence, the energy of tunnelling electrons) corresponds to the vibronic levels of an adsorbed molecule. Examples of vibrational spectra for several single molecules are shown in Fig. 17.

Vibrational spectroscopy of a single molecule exactly reproduces its portrait and permits one to follow its dynamics (rest time) and chemical fate.⁷⁸ This opens up new prospects for the science of

catalysis. The ways for detecting electron paramagnetic resonance of a single spin are clear and have already been theoretically substantiated.⁷⁹ A great number of new ideas are originating in *atomic-resolution chemistry*.

X. Conclusion

Chemistry as a fundamental science has no limits; it is impossible to represent even its outline within one paper. The face of chemistry is being permanently renewed; new beautiful features appear, which include coherence, atomic resolution (in time and in space), magnetic script of chemical reactions, chemical radio-physics, new ideas in molecular architecture and new molecular assemblies. A special part in the modern chemistry is assigned to the coherent chemistry, which introduces a third controlling factor, the phase (in addition to the energy and spin). In this review, we have discussed the quantum vibrational coherence, the quantum spin coherence and the macroscopic coherence with characteristic times of 10^{-15} – 10^{-13} , 10^{-9} – 10^{-7} and 10^{-1} – 10^{-3} s, respectively. A new level of this field of science would be associated with the generation of electron coherence, *i.e.* creation of electronically coherent wave packets with characteristic times of 10^{-18} – 10^{-15} s.

The intrinsic order and the structure of chemistry and also everything created by chemistry display the charm of strict logic, substantiation and perfection. This is yet another feature of chemistry, which makes it a fundamental science. The scope of chemical research is constantly expanding; it is possible (and useful) to make predictions only regarding the tendencies of development. We cannot foresee the particular events in science; this is clearly demonstrated by the achievements of the last three decades (fullerenes, telomerase, superconducting ceramics, etc.). However, we can make use of our scientific intuition, foresight and professional sense of understanding of the general movement of science and thought.

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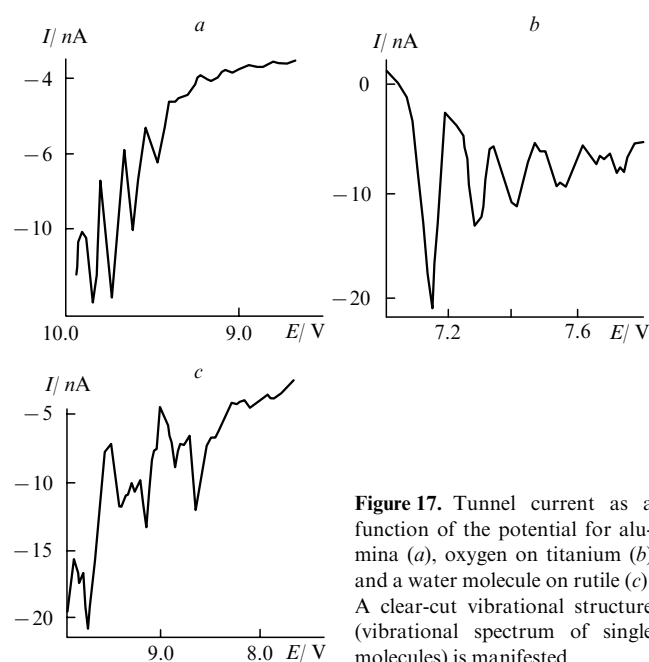


Figure 17. Tunnel current as a function of the potential for alumina (a), oxygen on titanium (b) and a water molecule on rutile (c). A clear-cut vibrational structure (vibrational spectrum of single molecules) is manifested.

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Simulation of nanotubular forms of matter

A L Ivanovskii

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Abstract. Data on the electronic and chemical structure of a new quasi-one-dimensional form of matter, *viz.*, nanotubulenes, are generalised and systematised. Methods and approaches used in modern quantum chemistry for the simulation of the composition, structure, and properties of isolated tubulenes based on layered phases (graphite, boron nitride, boron carbide and boron carbonitride), nanotubular composites and nanotube crystals are described. The role of quantum theory in the development of the concepts of fundamental properties of substances in the nanotubular form and methods of their targeted modification is discussed. Prognostic potentials of theoretical models in solving material science problems are considered. The bibliography includes 197 references.

I. Introduction

The study of nanomaterials (NM) is one of the leading areas of investigation in modern chemistry. Nanomaterials that are currently produced in the form of isolated clusters, powders, films, and consolidated systems with a characteristic size of crystallites not more than 100 nm possess many unusual properties that are promising for the development of high technologies.^{1–8} In addition, they form a unique class of objects used for studying fundamental problems of the metastable state of matter and the prospects of producing its new forms that have no analogues in nature.^{2,6,8}

The greatest progress in this area has been achieved in the field of synthesis and comprehensive studies of a new allotropic modification of carbon, fullerenes, and first of all, ‘classical’ spheroidal carbon clusters (C₆₀ and C₇₀), endohedral complexes, as well as film and crystalline materials based on these substances (fullerites).^{1,2,8}

The topology and physicochemical properties of nonspherical carbon clusters built of a large number of atoms (the so-called giant fullerenes C_n, *n* > 70) have become the subject of numerous

recent studies in which different types of closed carbon structures (capsulenes, torrenes, barrellenes, *etc.*) were discussed.^{1,2}

Iijima⁹ has discovered quasi-one-dimensional (quasi-1D) hollow tubular carbon fibres, *viz.*, nanoscale carbon tubes (nanotubulenes), which are extended cylinders whose walls are formed by rolled graphite sheets. Carbon nanotubes with diameters ranging from five to several tens of nanometres and consisting of 2 to 50 coaxial graphite cylinders [the so-called multilayered nanotubes (MNT)] were detected⁹ by transmission electron microscopy (TEM) in the soot obtained in arc-discharge experiments using graphite electrodes. More recently, both multilayered and single-layered nanotubes (SNT) were obtained.^{10–16}

It was suggested^{8,10} to consider nanoscale tubular structures as a new, quasi-1D form of carbon that occupies a ‘vacant’ position in the series of the known forms of carbon of different topological dimension 3D (diamond), 2D (graphite), and 0D (fullerene).

Almost simultaneously with the first reports on the syntheses of carbon NT,^{10–16} several studies devoted to simulation of their electronic structure were carried out,^{17–24} and unexpected and extremely interesting results were obtained. It was established that, depending on the NT diameter and the type of helical ordering of carbon atoms constituting the cylinder walls, tubulenes can possess both metallic and semiconducting properties.

The predicted possibilities of targeted modification of carbon NT conductivity have at once become the subject of daring hypotheses for their use in diverse exotic devices and elements of electronic circuits of uniquely small sizes (nanocoils, nanowires, *etc.*).^{10,16} The list of possible ‘nanoscale devices’ in which electronic, optical, catalytic, capillary, and other properties of NT can be used, is increasing rapidly.^{25–31}

In the first stage of experimental studies, methods of production of carbon NT and a number of nanotubular composites were developed. The results of these studies were generalised in a monograph.⁸

Recently, stable nanotubular structures based on several layered compounds, *viz.*, BN,^{32–36} BC₃,³⁷ BC₂N,^{37,38} and MoS₂^{39,40} have been synthesised and it was suggested that nanotubular forms of silicon^{41,42} and boron⁴³ as well as consolidated nanotubular materials^{44,45} can be obtained.

Research in the field of the synthesis and study of the properties of nanotubular forms of substances is intimately associated with the development of quantum chemistry of tubulenes, which is caused by several reasons. The interest of investigators in quasi-1D carbon NT and initiation of large-scale projects in the field of

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synthesis, physical chemistry, and material science of NT is to a great extent due to predicted unusual electronic properties of these objects.^{17–24}

Nanotubulenes are obtained by vapour deposition in various media (see, *e.g.*, Refs 6, 8). For instance, carbon tubulenes are synthesised in arc-discharge apparatus in the presence of catalysts. As a rule, the final product is a mixture of NT and other carbon-containing species (*e.g.*, metal carbides), which hampers substantially the studies of the properties of NT themselves. Suffice it to say that the isolation of NT possessing semiconducting and metallic properties predicted in 1992^{17–24} was reported only recently.^{46, 47}

Theoretical simulation of NT plays an extremely important role in the solution of the problem of obtaining the nanotubular substances 'in pure form': almost all the known substances in the nanotubular form and many of their properties were predicted from the results of calculations.

In the present review, the main stages of the development of ideas of the electronic properties of substances in the nanotubular form calculated first of all using modern quantum-chemical methods are considered. Particular attention is paid to the application of theory to the simulation of the structure and description of physicochemical properties of non-ideal nanotubulenes, nanotubular composites, and nanotubular crystals that are most interesting from the viewpoint of their practical use.

II. Theoretical models of electronic properties of ideal carbon nanotubulenes

The principles of theoretical description of ideal carbon single-layered NT were developed in 1992.^{17–24} Schemes of NT classification were proposed and fundamental dependences between the atomic structure of cylindrical nanostructures and their electronic properties were established.

Saito *et al.*¹⁸ considered the principles of the formation of two types of NT taking closed tubulenes as an example. Fullerene C₆₀ hemispheres were taken as the end groups; they can be obtained as a result of dissecting the C₆₀ framework in such a manner that the section plane contained 9 or 10 carbon atoms (Fig. 1). This respectively corresponds to the so-called 'arm-chair' or 'zigzag' cross sections. Since the type of ordering of the atoms constituting the cylinder walls closed by the above-mentioned end groups will be determined uniquely, the corresponding terminology is also used for the description of the NT obtained, and 'arm-chair' or 'zigzag' NT are considered (Fig. 2).

'Open' NT can also be constructed by rolling a planar atomic graphite sheet. In this case each cylinder is characterised by its diameter and the type of helical atomic ordering (chirality).^{18, 19}

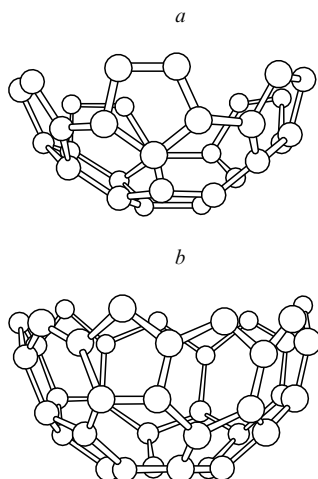


Figure 1. 'Arm-chair' (a) and 'zigzag' (b) cross sections of fullerene C₆₀.

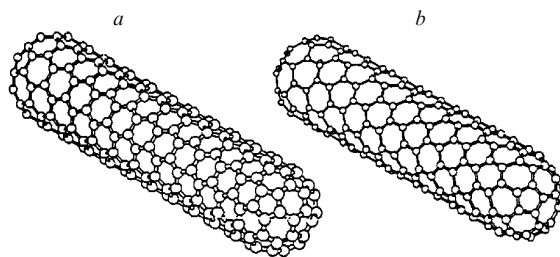


Figure 2. Structure of 'arm-chair' (a) and 'zigzag' (b) tubulenes.

Using the basis vectors of the graphite sheet **a**₁ and **a**₂ (Fig. 3), the diameter (*d*), and the pitch angle (*θ*), the vector

$$\mathbf{c}_n = n\mathbf{a}_1 + m\mathbf{a}_2$$

is given [the so-called (*n*, *m*)-NT]. The parameters *d* and *θ* are defined by the following relationships:

$$d = \frac{|\mathbf{c}_n|}{\pi} = \frac{a\sqrt{3(n^2 + m^2 + nm)}}{\pi},$$

where *a* is the interatomic distance in the planar sheet, and

$$\theta = \arctan\left(-\frac{\sqrt{3}m}{2n + m}\right).$$

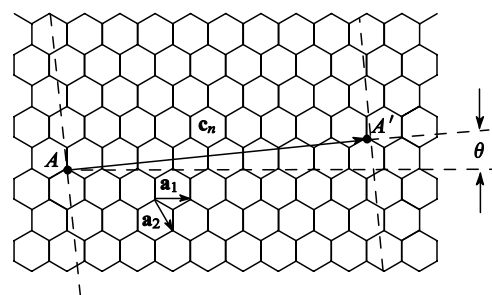


Figure 3. The method for selecting the vector **c**_{*n*} that defines the diameter and the pitch angle *θ* for an 'open' nanotube that can be constructed by rolling a graphite sheet (by matching the points *A* and *A'*).

Depending on the indices *n* and *m*, chiral (*n*, *m*) and achiral (*n*, 0) nanotubes are distinguished.

Calculations of electronic properties for a large number of SNT with variable indices *n* and *m* were performed.^{17–24} In Fig. 4, the distributions of the density of states (DOS) calculated by the tight-binding (TB) method for the (10, 0) and (9, 0) 'zigzag' carbon NT¹⁹ are shown as an example. The energy bands are formed by mixed $\pi(2p_z)$ and $\sigma(2s, 2p_{x,y})$ carbon states. Depending on the radius of curvature, carbon nanotubulenes can possess either metallic or semiconducting properties.

According to calculations,^{17–24} there is a clear dependence between the structural indices (*n*, *m*) and conducting properties of ideal cylindrical single-layered tubulenes. All carbon (*n*, *n*)-NT possess a metallic type of conductivity. If *m* ≠ 0 and *n* = *m* + 3*q*, where *q* is an integer, then the corresponding tubulenes are semiconductors with narrow band gaps, for which the band gap (ΔE_g) depends on the NT radius

$$\Delta E_g \simeq R^{-2}.$$

All other NT possess properties of semiconductors with wide band gaps, for which

$$\Delta E_g \simeq R^{-1}.$$

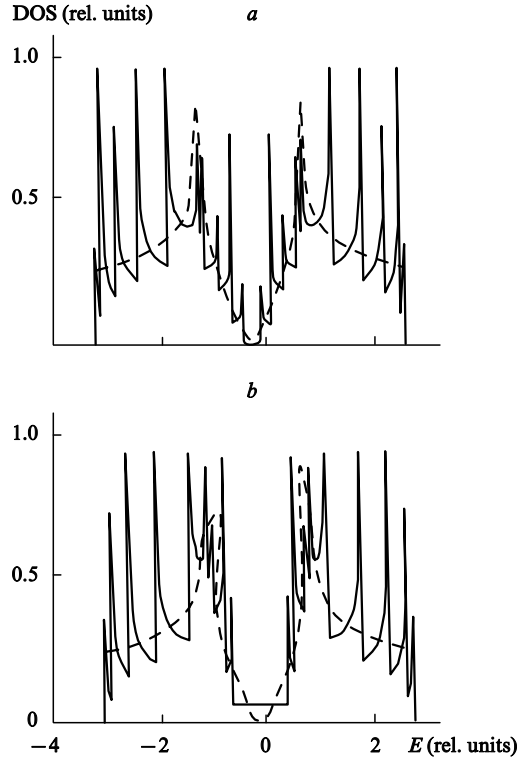


Figure 4. The total density of states (TDOS) for the ‘zigzag’ (10, 0)- (a) and (9, 0)-carbon nanotubes (b).¹⁹ The TDOS for a planar graphite sheet is shown by dashed lines. Calculations by the TB method.

It is natural that the relationships listed above are valid for the tubes of relatively small diameters, whereas at $d \rightarrow \infty$ the band structure of NT is transformed into that of a planar graphite sheet. This fundamental dependence of electronic properties of NT on their structure^{17–24} was confirmed experimentally.^{46,47} Two groups of NT with varied chirality were isolated and their current *vs.* voltage characteristics were measured. In accordance with theoretical predictions, a metallic or semiconducting type of conductivity was observed for these groups of NT depending on their structure.

Refinement of the details of electronic structure of carbon SNT was reported.^{48–64} For instance, it was pointed out that σ - π -hybridisation should be taken into account in the case of semiconducting tubulenes of small radius.⁵⁰ A detailed study of this effect for NT with wide band gaps in the framework of the TB method made it possible to suggest an analytical dependence of ΔE_g on the tube radius.³⁴ The results of some calculations of (n, m) -NT with wide band gaps are listed in Table 1.

Table 1. Dependence of ΔE_g for carbon (n, m) -NT with wide band gaps on their radii.^{26, 54}

(n, m)	$R/\text{\AA}$	$\Delta E_g/\text{eV}$		
		see ^a	see ^b	see ^c
(7, 0)	2.7	0.79	1.11	1.00
(8, 0)	3.1	1.12	1.33	1.22
(10, 0)	3.9	0.65	0.87	0.85
(11, 0)	4.3	0.80	0.96	0.88

^a Calculations⁵⁴ by the TB method in the parametrisation by Tomanek and Schluter.⁵⁹

^b Calculations⁵⁴ by the TB method in the parametrisation by Su *et al.*⁶⁵

^c Data taken from Ref. 26.

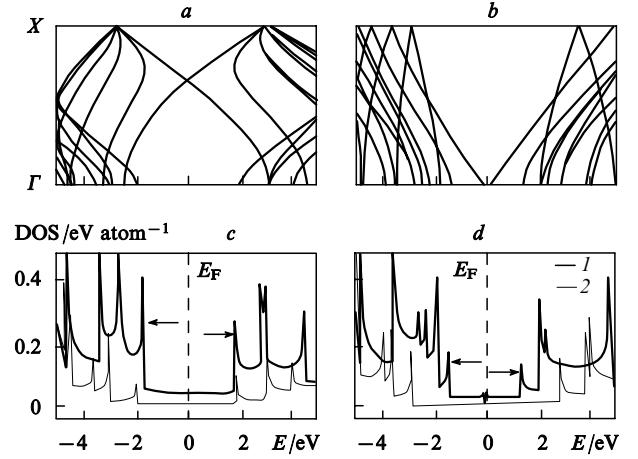


Figure 5. Dispersion of the energy bands (a, b) and the density of p (solid line) and s (dashed line) states of NT, (c) and (d), respectively; (a) and (c) (10, 5)-tubulene; (b) and (d) (9, 0)-tubulene. The δ -shaped DOS resonances near the Fermi level are shown by arrows.

The dependence of the DOS distributions on the NT radii and pitch angles was considered taking a group of metallic NT as an example.⁵⁰ The presence of a DOS ‘plateau’ near the Fermi level between the δ -shaped peaks (Fig. 5) separated by the E interval is a characteristic feature of carbon nanotubes with metallic (and quasi-metallic) types of conductivity [e.g., the (10, 5) and (9, 0)-NT, respectively]. A general relation describing the $E(\theta, R)$ dependence was derived and numerical calculations of this spectral parameter were performed (Fig. 6). As can be seen, the E value (the width of the DOS ‘plateau’ near the Fermi level) is determined by the tube size, *viz.*, E decreases substantially as R increases. For this reason, the parameters of the electronic states of tubulenes possessing metallic and semiconducting properties depend explicitly on their geometric indices.

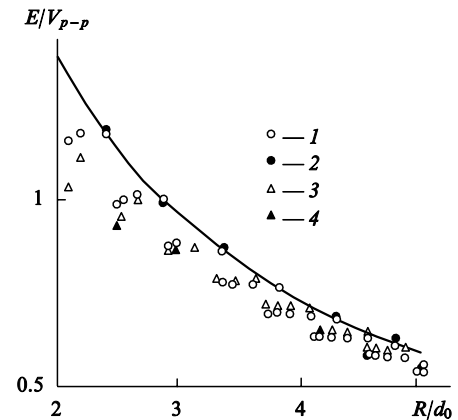


Figure 6. Dependence of the energy interval (E/V_{p-p}) between the δ -shaped DOS resonances near the Fermi level (see Fig. 5) for NT with metallic (1), (2) and quasi-metallic (3), (4) types of conductivity on their radii (R) referred to the C–C interatomic distance (d_0); V_{p-p} is the energy parameter used in TB calculations and determining the interaction between p - p orbitals; (1), (2) $\theta = 30^\circ$; (3), (4) $0 \leq \theta \leq 30^\circ$.

The Peierls type of instability effects for metallic 1D-tubulenes was considered.^{17–19} Based on the results of *ab initio* self-consistent calculations, it was shown¹⁷ that, unlike, e.g., *trans*-polyacetylene,⁵⁸ the temperature of the Peierls transition for the metal-like NT should be much higher than room temperature.⁵⁹

The dependence of the stability of carbon tubulenes on their sizes was evaluated⁶⁰ and compared to similar data for other carbon nanoscale structures and macrostructures. The analysis was based on calculations of carbon atom binding energies (E_b) in NT. The calculations were carried out using two empirical potentials^{61,62} for a total of 169 nanotubes with $R < 9$ Å and pitch angles in the range $0^\circ < \theta < 30^\circ$ (the C–C distances were assumed to be equal to 1.44 Å). Several highly symmetric (n, n)-NT ($n = 3, 4, 5, 6, 7, 9$) were also calculated in the framework of the *ab initio* local electron density functional (LEDF) method.^{63,64} Figure 7 illustrates a clear dependence of the E_b of carbon atom on the NT geometric size ($E_b \sim R^{-2}$), according to which the binding energy of a carbon atom in NT approaches that of a carbon atom in graphite as the NT radius increases. As can also be seen, the E_b values of carbon atoms in fullerenes C_{60} , C_{180} , and C_{240} are higher than those of carbon atoms in the NT of corresponding radii. It was concluded that the formation of tubular or spheroidal nanoscale forms of carbon will be controlled not only by the energy state of a system, but also by the kinetics for the conditions of growth.

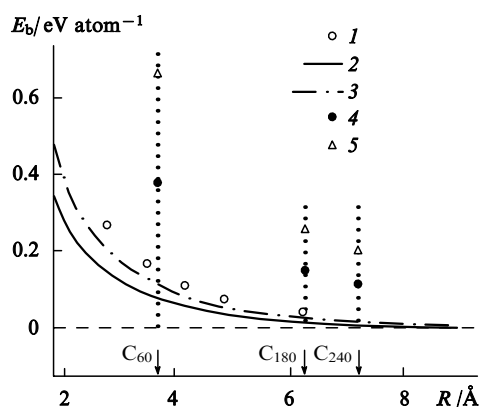


Figure 7. Binding energies of carbon atoms for nanotubes of various radii; (1) LDA calculations; (2) and (3) calculations by the pseudopotential method using data taken from Refs 27 and 28, respectively. The dashed line corresponds to the binding energy of carbon atoms in graphite. The binding energies of carbon atoms in fullerenes C_{60} , C_{180} , and C_{240} are also shown [the data were taken from Refs 27 (4) and 28 (5)].

The electron energy spectra (EES) of multilayered NT are much less studied than those of SNT. A double-layered NT (the radii of the ‘outer’ and ‘inner’ cylinders were 3.4 and 6.8 Å, respectively) was considered using the approximate density-functional computational scheme.⁶⁶ The calculations were carried out assuming a uniform surface electron density distribution without taking into account specific features of individual atomic geometry of the cylinders. It was found that the total density of states (TDOS) distribution for the double-layered NT was similar to that of SNT with characteristic oscillations reflecting the van Hove DOS singularities for 1D systems (Fig. 8). It is believed⁶⁶ that an

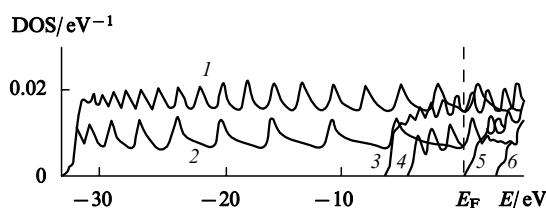


Figure 8. Decomposition of the TDOS for a double-layered NT into partial *s*- (1), (2), *p*- (3), (4), and *d*-components (5), (6) for the inner (1), (3), (5) and outer (2), (4), (6) nanotubes.²⁹

increase in the number of layers will lead to the DOS of MNT approaching that of graphite.

On the whole, the results of quantum-chemical simulation of ideal cylindrical SNT made it possible to obtain a detailed description of their electronic properties and establish clear correlations between the parameters of the electron energy spectra, topology, and NT size. These results have become the basis for further calculations and predictions of some physicochemical properties of NT.

III. Defect structure of carbon nanotubulenes. Nanotubular composites

Investigation of defect NT is a certain stage of the development of the quantum chemistry of nanotubular forms of carbon. Both ‘intrinsic’ structural defects of tubulenes and various heterostructures involving NT (the so-called nanotubular composites) are considered.^{6,8} Three main types of ‘intrinsic’ defects of NT are distinguished, *viz.*, topological defects, rehybridisation defects, and defects of unsaturated (or ‘dangling’) bonds. In the first case, it is assumed that the rolled graphite sheet contains pentagons and heptagons (or their combinations). Rehybridisation defects are associated with the possibility of changing the standard sp^2 hybridisation of carbon atoms (*e.g.*, $sp^2 \rightleftharpoons sp^3$). The third type of defects is due to vacancies, impurities, dislocations, and to the structure of the end groups (open or closed) of NT.

1. Structural defects and relaxation processes

The effects of quasi-1D structural relaxation capable of distorting the ideal cylindrical geometry of model NT were assessed⁶⁷ by the molecular-dynamics (MD) Car–Parrinello method⁶⁸ for a number of chiral and achiral NT. The ‘optimised’ structure of the (10, 0)- and (11, 5)-tubulenes considered⁶⁷ virtually coincides with the initial structure of the model rolled graphite sheet (the difference in the interatomic distances does not exceed ~ 0.01 Å). A possible explanation⁶⁷ is that the substance in the tubular form retains the main types of interatomic interactions characteristic of graphitic sheets.

Donor (nitrogen) or acceptor (boron) substitutional impurities⁶⁷ cause perturbations of the electron density and can affect the conducting properties of carbon NT. Local relaxation rearrangements upon $N \rightarrow C$ substitution are insignificant. When NT are doped with boron, the carbon atoms closest to the boron atoms are shifted along the bond axis by ~ 0.11 Å.

Charge distributions in the presence of substitutional impurities (individual B, N, and Si atoms, anions, and cations) were investigated⁵⁷ in the framework of embedded cyclic cluster model⁶⁹ by the MNDO/PM3 method taking a (6, 6)-NT as an example. It was pointed out that discrete donor or acceptor levels appear in the band gap of the tubulene. Defect-induced perturbations are propagated along the NT axis to a larger number of neighbouring spheres than those propagated along the circumference of the cylinder. Charged defects produce larger perturbation areas than neutral ones.

A topological type of defect associated with the formation of a carbon vacancy was considered.⁷⁰ Taking a metal-like (4, 4)-NT as an example, it was found that the number of conductivity channels (according to terminology^{71,72}) decreases in the presence of carbon vacancies, which leads to suppression of conducting properties of the NT.

2. Radial deformations of nanotubulenes

Charlier *et al.*⁷³ discussed the effect of change in the curvature of atomic layers along the circumference of the carbon cylinder on the electronic properties of NT. The possibility for non-cylindrical carbon NT with pronounced ‘cut’ of the walls to be formed was confirmed by three-dimensional holographic TEM images.^{74–76}

It should be noted that the nature of microdeformations of carbon NT walls (the ‘ripples’ observed on the NT surface⁷⁷) is associated with the rehybridisation effect, *i.e.*, with the change in

the effective hybridisation of the carbon atom from sp^2 to sp^3 (diamond). In this case, local protrusions of the surface that form ‘structural waves’ (folds) with variable curvature will be characterised by averaged $sp^{2+\alpha}$ carbon hybridisation, where the parameter α depends on the curvature of the microarea of the NT surface.

The edges of prismatic NT can be considered as visual lines of rehybridisation that occurs upon the change in the atomic configurations from sp^2 to sp^3 , or as lines of hybridisation defects.⁷⁷

Tight-binding DOS calculations for a cylindrical (10, 0)-tube and (10, 0)⁵-tubes with n -gonal cross sections showed that in the latter case there is a number of peculiarities on the DOS profile such as clearly seen effects of $\sigma^* - \pi^*$ hybridisation and appreciable changes in the energy band structure. These peculiarities are characteristic of small-diameter NT.

In Fig. 9, the energy band structures of the (10, 0)- and (10, 0)⁵-NT are shown as an example. The π^* -band energy of the (10, 0)⁵-NT decreases substantially (the so-called NT ‘metallisation’). The nature of this phenomenon becomes clear from comparing the charge density distributions (ρ) in the cross-sectional planes of cylindrical (10, 0)- and pentagonal (10, 0)⁵-NT for the Γ -states near the Fermi level. The clearly seen ρ anisotropy at the vertices of the pentagon, partial outward shift of the charge density (the formation of σ -like states), and the reduction of the symmetry of the system lead to a substantial decrease in the band gap and to a change in the type of conductivity from semiconducting for the (10, 0)-NT to metallic for the (10, 0)⁵-NT.

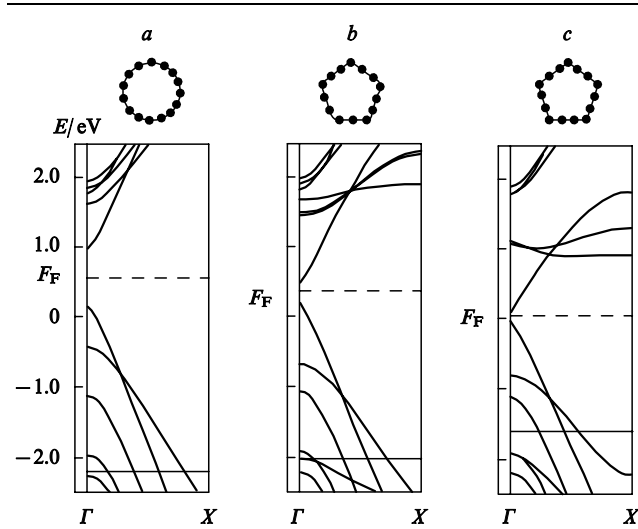


Figure 9. The energy band structures of (10, 0)- (a) and (10, 0)⁵-NT (c), and a tubulene with ‘intermediate’ type of cross section (b).

Changes in the energy band structure of metal-like NT upon ‘polygonisation’ of their cross sections were considered taking (12, 0)ⁿ-NT ($n = 6, 4, 3$) as examples.⁷³ It was established that the conducting properties of the NT change in the following order: metallic [(12, 0)-NT] → semiconducting [(12, 0)⁶-NT with a band gap of about 0.5 eV] → metallic [(12, 0)⁴- and (12, 0)³-NT], which is mainly determined by the energies of the $\pi - \pi^*$ bands.

3. Uniaxial compression (tension) of nanotubes

Along with radial deformations in the cross-sectional plane, nanotubes can undergo longitudinal compressions (in particular, axial ones). This type of effect becomes of particular interest in connection with the investigation of mechanical properties of NT.^{6, 8, 78, 79}

The effect of uniaxial stress on the density of states and type of conductivity of SNT was studied by the TB method taking ‘zigzag’

($n, 0$) and ‘arm-chair’ (n, m) carbon nanotubulenes as examples.⁸⁰ A homogeneous uniaxial compression ($\sigma < 0$) and tension ($\sigma > 0$) was simulated by displacements of carbon atoms. Uniaxial stress will lead to the change in the NT chirality, which determines the energy characteristics of the cylindrical structures. It was found⁸⁰ that, depending on the index n and considering it as $(3q - 1)$, $3q$, or $(3q + 1)$, where q is an integer, the ($n, 0$)-NT can be arbitrarily classed into three groups. The band gaps of $(3q + 1)$ -NT will increase while those of $(3q - 1)$ -NT will decrease upon compression of ($n, 0$)-NT. The type of conductivity of the $(3q, 0)$ -NT changes from metallic to a semiconducting one; for this reason, these NT are the most convenient objects for experimental testing of the dependence predicted.⁸⁰

For all ($n, 0$)-NT considered,⁸⁰ the band gaps depend linearly on the modulus of compression (σ). According to the estimates⁸⁰ the band gap sensitivity to stress, $|dE_g/d\sigma|$, is about $10.7 \text{ meV GPa}^{-1}$ in the range $|\sigma| < 10 \text{ GPa}$. All metal-like ‘arm-chair’ (n, m)-NT retain their properties upon uniaxial stress.

The effect of compression on the electronic characteristics and other properties (in particular, on chiral currents) of nanotubulenes was studied by the self-consistent electron density functional method taking a group of carbon NT as an example (Table 2).⁸¹ It was found that the major effect of compression of (9, 7)-NT consists in an appreciable increase in the band gap due to a decrease in the dispersity of π and π^* bands near the Fermi level. It is possible to make the system conducting by introducing hole or electron carriers. This can be done by doping NT with atoms of alkali metals (AM) or halogens. Miyamoto⁸¹ simulated this effect by fixed shift of E_F . By solving the Boltzmann equation the components of the conductivity tensors of NT were found and the pitch angles for charge carrier currents were determined (see Table 2). It was stated⁸¹ that violation of the symmetry of the hexagonal atomic ordering of the cylinder walls upon its compression can cause chiral currents to flow. This effect is most pronounced for the ‘arm-chair’ NT.

Table 2. Geometric parameters of compressed (n, m)-NT and pitch angles of chiral currents (θ') in the case of doping with electrons (e) and holes (h).

Geometric parameters of (n, m)-NT				θ' / deg (see ^a)
(n, m)	$d / \text{\AA}$	θ / deg	degree of compression (%)	
(13, 1)	10.78	4.1	10	1.6(h) 8.8(e)
(11, 4)	10.60	15.5	10	0.5(h) 12.4(e)
(9, 7)	10.97	24.9	5	4.2(h)

^a The calculations were carried out assuming that E_F is shifted by 50 meV from the bottom of the conduction band and from the top of the valence band upon doping of NT with electrons and holes, respectively.

TEM images^{82–84} indicate that carbon NT can undergo diverse changes in their shapes and spatial configurations and that the types of NT deformations considered (radial and uniaxial) are a particular case of such changes. Studies of arbitrarily deformed NT are scarce due to the complexity of the description of their electronic properties.

4. Deformations of carbon nanotubulenes

As a rule, the problems of deformational behaviour of NT are studied in the context of the development of ‘nanomechanics’. Most of experimental studies in this line^{6, 8, 78, 79, 85–90} have been devoted to investigation of the brittle–elastic properties of NT under different conditions of external strain.

The microscopic simulation of the energy characteristics of mechanically deformed NT was performed by MD methods^{88, 91}

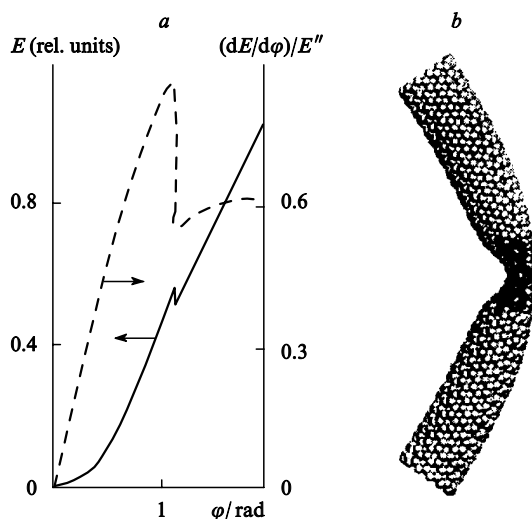


Figure 10. Dependence of the strain energy (E) and its derivative ($dE/d\phi$) on the bending angle (ϕ) for the (13, 0)-NT (a) and the NT shape upon 'kink' (b).

using many-body interatomic potentials^{61,62} and energy parameters obtained in band structure calculations of 'slightly deformed' NT.^{60,92,93}

Typical of this investigation line are MD calculations of the brittle–elastic properties of NT exposed to classical types of deformation (compression, bending, and torsion).^{88,91} Figure 10 illustrates the results obtained from MD calculations of the strain energy dependence of a (13, 0)-NT, 8 nm in length and 1 nm in diameter, on the tube bending angle. External strain was applied to both tube ends. The strain energy smoothly increased before the tube 'kink' (or inelastic bending) and sharply decreased afterwards.

The results of calculations^{88,91} reproduce the observed singularities on the strain–stress curves of NT of different dimensionality and are in good agreement with the experimental results.^{8,85–89} This makes it possible to point to the development of theoretical foundations of the nanomechanics of nanotubular objects.

Quantum-chemical calculations of electron states were carried out only for certain possible configurations of deformed NT, *e.g.*, for uniform and non-uniform tubular helices (Fig. 11)⁹⁴ both predicted theoretically⁹⁵ and observed using the TEM technique.^{96,97} In addition to hexagons, the walls of helices include various heptagon/pentagon combinations. Helical NT are an extensive class of objects related to toroidal carbon nanostructures.^{8,20,98–102} The topology of helical NT is

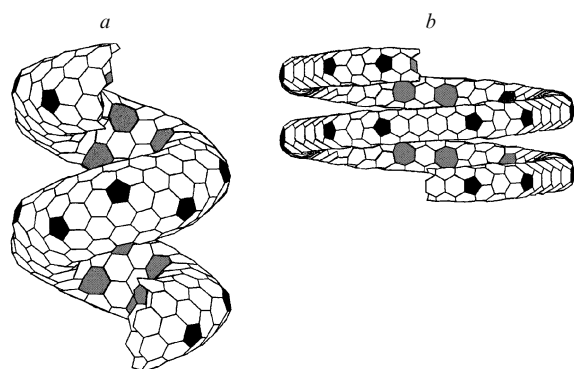


Figure 11. Models of helically deformed uniform (C_{360}) (a) and non-uniform (C_{540}) (b) tubular structures.⁹⁴

described^{96,103} using the Kekule structures and the concept of 'phason lines'.¹⁰⁴ Tight-binding calculations⁹⁴ showed that the energy band structure (in particular, the change in the band gap ΔE_g) depends strongly on the topology of the NT helices: an interrelation has been found between the arrangement of the 'phason lines' in the helices and the type of their conductivity.

5. Connection of nanotubulenes

Targeted introduction of topological defects into an NT, *i.e.*, replacement of a part of hexagons in the rolled graphite sheet that forms tubulene walls by other polygons (heptagons or pentagons) can change substantially its electronic properties. In this case, the theoretically predicted possibility of the formation of heterojunctions based on NT^{6,8} opens wide prospects for using carbon NT as the elements of integrated circuits of uniquely small size.

This situation can be considered from the viewpoint of longitudinal connection of two different tubulenes in which heptagons, pentagons, and their various combinations play a determining role in the formation of matched structures of NT (Fig. 12), thus opening new possibilities of producing electronic n – p transitions.

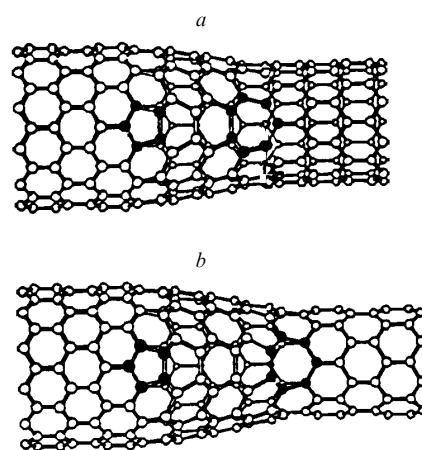


Figure 12. Variants of longitudinal connection of 'zigzag' carbon tubulenes; (a) (12, 0)/(9, 0)- and (b) (12, 0)/(8, 0)-tubulenes. Carbon atoms participating in the formation of heptagons and pentagons in the structure of intertubular connectors are shown as bold solid circles.

It should be noted that the above-mentioned polygons (pentagons and heptagons) can be constituents of the ends of 'open' nanotubes and impart to them a conical shape of variable conicity, which can become of great importance for the development of nanoscale electron-emitting devices based on NT.¹⁰⁵

Different types of matching and the properties of carbon NT of different diameter involving a heptagon–pentagon pair were simulated by the TB method taking (12, 0)/(9, 0)- and (12, 0)/(8, 0)-tubulenes as examples (see Fig. 12).¹⁰⁶ According to calculations performed taking into account only π -states, there are delocalised states for each of the tubulenes and localised states corresponding to open ends of NT ('dangling' bonds) in the spectrum of the entire system. The estimates¹⁰⁶ of the dependence of conducting properties on the voltage applied (U) showed that the current I increases as U increases for matched (12, 0)/(9, 0)-nanotubes with metallic type of conductivity and that oscillations corresponding to resonances of tunnelling probability between the two NT are observed on the current *vs.* voltage plot. The conductivity of the system of connected metallic (12, 0)- and semiconducting (8, 0)-nanotubes will be determined by the contribution from the (12, 0)-tubulene to the region near the Fermi level in the spectrum of the entire system.

A more detailed consideration of the EES of carbon NT with variable number of topological defects (pentagon–heptagon pairs, or 5/7-defects) of the wall surfaces of 'zigzag' (n , 0)-tubu-

lenes was carried out.¹⁰⁷ A system of (12, 0), (11, 0), and (9, 0)-nanotubulenes matched in pairs using one, two, and three pentagon–heptagon pairs arranged either along the cylindrical axis or along the cylinder circumference was calculated. The data listed in Table 3 illustrate the change in the energy of NT with topological defects (relative to that of ‘perfect’ tubulenes). As can be seen, in the general case, an axial arrangement of the 5/7-defect is the most energetically favourable. Even more energetically favourable is the formation of a specific type of defect in which a pentagon and a heptagon are separated by rings of hexagons (the 5/6/7-defect, see Table 3).

Table 3. Energy changes (relative to the energies of ‘perfect’ tubulenes) for different types of nanotube connection depending on the type of the arrangement of topological defects.

NT system	Number of defects	$\Delta E / \text{eV atom}^{-1}$		
		5/7 defects along the circumference	axial 5/7 defects	specific defect ^a
(12, 0)/(11, 0)	one 5/7	0.132	—	—
(12, 0)/(11, 0)	two 5/7	0.258	0.249	0.208
(12, 0)/(9, 0)	three 5/7	0.405	0.291	—

^a 5/6/7-Defect, see text.

Regularities of the rearrangement of electron states near the Fermi level in the region of hetero-junction can be traced taking a matched (12, 0)/(11, 0) metallic–semiconducting NT with optimised geometry as an example (Fig. 13). On going from the last segment of the (12, 0)-NT to the first segment of the connection structure, the DOS oscillations relative to the DOS ‘plateau’ of isolated (12, 0)-NT are observed near E_F . Similar DOS oscillations of gradually decreasing amplitude are observed when moving further along the connection structure toward the first segment of the (11, 0)-NT. The first segment of the (11, 0)-NT is gapless, which manifests itself as a smooth metal to semiconductor transition. The DOS of the hetero-junction structure approaches those of individual nanotubulenes at a distance of $\pm 20 \text{ \AA}$ from the connection structure on each side of the cylinders.

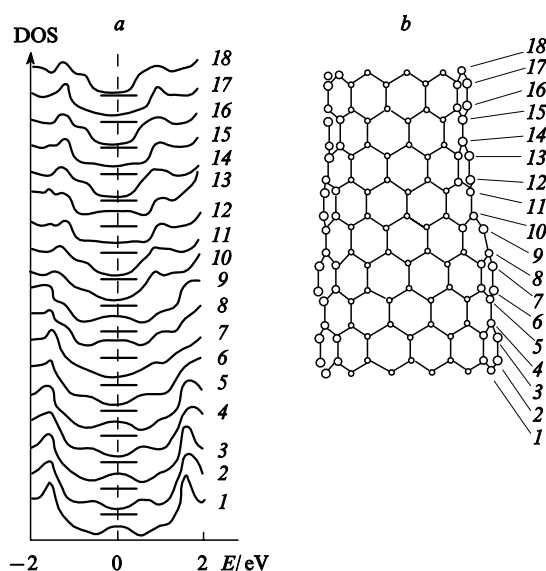


Figure 13. The electron density of π states (a) and the cross sections (1)–(18) of the intertubular connector structure for the (12, 0)/(11, 0)-NT (b).

6. Nanotubular composites: intercalation of carbon nanotubulenes

Intercalation of NT with atoms of various elements makes it possible to obtain quasi-1D nanomaterials with varied properties. For instance, it is possible to obtain composites by incorporating metal wires into NT. These can be used as nanowires of uniquely small cross section in which the tubulene simultaneously acts as both an insulator and a protective shell (*e.g.*, in oxidation processes). The properties of the components can change substantially upon interaction between the metal nanowire and NT (*e.g.*, new phases of a metal ‘encapsulated’ into the NT can be formed). This interaction can also cause a non-trivial modification of the properties of the entire hetero-system. For instance, its electron-phonon spectra and superconducting properties can be changed appreciably by intercalating the NT with alkali metals (AM), as is observed for fullerenes doped with AM or for intercalated graphite (see, *e.g.*, Ref. 8).

In most of experiments on NT intercalation, multilayered tubulenes of large diameter ($> 100 \text{ \AA}$) were obtained, which were filled (either directly in the synthesis or using the capillary effect) with Mg, Bi, Pb, several transition metals, lanthanides, and their carbides.^{108–117}

These systems are considered in the framework of several computational schemes. Semiempirical MNDO calculations⁵⁷ of ($n, 0$)-tubulenes ($n = 6, 8$) with one or two encapsulated monatomic potassium wires oriented along the cylinder axis were performed using the embedded cyclic cluster model. It was found that the band gaps characteristic of initial NT disappear in the intercalated systems because of the appearance of new $K 4p$ states. As a result, the $K@(n, 0)$ systems are 1D conductors.

A quasi-1D hetero-structure consisting of a carbon nanotube ($R = 3.4 \text{ \AA}$) filled with a Pb nanowire ($r = 2.4 \text{ \AA}$) was considered.⁶⁶ Taking into account the approximations used in the calculations (a numerical method¹¹⁸ was employed), Östling *et al.*⁶⁶ could only suggest that the electron states of the Pb nanowire will hybridise mainly with the near-the-Fermi-level π -states of the tubulene.

More rigorous calculations of (4, 4)-NT intercalated with 1D potassium and aluminum wires were carried out by the *ab initio* pseudopotential method.^{119, 120} It was assumed that the metal wires and the (4, 4)-NT constitute commensurate ‘phases’ and that the interatomic distances in the wires are the same along the whole tube length. For the $K@(n, n)$ -NT system, the energy effect of intercalation (heat of formation) was also calculated depending on the tubulene diameter ($\sim 1 \text{ eV atom}^{-1} \text{ K}^{-1}$).¹¹⁹ The corresponding value for the $Al@(4, 4)$ -NT system was found to be negative¹²⁰ and it was assumed that intercalation of Al into the (4, 4)-NT can occur only in the gas phase under high pressure. Under normal conditions, only carbon nanotubes of large diameter can be intercalated with aluminum.

The results obtained^{119, 120} show that quantum-chemical methods can be effectively used for solving important problems related to search for compositions of nanotubular composites and conditions of their production. Taking into account promising technological applications of these materials, one can expect the development of the material science of this class of substances.

IV. Electronic properties of several non-metal compounds in the nanotubular form

The progress in the synthesis and the study of the properties of carbon NT has initiated investigations on the search for tubular nanostructures of other substances. Hexagonal boron nitride (h-BN), an isoelectronic and isostructural graphite analogue, was proposed^{121, 122} as the first candidate. It should be noted that the syntheses of the nanotubular form of BN and some other boron compounds^{32–38} were performed on the basis of predictions made in the first theoretical studies on their structure and properties.^{121–124}

Based on similarity in the structural and electronic properties of the known 2D boron compounds (h-BN, BC_3 , and BC_2N ^{125, 126}) and graphite, the theoretical approaches successful in calculations on the tubular forms of carbon were used.^{121–124}

1. Boron nitride-based nanotubulenes

Electronic properties of nanotubes based on h-BN were considered.^{121, 122, 127} The dependence of the EES of chiral and achiral (n, m)-NT on their diameters was studied using a simple s, p TB model.¹²² It was found that all the boron nitride nanotubulenes (BNT) considered are semiconductors in which the band gap (ΔE_g) decreases as the tube radius decreases. Chiral (n, m)-NT are less sensitive to variations of the tube radius than ($n, 0$)-NT. In addition, ($n, 0$)-NT are semiconductors with direct gaps ($\Gamma-\Gamma$), whereas (n, m)-NT have indirect band gaps ($\Delta-\Gamma$). Changes in ΔE_g upon varying pitch angles θ are most pronounced for the tubes of small diameter. Nanotubes with $d > 12 \text{ \AA}$ have wide band gaps which depend slightly on θ . The following qualitative explanation can be proposed: in NT of small radii, the number of nonadjacent atoms is larger, and the distances between them appear to be comparable with interlayer separations in h-BN.

MNDO calculations of the electronic properties of ($n, 0$)- and (n, n)-BNT ($n = 6, 7, 10, 12$) were performed.⁵⁷ All NT were referred to dielectrics ($\Delta E_g \approx 4.8 \text{ eV}$). The position of the bottom of the conduction band is determined mainly by boron s, p states, whereas that of the top of the valence band is determined by nitrogen states.

More rigorous LDA calculations¹²¹ of ($n, 0$)- and (n, n)-BNT with diameters in the range from 4.0 to 12.0 $\text{\AA}$ indicate that they are semiconductors with wide band gaps ($\Delta E_g \approx 5.5 \text{ eV}$). Because of this, the dependence of the electronic properties of BNT on their size and structure is less pronounced than in the case of graphite-based tubes. This fact is of importance for the preparation of nanomaterials with preset parameters.

When analysing the bands near the Fermi level, it was found that the states of the bottom of the conduction band are similar to those of ‘quasi-free’ electrons.¹²¹ These states are concentrated in the inner part of the tube (Fig. 14). This peculiarity may have important technological applications in the doping of BNT with electron carriers, which would make it possible to vary their electrophysical properties over a wide range.

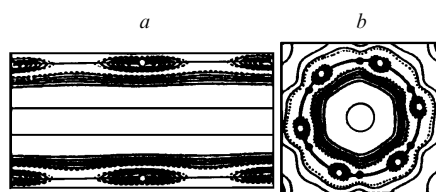


Figure 14. The total charge density distribution in the longitudinal section (including nitrogen atoms) (a) and in the cross section (b) of the (6, 6) BNT (LDA calculations).

Interesting results were obtained in the optimisation of the geometry of BNT.¹²¹ It was shown that this tubular structure can be considered as a ‘double-layered’ structure consisting of oppositely charged coaxial cylinders that form a specific quasi-1D dipole. The boron ions constitute the ‘outer’ cylinder, while the nitrogen ions constitute the ‘inner’ one. The ‘intercylinder’ distance depends slightly on the tube chirality and decreases as its diameter increases. The total energy (E_{tot}) of BNT appeared to be lower than that of carbon NT of the corresponding diameter (Fig. 15). Comparison of the total energies of a BNT and an h-BN ‘strip’ obtained upon the ‘development’ of the corresponding cylinder showed that the ‘strip’ form of h-BN is much less stable than its tubular form.

It was established that if the distance between the tube walls in double-layered BNT [e.g., a (4, 4)@(9, 9)-NT] is comparable with

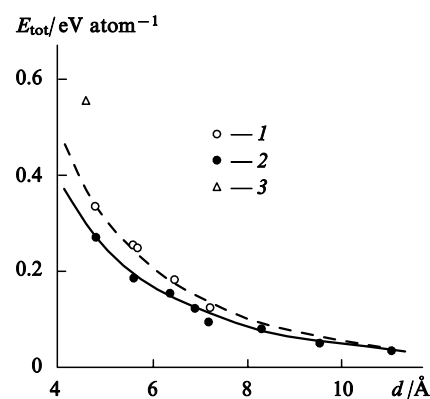


Figure 15. Dependence of the total energy (E_{tot}) on the diameter (d) for carbon (1) and BN (2) nanotubes. The E_{tot} value for a ‘strip’ obtained by ‘developing’ the (6, 0)-BN nanotube (the point 3) is shown.

the interlayer separation in crystalline h-BN, the intertubular interaction has virtually no effect on the structure of electron states of individual NT. Single-layered and multilayered BN tubulenes are stable semiconductors with wide band gaps.¹²¹

Simulation of hetero-structures based on boron nitride tubulenes was first performed by Rubio *et al.*¹²⁸ who considered (4, 4)-BN-tubulenes intercalated with K and Al. It was assumed that, taking into account the peculiarities of the electronic structure of BNT,^{121, 122} the interaction between the metal atoms and the NT walls will be appreciably weaker than for carbon tubulenes. The estimated intercalation energies (the difference between the total energies of the composite and its components, *viz.*, the tubulene and the metallic wire) of these hetero-structures appeared to be much lower than those of analogous systems based on carbon NT. The K 4s states of the K@ (4, 4)-BNT were found to interact with the tubulene band near the Fermi level (Fig. 16). For an Al@ (4, 4)-BNT, it was found that additional Al s and p_z levels

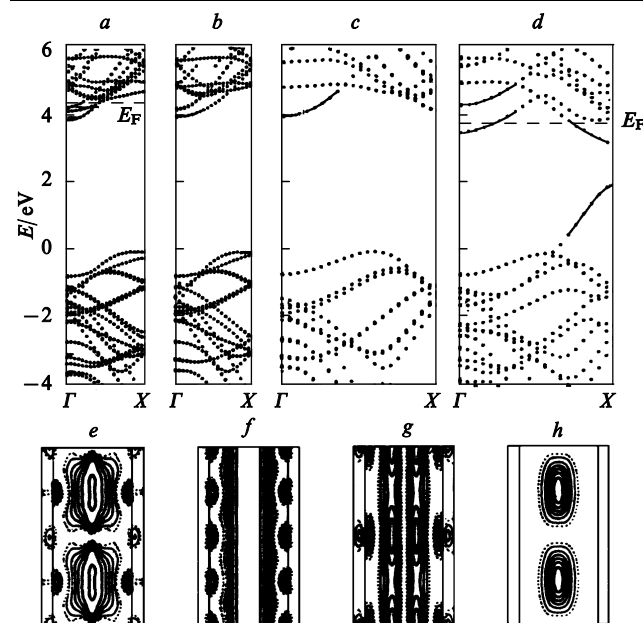


Figure 16. Energy band structures (a)–(d) and charge distributions (e)–(h) for the (4, 4)-BNT and for the composite K@ (4, 4)-BNT and Al@ (4, 4)-BNT.

The energy bands: (a) K@ (4, 4)-BNT; (b) and (c) (4, 4)-BNT for single and double unit cells, respectively; and (d) Al@ (4, 4)-BNT. Charge distributions for the states near the Fermi level are shown for longitudinal sections of the tubes. For the composite Al@ (4, 4)-BNT, the contributions from Al s states are shown by solid lines.

appear in the band gap. The EES of the $\text{Al}@ (4, 4)\text{-BNT}$ appeared to be close to a simple superposition of the spectra of a monatomic Al wire and a (4, 4)-tubulene, which indicates a weak interaction between them. The plots of the charge density distributions for the near-the-Fermi level states in the $\text{K}(\text{Al})@ (4, 4)\text{-BNT}$ (see Fig. 16) show that the density of electron carriers that control the conductivity of intercalated BNT is localised inside the cylinder. This differs these systems from composites based on carbon NT in which the contribution to the conductivity from the tubulene walls dominates. For this reason, BNT can be preferred (as compared to carbon tubulenes) for production of the nanowires with preset properties. The possibility of intercalation of BNT with Ag and Au atoms for production of continuous nanowires¹²⁷ cannot also be ruled out.

2. Boron carbide-based nanotubulenes

Electronic characteristics of some hypothetical $(n, 0)\text{-NT}$ based on layered BC_3 were considered.¹²⁴ The conductivity type changes from metallic to semiconducting as the NT diameter increases. This effect is associated with noticeable deviations of the bond angles (for NT of small diameter) from 120° . With an increase in the NT diameter, the bond angles approach the ideal value for planar sheets (120°), and ΔE_g for NT approaches the band gap of single BC_3 sheets (see, e.g., Refs 125 and 126). The analysis of the DOS distribution for a $\text{BC}_3\text{-tubulene}$ shows that the lowest unfilled bands are composed of π - and π^* -states and the highest filled bands are composed of σ -states. Near the Fermi level, the density of σ -states is considerably higher than that of π -states. It is assumed that the conductivity of a $\text{BC}_3\text{-NT}$ of a fixed diameter can be varied over a wide range upon doping by varying the degree of filling of the energy bands. In this case, ‘metallisation’ of the σ -band, i.e., a decrease in the concentration of electrons, will be a more efficient way of increasing the NT conductivity. Additional holes can appear upon partial replacement of carbon atoms by ‘superstoichiometric’ boron atoms. Atoms of halogens (Cl, Br, I) can also act as hole donors, as is the case for, e.g., intercalated graphite-based compounds.¹²⁴

Strain energies of BC_3 nanotubes were calculated.¹²⁴ The total energies of these tubulenes appeared to be lower than those of graphite-based NT. Further studies of $\text{BC}_3\text{-nanotubes}$ should be carried out taking into account not only single-, but also multi-layered nanotubes, since it is known that the interlayer interaction plays a decisive role in the formation of conducting properties of crystalline BC_3 .¹²⁵

3. Boron carbonitride-based nanotubulenes

Depending on the ordering type of atoms (B, C, N) constituting the layers and on the type of layer-by-layer packing, graphite-like boron carbonitrides can possess either metallic or semiconducting properties.^{125, 126} In addition, the strong ‘intralayer’ anisotropy of charge distributions suggests that circular chiral currents can arise upon rolling the single layers into cylinders. In this case the NT can be considered as nanoscale solenoids.

The geometry of several $(n, n)\text{-BC}_2\text{N}$ nanotubes was calculated by the TB method.¹²³ Nanotubulenes of small diameters ($n = 2$) retain the conductivity type intrinsic in the initial BC_2N single layers.¹²⁵ However, for $(n, m)\text{-NT}$ the change in the conductivity type from metallic to semiconducting is possible depending on their diameters and chirality (like for graphite-based NT). It is assumed that $(n, n)\text{-NT}$ should be the most stable, since their atomic configuration provides the maximum number of the strongest C–C and B–N bonds.

According to Miyamoto *et al.*,¹²³ partial replacement of carbon atoms by ‘extra’ B or N atoms leads to the appearance of donor or acceptor impurity levels, respectively, in the band energy spectrum of carbonitride NT. This occurs due to the increase in the concentration of electrons or holes in $\text{B}_{1-x}\text{C}_{2+x}\text{N}$ or $\text{BC}_{2+x}\text{N}_{1-x}$ nanotubes, respectively. Calculations of chiral currents for doped BC_2N -tubulenes were carried out and the magnitude of induced magnetic field was evaluated.¹²⁹

4. ‘Mixed’ boron carbonitride-based nanotubulenes

Hypothetical ‘mixed’ single-layered NT built of segments of carbon and BN hexagons that alternate either along the tube circumference or along the tube axis are considered as an example of possible quasi-1D systems possessing interesting quantum properties. They were studied by the MNDO method.⁵⁷ The following combinations of packing of carbon and BN hexagons were considered: alternation of C_6 and B_3N_3 ‘belts’[†] along the circumference of a (6, 6)-NT ($k\text{B}_3\text{N}_3 + l\text{C}_6$; $k = 3, 2, 1$; and $l = 1, 2, 3$, respectively) and alternation of strips[†] of hexagons along the tube axis ($k\text{B}_3\text{N}_3 + l\text{C}_6$; $k = 1, 2, 3, 4, 5$; and $l = 5, 4, 3, 2, 1$, respectively). We present here only the most important conclusions.⁵⁷ The introduction of a ‘belt’ or a strip of carbon hexagons substantially reduces ΔE_g of the boron nitride NT. An increase in the number of carbon fragments is accompanied by further decrease in the ΔE_g value. The introduction of ‘belts’ or strips of carbon hexagons between dielectric B_3N_3 ‘belts’ or strips leads to the appearance of additional states in the band gap of the (6, 6)-BN tubulene, with the major contribution from the ‘frontier’ atoms of contacting different strips or ‘belts’. For a ‘belt’ structure of mixed tubulenes, the contribution of carbon states to the bands near the Fermi level dominates, thus controlling the conducting and magnetic properties of the C_6 ‘belts’.

5. On the possible existence of nanotubular forms of boron

The results of calculations^{43, 130–134} of elemental boron clusters have led to unexpected and non-trivial conclusions about possible directions of structural evolution of isolated boron microparticles upon their aggregation into larger associates.

Calculations^{43, 130–134} were carried out using the Hartree–Fock methods with different basis sets (STO-3G, 3-21G, and SCF/DZ) and the local electron density functional method. The energy band structure was calculated for boron clusters with optimised geometry. A large number of topologically different B_n forms (starting from B_7) was designed. Three main possible types of their structural evolution were revealed, which lead to the formation of stable forms of boron clusters: (1) three-dimensional (3D) due to the growth of individual fragments of the structure of crystalline boron; (2) convex clusters (segments of a sphere or a cylinder); and (3) quasi-planar clusters.¹²⁶

Nanotubes can also be formed in the bulk of α -boron quasi-crystals.^{132, 133} This follows from calculations of possible local structural transformations in the bulk of an α -boron quasi-crystal with a ‘compressed’ rhombohedral unit cell for one of its fragments, viz., joined B_{12} icosahedra, lying on the minor diagonal of the rhombohedron. The structure of the B_{24} group changes substantially in the course of optimisation. The stages of structural evolution of the B_{24} fragment are illustrated in Fig. 17. ‘Diffusion’ of the boron atoms located between the B_{12} icosahedra leads to the formation of a closed pseudotubular group (see

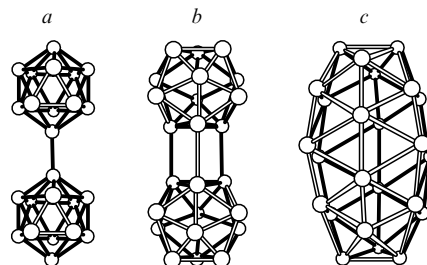


Figure 17. Structural evolution of the B_{24} fragment in the bulk of rhombohedral α -boron quasi-crystal in the course of geometry optimisation.

[†] According to terminology used in Ref. 57, a ‘belt’ is a tube segment ‘cut’ perpendicular to the tube axis, whereas a ‘strip’ is ‘cut’ along the tube axis.

Fig. 17 *c*), which can become a ‘protoform’ of extended nanotubular boron structures.

It was emphasised^{43, 132–134} that the structure and properties of proposed nanostructural forms of elemental boron (including a nanotubular form of boron) can differ fundamentally in the presence of impurities of other elements (*e.g.*, carbon, nitrogen, silicon, *etc.*). However, neither detailed studies along this line nor calculations of the electronic structure of the nanotubular form of boron have been carried out so far.

V. Theoretical models of the growth and morphology of nanotubes

One of the fundamental challenges of theoretical investigations is to describe the nature, the kinetics of nucleation and growth, and the morphology of nanotubular structures on the microscopic level.

Thermodynamic aspects of the formation of tubular and spheroidal carbon structures have been discussed.^{8, 11, 14} It was emphasised^{135, 136} that a symmetry axis determining the direction of the structure growth is required in the reaction zone in order to form tubulenes. In the synthesis of cylindrical structures, such a direction can be specified, *e.g.*, by a beam of accelerated carbon ions^{135, 136} or catalysts.⁸

The most widely used method for the NT synthesis is their growth in an electric arc discharge apparatus between graphite electrodes in the presence of various catalysts. It is not possible, in the present state-of-the-art in the field of NT synthesis, to control their size and chirality exactly. Along with NT (or NT bundles whose diameters vary over a wide range), the end product contains fullerenes, other nanoparticles, and soot.^{8, 11, 14, 135–138}

The nature and mechanism of NT growth became the subject of discussion in the first studies in which the preparation of NT was reported.⁸ Fullerene hemispheres were considered to be precursors,^{18, 19, 139, 140} and the growth of tube walls was explained by successive addition of C₂ dimers to the carbon atoms at the hemisphere circumference.

Yet another type of mechanism of SNT growth involving cyclic structures as precursors was proposed.¹⁴¹ These structures were found in the studies of laser ablation of graphite.^{142–144} The most typical structures of C_n species (10 ≤ *n* ≤ 40) are planar cyclic structures,^{143–145} whereas spheroidal structures are formed at *n* > 40. Two mechanisms of growth of the structures built of carbon rings were suggested,¹⁴¹ *viz.*, the formation of either a fullerene or an NT. According to the model proposed by Kiang and Goddard,¹⁴¹ tubular structures are formed due to the presence of catalysts that activate the process.¹³⁸

The model of NT growth from a nucleus (a carbon ring) is illustrated in Fig. 18. In the first stage, a planar ring is distorted in arc plasma in the presence of a catalyst (*e.g.*, cobalt carbide, Co_mC_n) to adopt a *cis*- or a *trans*-form analogously to crystalline carbyne rings.¹⁴⁶ The *cis*-form of the ring can act as a precursor in the synthesis of achiral NT by addition of C₂ dimers. The *trans*-form of the carbon ring may give rise to a larger number of cylindrical structures. The formation of the NT geometry occurs without involving the catalyst species.¹⁴¹

In other models of NT growth, the primary emphasis is placed on the role of the substrate and the catalyst. A phenomenological model of mechanism of SNT growth on diamond-like crystallites was proposed.¹⁴⁷ The (111) type of the surface was considered and it was found that the prerequisite for the beginning of the process is the presence of a nanoscale surface defect, *e.g.*, an atom of another element that ‘shades’ one of the carbon atoms of the upper monatomic layer. A ‘nanoisland’ that formed is surrounded along its circumference by carbon atoms that have free bonds oriented normal to the surface and interact with the ions in the vapour phase. The ions that precipitate form a ring, an NT ‘root’ capable of further independent growth. The formation of the first layer according to the model proposed by Chernozatonskii¹⁴⁷ is

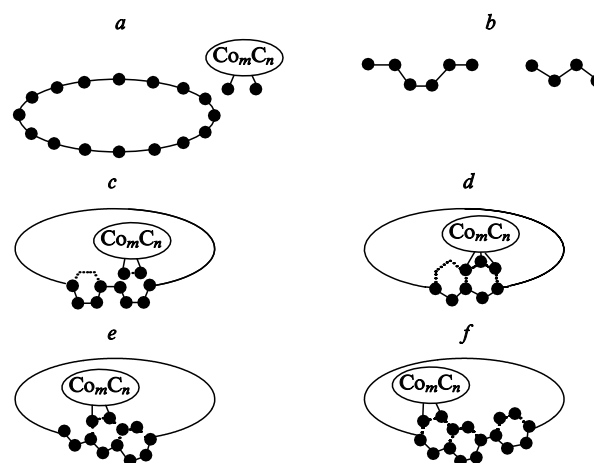


Figure 18. A model of the formation of seeds of nanotubular structures based on cyclic structures: (a) initial planar ring; (b) local deformation involving the planar ring with the formation of *cis*- and *trans*-forms; (c) nucleation of an achiral nanotube based on the *cis*-form; (d) nucleation of an achiral nanotube based on the *trans*-form; and (e), (f) nucleation of chiral nanotubes based on the *trans*-form.

depicted schematically in Fig. 19 taking a (6, 0)-NT as an example.

The above-mentioned model¹⁴⁷ is versatile and provides a qualitative explanation for the NT growth under any conditions of their synthesis. An important point is that the size of the nucleus (a surface defect) or that of metal particles (catalysts) should be smaller than the characteristic diameter of the SNT. Then, taking into account that each preceding carbon atom interacts with the ‘surface’ states of the nanostructure to form its own ‘free’ bond and becomes an active adsorption centre for the succeeding atom, the process can be interpreted simply.¹⁴⁸

In the case of metal particles whose size is larger than the characteristic SNT diameter, a carbon (carbide) layer is formed on the surface in the first stage of precipitation, which is then followed by growth of the SNT nuclei (roots). For several metals (*e.g.*, lanthanides) it was found^{8, 149, 150} that, depending on the surface morphology, SNT can grow in the form of compact bundles radiating from the nucleus. In this case it is assumed that nanoscale inhomogeneities (protrusions) of the surface of metal grains play the role of ‘active nuclei’ in the formation of SNT roots.

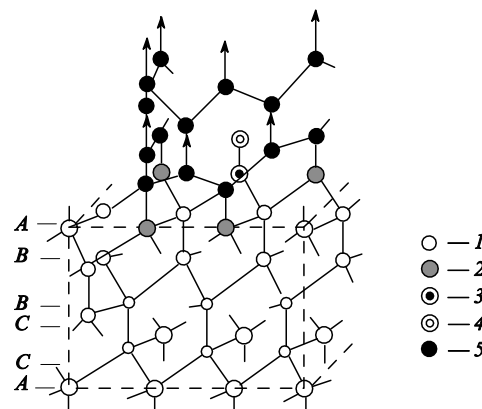


Figure 19. A scheme of the formation of the (6, 0)-NT on the diamond (111) surface. The substrate atoms (1), the tube ‘root’ atoms (2) surrounding the surface atom (3) ‘shaded’ by a univalent ion (4), and the atoms of tubulene walls (5) are shown. The surface (A) and near-surface (B), (C) atomic layers are shown.

A microscopic model of growth of carbon NT on the surface of a metal catalyst was developed.¹⁵¹ The process on a planar metal surface covered with a hexagonal network of carbon atoms formed upon primary precipitation was considered. Special emphasis was placed on the energy effects upon the rearrangement of the initial layer geometry in the region of curving the elementary polygons that form the SNT base (Fig. 20). It was shown that such a rearrangement results in the formation of pentagons and heptagons. The carbon atoms that precipitated successively on the metal carbide surface migrate toward the SNT base to form 'belts' of hexagons constituting the SNT stem. This provides the possibility for the tube wall surrounding the protrusion on the substrate surface to grow. The model¹⁵¹ makes it also possible to explain why multilayered NT do not grow.

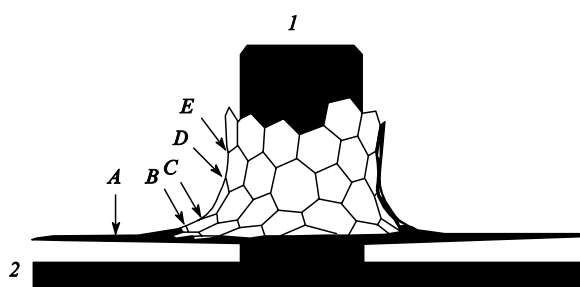


Figure 20. A scheme of growth of single-layered carbon nanotube on a protrusion (1) of a surface layer (2) of a metal catalyst. (A)–(E) are characteristic positions of carbon atoms migrating from the SNT base toward its stem (according to the model by Maiti *et al.*¹⁵¹).

Starting from the first study by Iijima,⁹ the MNT were considered as a system of ideal coaxial cylinders formed by rolled graphitic sheets. The conditions of the MNT growth depending on the substrate (diamond) structure were considered.¹⁴⁷ It was argued that the presence of the (111) crystallite terraces is a prerequisite for the MNT growth. In this case, 'nucleation ring seeds' consisting of the atoms separated from one another by a distance of several Angström can be distinguished. It has been pointed out that the MNT growth can give rise to intercylindrical interactions and narrowing of the walls of individual NT. As a result, the MNT can be 'shrunk' into cones,¹⁵² thus forming a peculiar kind of 'graphite caps' that close the protrusions of diamond crystallites.

Mention may be made of yet another structural model of a 'quasi-tubular' form of carbon. The conditions under which 'hangars' (multilayer 'arches' of graphene sheets 'resting' on the substrate surface) are formed have been discussed.¹⁴⁷ There are open 'hangars' and those closed at the ends with truncated spheroidal structures.

A growth model of conical multilayered tubular structures was proposed¹⁵³ and the possibility of the formation of a helical MNT structure was considered.^{154,155} Successive stages of the growth of helical MNT are shown in Fig. 21. The NT nucleus was assumed to consist of a fullerene hemisphere formed at the substrate surface. Depending on the type of the hemisphere cross section, the 'primary' tube stem can grow in different ways. Ideally, this is a right circular cylinder;¹⁵³ however, if the tube base contains pentagons (a 'zigzag' C₆₀ cross section), the NT walls can be tilted with respect to the normal to the surface. The first tube type and the corresponding energy of interaction between the pair of graphitic sheets clearly defines the nucleation template (achiral or chiral) of the graphite layer of the next tube walls. The structure of the third sheet (the outer one with respect to the first and second sheets) is not unambiguously defined. This allows mutual reorientations of the system of coaxial tubes (*e.g.*, rotations about a common axis). Effects of NT sliding over one another in MNT have been discussed.⁸

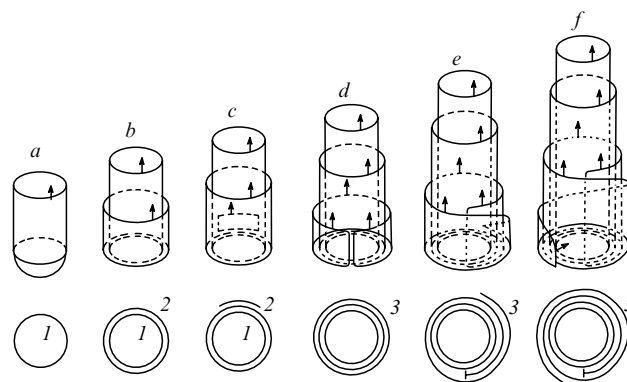


Figure 21. The major stages of growth of helical NT (a)–(f).¹⁵³ (1)–(3) graphitic layers in the cross sections of corresponding structures; the edges of dislocations are shown. Arrows indicate the direction of MNT growth.

The increase in the number of graphitic sheets (see Fig. 21) can lead to the formation of lateral dislocations that are considered as energy stabiliser of the system.¹⁵³ As a result, the MNT structure is transformed into a helical one and the MNT grows by building up a helix rather than by nucleating the next graphitic sheet. It is of importance that a pair of lateral dislocations of opposite signs should be present in each helical nanotube.

The presence of dislocations will lead to some increase in the tube volume. The MNT growth is terminated when dislocations become oriented parallel to the tube axis.¹⁵³

The authors of the above-mentioned models of MNT growth used qualitative ideas of a specific type of interatomic interactions in the systems in question. Kwon *et al.*¹⁵⁶ studied growth conditions, morphology, and stability of achiral double-layered (5, 5)@(10, 10)- and (9, 0)@(18, 0)-tubulenes consisting of coaxial cylinders with respectively 'arm-chair' and 'zigzag' edges by performing rigorous *ab initio* calculations in the framework of the electron density functional formalism (a cluster model with geometry optimisation according to the DMol version).

During the NT growth process, adatoms can either build up the open end of either tube or connect these ends to become bridging atoms (see respectively configurations 1 and 2, 3 in Fig. 22). For each of the configurations considered, *ab initio* calculations of energy parameters and electronic structure were carried out. The tube growth was analysed with an increment of 10 extra atoms arranged as described above. Relaxation effects were taken into account by the MD method.

Let us illustrate the results of calculations¹⁵⁶ taking a double-layered (5, 5)@(10, 10)-MNT as an example. Placing extra carbon atoms exactly on the tube edges leads to the formation of a system of 'dangling' bonds. However, in this case the cohesive energies of MNT remain virtually unchanged. For bridging atoms, the

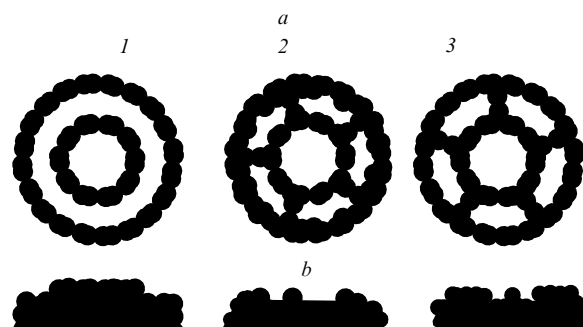


Figure 22. Cross (a) and longitudinal (b) section of possible growth structures (1)–(3) of a two-layer (5, 5)@(10, 10)-NT.¹⁵⁶

situation is markedly different. For a fully optimised structure, the energy gain per each extra atom is rather large ($\Delta E \simeq 0.42$ eV), which confirms the assumption¹⁵⁸ of stabilising contribution of ‘lip-lip’ interactions between the walls of neighbouring tubes to the total energy of the system. The stabilising effect of bridging atoms depends on their distance from the tube interior and on the type of the polygons formed by these bridging atoms and the atoms of tube walls in the NT cross section. Thus, the configuration 3 in Fig. 22 is unstable ($\Delta E \simeq -3.52$ eV). Analogous conclusions can be drawn from the analysis of the (9, 0)@(18, 0)-MNT. The optimum NT morphology is determined by a combination of the above-mentioned factors.

Ab initio studies of MNT growth and termination depending on the number of extra atoms have also been carried out.¹⁵⁶ The main parameter used in the case of a growing cylindrical MNT was the degree of the edge coverage

$$\varepsilon = \frac{N}{N_a},$$

where N is the total number of carbon atoms on the tube edge and N_a is the number of added (extra) atoms. Then the energy parameter was calculated as a function of ε

$$E_c = \frac{E_{\text{tot}}(C_N) - NE_{\text{tot}}(C_\infty)}{N_a},$$

where $E_{\text{tot}}(C_N)$ is the total energy of the truncated NT of a given length and $E_{\text{tot}}(C_\infty)$ is the total energy of an infinite tube.[‡] It was assumed that NT growth is favoured to the greatest extent at a minimum E_c value that can be achieved at a certain concentration and for particular configurations of adatoms on the tube edge when the ‘growing’ tube has a minimum energy as compared to the ‘end reaction product’, a perfect infinite MNT.

The results of calculations for a (5, 5)@(10, 10)-NT are shown in Fig. 23. Stabilisation of the structure is at $\varepsilon = 2/3$. The ‘lip-lip’ interactions play an important role in the structure stabilisation. Stable structures of MNT growth contain carbon hexagons and pentagons, but no squares or triangles. In the range $0 < \varepsilon \leq 2$, the initial tube growth is simulated. The interval $2 < \varepsilon \leq 4.5$ corresponds to an ‘intense edge coverage’ of the tubulene. Changes in the relative energies of dome closure, which terminates the process of nanotube growth, are also shown. The simplest types of the domes for closing the inner and outer tubes of the (5, 5)@(10, 10)-NT are hemispheres of the C_{60} and C_{240} fullerenes, respectively. To form closed noninteracting domes, the degree of the edge coverage should lie in the range $8/3 < \varepsilon < 14/3$.

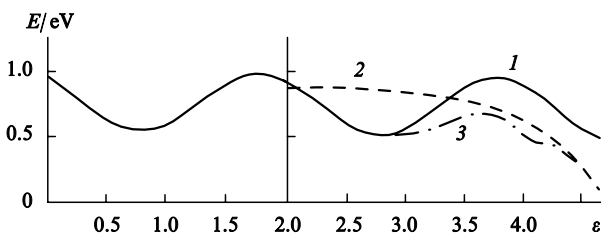


Figure 23. Dependence of the energy (E) of edge groups of the (5, 5)@(10, 10)-NT on the number of adatoms ε (see text). The interval $0 < \varepsilon \leq 2$ corresponds to the MNT growth; curves (1)–(3) in the region $2 < \varepsilon \leq 4.6$ describe how E changes for continuous NT growth (1) and for the dome closure of the nanotube without (2) and with (3) account of ‘lip-lip’ interactions.¹⁵⁶

The mechanism of double-layered NT growth and conditions of its termination¹⁵⁶ can be extended to MNT with any number of layers. However, problems can arise in the case of odd-walled

MNT. It is much more difficult to determine optimum conditions of the saturation of ‘dangling bonds’ in this case. Probably, MNT with an odd number of layers are less stable. This is indirectly confirmed by larger abundance of MNT with an even number of layers.¹⁵⁸ At the same time, the proposed growth mechanism can be corrected to a certain extent for the presence of ‘passivating’ elements as impurities (‘covalent spot welds’) capable of saturating one or several free (‘dangling’) bonds of the carbon atoms of outer cylinders.

VI. Nanotube crystals

Nanotube crystals (NTC) are regular 3D structures formed by individual NT.

To date, theoretical models of crystalline nanotubular forms of matter and predictions of their characteristics have been reported only for certain possible crystalline forms of nanotubular carbon. It was suggested that NTC be considered as a new phase of crystalline carbon with quasi-one-dimensional, strongly anisotropic properties.

Progress in the synthesis of single-layered NT and, in particular, the possibility of producing NT of most plausible diameters^{6,8} under specified conditions of plasmachemical process provides an experimental basis for performing theoretical studies. Production of compact nanotubular associates, e.g., NT bundles and ropes, as well as nanotube films with regular arrangement of individual cylinders has been reported.^{6,8,159–169}

Let us consider the main lines of theoretical investigations of nanotube crystals.

1. Intertubular interactions in nanotube crystals

In the studies of NT packed into regular 3D structures, the problem arises of establishing the form of their packing and the nature of interaction between individual NT, and of determining the energy effect of this process. It is assumed^{166,167} that the intertubular bonding is due to the van der Waals interactions (as is the case, e.g., for fullerenes⁸).

Optimum ways of packing individual NT into a periodic 3D structure were studied.¹⁶⁸ Nanotube crystals formed by (6, 6)-nanotubulenes with parallel cylindrical axes were calculated. Depending on the type of mutual arrangement of individual NT in the nanotube crystal, a tetragonal and a hexagonal unit cell was investigated. In the latter case, calculations were performed for two types of packing of single-layered NT, which correspond to the hypothetical graphite *AAA...* stacking and to the conventional graphite *ABAB...* stacking.

It was found that the system in which carbon atoms of neighbouring tubes are packed similarly to graphite *ABAB...* stacks is the most stable (Fig. 24). In addition, the ‘intertubular’

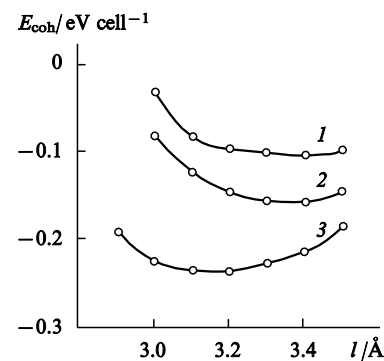


Figure 24. Dependence of the cohesive energy of an NTC formed by (6, 0)-NT on the distance (l) between individual NT for tetragonal (1) and hexagonal (2), (3) unit cells. Type of the NT packing in hexagonal unit cells: (*AAA...*) (2), and (*ABAB...*) (3).

[‡] An idealised model of a quasi-1D structure is an infinite tube.

cohesive energy E_{coh} in NTC ($9.76 \text{ meV atom}^{-1}$) is lower than the interlayer energy in graphite (20 meV atom^{-1})¹⁷⁰ and comparable with the energies of intercluster interactions in condensed fullerenes ($\sim 10 \text{ meV atom}^{-1}$). It can be assumed that the conditions of the formation of 3D NTC from tubes of different diameters control the degree of close packing of individual NT and the possibility of the *AB* type of packing of the carbon atoms in neighbouring tubes. Any violation of the optimum combination of these factors will lead to destruction of crystal structure and to orientational disorder in the NT arrangement.

The energy band structure of a hexagonal carbon NTC is characteristic of a mixed 1D–3D electronic system.¹⁶⁸ The main dispersive effects are due to ‘intratubular’ interactions; at the same time, intertubular interactions also make a noticeable contribution. The NTC analysed possess a metallic type of conductivity, which means that packing of individual (6, 6)-NT into a crystal does not change the nature of their conductivity.

2. Radial deformations of nanotubulenes in crystals

Charlier *et al.*¹⁶⁸ considered an NTC in which the shape of NT constituting the crystal was assumed to be preset and unchanged upon packing into the 3D structure. The problem of possible deformations of SNT in the interaction was posed.^{8, 166, 167}

The original concepts of the effect of the interaction between two NT on their cross section geometry were developed by Ruoff *et al.*¹⁶⁶ who calculated structural deformations for a pair of nanotubes using a many-body interaction model. It was established that, first, the walls of neighbouring NT become ‘flattened’ so that the respective regions of NT reproduce the geometry of planar graphite sheets (which corresponds to a maximum interaction energy) and, second, the intertubular volume is decreased (Fig. 25). It was also pointed out¹⁶⁶ that the degree of deformation depends strongly on the NT diameter and increases as the diameter increases.

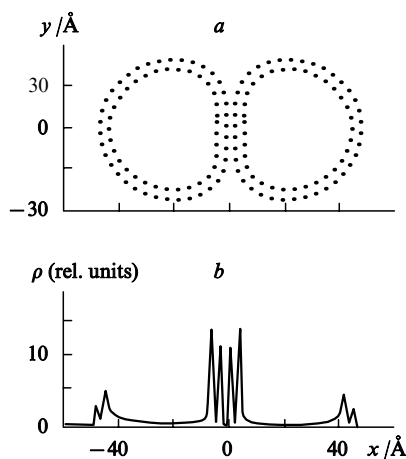


Figure 25. Radial deformations of a pair of contacting NT upon their interaction (a) and the charge density ρ distribution (b).

The above-mentioned peculiarities of deformation of two individual cylinders upon their packing into a 3D structure are clearly illustrated in Fig. 26. The principles of calculations of structural distortions for a pair of contacting cylinders¹⁶⁶ were extended to 3D NTC.¹⁶⁷ In Fig. 26, one can clearly see the formation of a ‘honeycomb’ structure of the NTC cross section with gradual transformation of the cross sections of cylindrical NT into those of hexagonal prisms as the tube diameter increases. In the framework of the model used,¹⁶⁷ the ‘flattening’ effects of NT walls are detected starting from $d \approx 15 \text{ \AA}$.

These structural deformations will play an important role in the formation of cohesive and elastic properties of NTC. In the general case, one can expect that the increase in the NT diameter

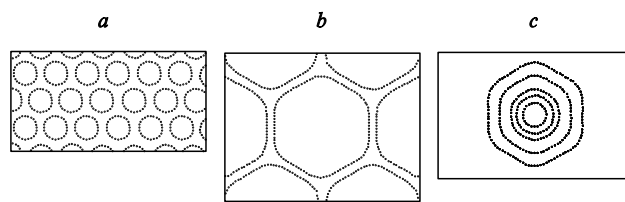


Figure 26. NT deformations in the NTC as a function of tubulene diameter; (a) $d = 10 \text{ \AA}$; (b) $d = 40 \text{ \AA}$; and (c) hexagonal distortions of a nanotube cross section in the crystal with an increase in the NT diameter (for an NT with $d = 10, 15, 20, 30$, and $40 \text{ \AA}$). The points correspond to the carbon atoms in the NT cross section.

will be accompanied by weakening of interparticle interactions (in the *XY* plane of the NTC) and reduction of its 2D cohesive characteristics. According to calculations,¹⁶⁷ the dependence of the cohesive energy and the modulus of elasticity on the NT diameter is noticeably nonmonotonic (Fig. 27). The formation of a ‘honeycomb’ structure imparts an anomalous hardness to the NTC that is maintained upon further increase in the diameter (starting from $d \approx 25 \text{ \AA}$) of NT constituting the crystal. It is suggested that NTC be divided arbitrarily into two groups with ‘small’ (or ‘large’) diameters of NT constituting the crystal, possessing respectively a nonmonotonic and a monotonic dependence of the cohesive energy on the NT diameter. Presumably, these groups of NTC will have substantially different physicochemical properties and will respond differently to the effects of doping (*e.g.*, upon introduction of alkali metal ions into intertubular channels) upon the formation of composites, *etc.*

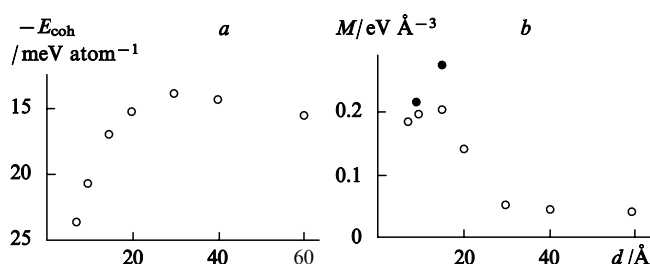


Figure 27. Dependence of the cohesive energy (E_{coh}) (a) and the modulus of elasticity (M) (b) for a nanotube crystal on the diameter (d) of nanotubes constituting the NTC. Filled circles correspond to analytical extrapolation of the results of calculations of NTC consisting of nanotubes of small diameter.

3. Hetero-junctions in nanotube crystals

In the formation of 3D structures of regularly packed NT it may happen that the geometric and electronic parameters of a pair of neighbouring NT are different or an NTC contains the domains consisting of different NT. It is obvious that in this case one can suggest the existence of ‘interphase domains’ (or ‘interface domains’) between nanotube ‘polycrystals’. Chico *et al.*⁷⁰ considered hetero-junctions in pairs of (12, 0)/(6, 6)- and (9, 0)/(6, 3)-NT and possible differences in electronic properties between the ‘interphase domain’ and the NT constituents using Green’s functions formalism. This study can be considered as the first attempt to describe the above-mentioned systems by semiempirical quantum-chemical methods.

The development of the ideas of condensed regular nanotubular forms of matter as 3D periodic structures, *viz.*, nanotube crystals, makes it possible to consider these solids taking into account all factors determining the ‘composition–structure–properties’ interrelations inherent in all ‘conventional’ solids.

Assuming that isolated nanotubes whose properties can be varied over a wide range can be considered as ‘structural elements’

of NTC, one can accept the idea of a defect (impurity, vacancy) structure of NTC and consider the order–disorder problem therein. Such an approach makes it possible to consider NTC in the context of general problems of the description of specific properties of crystals (including electronic ones) and to pose the problems of surface states of NTC, interfaces between nanotube polycrystals, etc.

The above-mentioned lines of the development of the ideas concerning fundamental properties of NTC are still in a primitive state even for carbon NTC. One can expect that they will be useful for the development of the problems of quantum materials science and their application to NTC forms of other substances including those considered in this review.

VII. Conclusion

The discovery of the nanotubular form of matter was one of the major achievements of physical chemistry in the last decade. Unique properties of nanotubulenes offer extremely attractive prospects of their use in technology and are of considerable interest for fundamental research.

Only the principal results of the studies of electronic structure of NT by methods of solid state quantum chemistry have been covered in this review. The most considerable progress has been achieved in the studies of single-layered isolated nanotubes and prediction of their properties.

Recent studies on the synthesis of NT and nanotubular materials^{171–174} are intimately associated with the development of theoretical models. One of the most important theoretical problems is to describe the ‘life cycle’ of tubulenes (nucleation–growth–disintegration). Currently, considerable interest is demonstrated in ‘intermediate’ nanoscale forms (barrellenes,^{175–177} onions,¹⁷⁸ calabashes,¹⁷⁹ and other nanoscale structures and mesostructures^{180,181}) which can act as intermediates in the formation or disintegration of NT.¹⁸²

Topical are investigations of various nanotubular structures (tori,^{183–185} cones,¹⁸⁶ nanotubes with negative Gaussian curvature,¹⁸⁷ quasi-2D NT associates, and nanotubular layers and films^{188–191}), nanotubular superstructures,^{191–194} and ‘mixed’ nanoscale forms and composites (e.g., NT-fullerene,¹⁹⁵ amorphous nanotubular carbon¹⁹⁶) which can possess unusual properties.

The theory of adsorptive, capillary, electromagnetic, catalytic, mechanical, and other properties of NT that are of interest for researchers in the field of materials science is in the early stage.

The problem of whether the nanotubular form of matter is a universal form for the whole known diversity of inorganic substances or are there certain physical or chemical criteria clearly reducing the number of potential objects whose nanotubular forms can be obtained under certain (which?) conditions, is a basic problem which remains open so far.

The solution of the above-mentioned problems is one of the priorities in the quantum chemistry of nanotubulenes. It provides a basis for the development of the tubulene materials science, thus favouring their effective use in nanoscale electronics, in instruments and chemical engineering, and in other areas.

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Structural-chemical aspects of complexation in metal halide – macrocyclic polyether systems

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Abstract. The review surveys data on over 200 crystal and molecular structures of metal halide complexes with oxygen-containing crown ethers. The major types of the complexes are distinguished. The characteristic features of formation of these complexes and their coordination fragments are discussed. The bibliography includes 143 references.

I. Introduction

Structural aspects of the chemistry of macrocyclic polyether complexes with metal salts have been discussed in several reviews and monographs (see, for example, Refs 1–3). These data were most completely surveyed in the monograph² containing a bibliography up to 1989. In succeeding years, a large number of publications have been devoted to structural studies of crown compounds with metal halides prepared from organic media, including those devoid of water molecules, along with studies of salts of alkali and alkaline-earth metals (which comprise the major body of structural data throughout the period of studies of these compounds). The results obtained confirmed on the whole the existence of several structural types of crown complexes, which were suggested for the first time by Dalley⁴ and more recently by Poonia.⁵ The first group comprises complexes in which all the oxygen atoms of the crown ether (CE) molecule are coordinated to the metal atom, which is located within or outside the CE cavity (type A). The second group includes complexes in which only some of the oxygen atoms are involved in the coordination sphere of the metal atom (type B). The third group contains complexes in which the metal atom is located outside the cavity of the crown ether and is not directly bound to the oxygen atoms of the CE molecule (type C). Finally, complexes of the ‘half-sandwich’ type in which the metal atom deviates substantially from the mean

plane through the oxygen atoms of the CE molecule (type D) are documented.

The structural classification of crown compounds has been based on CE as such.^{2,3} At that time, this was quite reasonable because the data on structurally characterised crown ethers were scarce in the literature. Presently, it seems difficult to use this classification. In the present review, we consider structural features and compositions of crown compounds with metals in the order of increasing atomic numbers. We deliberately exclude CE complexes with sodium halides and with halides of the heaviest alkali metals from consideration since their structures are rather trivial and have been reported many times.

II. Systems with halides of the first-row elements

1. Lithium halides

The reaction of anhydrous lithium chloride with 12-crown-4 (12C4) afforded a molecular complex with composition $[(\text{LiCl}) \cdot (12\text{C}4)]$ (**1**).⁶ The lithium atom is coordinated by the chlorine atom ($\text{Li}-\text{Cl} = 2.290 \text{ \AA}$) and four oxygen atoms ($\text{Li}-\text{O} = 2.128 \text{ \AA}$) and deviates from the mean plane through the oxygen atoms by $0.929 \text{ \AA}$ (Fig. 1).

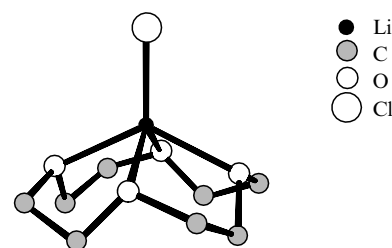


Figure 1. Structure of the complex **1**.

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The reaction of lithium chloride dihydrate with 18-crown-6 (18C6) in dry diethyl ether gave a molecular binuclear complex with composition $[(\text{H}_2\text{O})_2 \cdot (\text{LiCl})_2 \cdot (18\text{C}6)]$ (**2**).⁷ Therefore, the CE molecule with a large inner cavity serves as a ‘host’ simultaneously for two lithium atoms. The coordination environment about each lithium atom is a strongly distorted tetrahedron formed by two oxygen atoms of the polyether, one oxygen atom of the water molecule and one chlorine atom. This coordination

results in small five-membered rings with the following distances: $\text{Li}-\text{O}_{\text{cr}} = 1.980$ and $2.065 \text{ \AA}$, $\text{Li}-\text{O}_{\text{w}} = 1.865 \text{ \AA}$ and $\text{Li}-\text{Cl} = 2.277 \text{ \AA}$ (Fig. 2). The five-membered metallocycles in complex **2** adopt an envelope conformation.

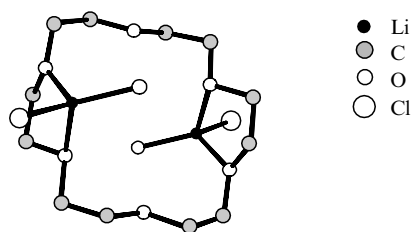


Figure 2. Structure of the complex **2**.

By contrast, this reaction in a typical solvent, which have not been dehydrated,⁸ gave structurally different ionic complexes with compositions $\{[(\text{Li})_2 \cdot (\text{H}_2\text{O})_4 \cdot (18\text{C}6)]^{2+} + 2\text{X}^-\}$, where $\text{X} = \text{Cl}$ (**3**) or Br (**4**), with a unique structure. In these compounds, two lithium atoms are also 'guests' but they are arranged nonsymmetrically with respect to the centre of the CE molecule. Both cations have a trigonal-bipyramidal environment (Fig. 3), one of them being coordinated by three oxygen atoms of the ether molecule and two oxygen atoms of water molecules, while the second cation, on the contrary, being coordinated by two oxygen atoms of the ether molecule and three oxygen atoms of water molecules. The bipyramids are linked to each other through a shared vertex formed by the bridging oxygen atoms. The $\text{Li}-\text{O}_{\text{cr}}$ bond lengths vary from 1.88 to $2.12 \text{ \AA}$ and the $\text{Li}-\text{O}_{\text{w}}$ bond lengths are in the range 1.90 to $2.00 \text{ \AA}$. In the crystal structure, an extensive three-dimensional network of $\text{OH} \cdots \text{O}$ and $\text{OH} \cdots \text{X}$ intermolecular hydrogen bonds exists.

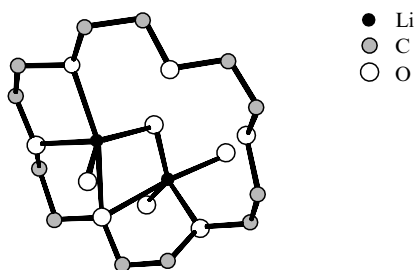


Figure 3. Structure of the cation in the complex **3**.

2. Beryllium chloride

Only one complex of BeCl_2 with crown ethers, *viz.*, $[(\text{BeCl}_2) \cdot (15\text{C}5)]$ (**5**), which was prepared by the reaction of anhydrous beryllium chloride with the polyether in anhydrous diethyl ether, was structurally characterised.⁹ In this complex, the beryllium atom retains the typical tetrahedral coordination formed by two oxygen atoms of the crown ether molecule

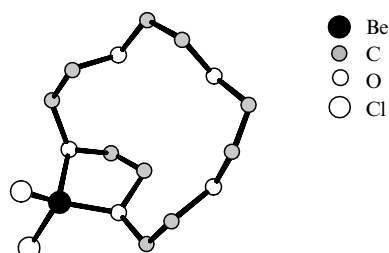


Figure 4. Structure of the complex **5**.

($\text{Be}-\text{O}_{\text{cr}} = 1.64$ and $1.73 \text{ \AA}$) and two chlorine atoms ($\text{Be}-\text{Cl} = 1.88$ and $2.0 \text{ \AA}$) (Fig. 4). Therefore, complex **5** is a typical representative of type B compounds. The bond angles in the O_2BeCl_2 tetrahedron vary from 90 to 118° , which is associated with steric hindrances due to coordination of two closely arranged oxygen atoms of the polyether.

3. Boron trifluoride

Presently, two complexes of BF_3 with 18C6, which have been prepared by the reaction of boron trifluoride etherate with the polyether, are known, *viz.*, the complex with composition $\{[(\text{BF}_3) \cdot (\text{OH}_2)] + (18\text{C}6)\}$ (**6**) solvated with toluene¹⁰ and the complex $\{2[(\text{BF}_3) \cdot (\text{H}_2\text{O})] + (18\text{C}6) + (\text{H}_2\text{O})_2\}$ (**7**) obtained when BF_3 and CE were taken in a 2 : 1 ratio.¹¹ Both compounds belong to type C complexes because the tetrahedral boron-containing fragments interact with the CE molecule through hydrogen bonds between the coordinated water molecules and the oxygen atoms of the crown ether molecule. In structure **6**, only two oxygen atoms of the ether molecule are involved in 'guest–host' interactions, while in structure **7** all six oxygen atoms of the ether molecule participate in these interactions.

The reaction of the complex $\text{BF}_3 \cdot \text{Et}_2\text{O}$ with dicyclohexyl-18-crown-6 (DCHex18C6) in the presence of atmospheric moisture¹¹ afforded a product with composition $\{[(\text{BF}_3) \cdot (\text{H}_2\text{O})_2] + (\text{DCHex}18\text{C}6)\}$ with intramolecular H-bonds analogous to those observed in structure **7**.

III. Systems with halides of the second-row elements

1. Magnesium chlorides

In the compound $\{[(\text{Mg}) \cdot (\text{H}_2\text{O})_6]^{2+} + (12\text{C}4) + 2\text{Cl}^-\}$ (**8**) (Fig. 5), which was prepared by the reaction of $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ with 12C4, the metal atom is not involved in direct bonding with the oxygen atoms of the CE molecule.¹² Hence, this complex should be assigned to type C. In the crystal structure of **8**, the $[(\text{Mg}) \cdot (\text{H}_2\text{O})_6]$ octahedra, the CE molecules and the chloride ions are linked to each other through a complex system of $\text{OH} \cdots \text{O}$ and $\text{OH} \cdots \text{Cl}$ hydrogen bonds. The $\text{Mg}-\text{O}_{\text{w}}$ distances in the cation vary from 2.052 to $2.082 \text{ \AA}$.

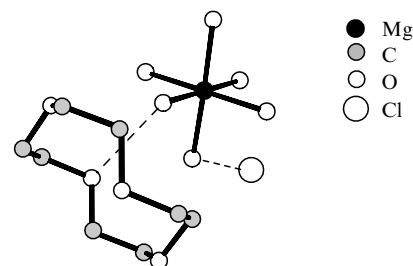
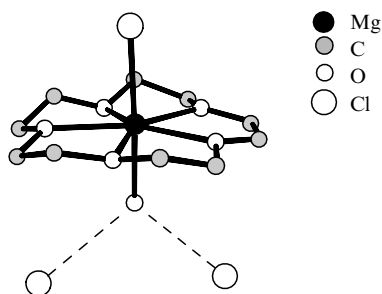


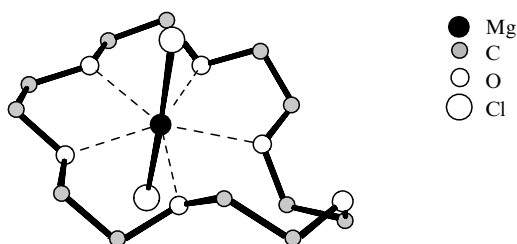
Figure 5. Structure of the complex **8**.

The reactions of slightly hydrated magnesium chloride with 15C5 in acetonitrile or chloroform gave related compounds with compositions $\{[(\text{H}_2\text{O}) \cdot (\text{MgCl}) \cdot (15\text{C}5)]^+ + \text{Cl}^-\} \cdot (\text{L})$, where $\text{L} = \text{CH}_3\text{CN}$ (**9**) or CHCl_3 (**10**), respectively. The magnesium atom is located in the cavity of the CE molecule (type A complex) and has a pentagonal-bipyramidal coordination.¹³ Five oxygen atoms of the crown ether molecule occupy the equatorial plane of the polyhedron ($\text{Mg}-\text{O}_{\text{cr}} = 2.11$ – $2.23 \text{ \AA}$). The water molecules ($\text{Mg}-\text{O}_{\text{w}} = 2.05$ and $2.06 \text{ \AA}$) and the chlorine atoms ($\text{Mg}-\text{Cl} = 2.42$ and $2.44 \text{ \AA}$) are located in the apical positions (Fig. 6). The coordinated water molecule forms intermolecular hydrogen bonds with the chloride ions ($\text{OH} \cdots \text{Cl}^- = 3.10$ – $3.11 \text{ \AA}$).

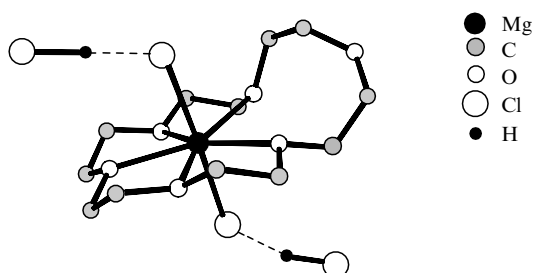
Figure 6. Structure of the complex **9**.

In the case of complete hydration of the above-described complexes, which is achieved by keeping these complexes in an atmosphere with 100% humidity,¹⁴ the apical chlorine atom is replaced by the second water molecule and the composition of the complex corresponds to the formula $\{[(\text{Mg}) \cdot (\text{H}_2\text{O})_2 \cdot (\text{15C5})]^{2+} + 2\text{Cl}^- + (\text{H}_2\text{O})\}$ (**11**). The $\text{Mg}-\text{O}_{\text{cr}}$ distances vary from 2.086 to 2.225 Å and $\text{Mg}-\text{O}_{\text{w}} = 2.045$ Å. In this crystal, the system of $\text{O}_{\text{w}}\text{H} \cdots \text{O}_{\text{w}}$ and $\text{OH} \cdots \text{Cl}$ hydrogen bonds is more complex than those observed in crystals of **9** and **10**.

The reaction of anhydrous magnesium chloride with 18C6 in anhydrous tetrahydrofuran¹⁵ afforded a molecular complex $[(\text{MgCl}_2) \cdot (\text{18C6})]$ (**12**) (Fig. 7). The coordination polyhedron

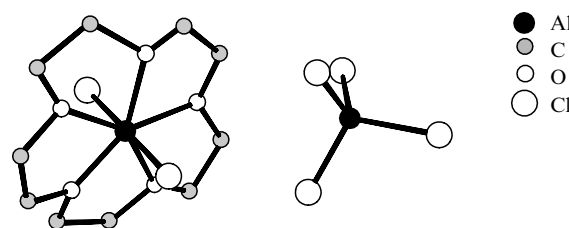
Figure 7. Structure of the complex **12**.

about the magnesium atom is a pentagonal pyramid. The coordination number of the Mg atom is 7, which is very untypical of this metal. The $\text{Mg}-\text{O}$ distances in complex **12** vary from 2.220 to 2.331 Å. The CE molecule also adopts an unusual conformation due to coordination of the metal atom by only five out of the six oxygen atoms. The magnesium atom has analogous coordination in the complex $\{[(\text{MgCl}_2) \cdot (\text{18C6})] \cdot (\text{HCl})_2\}$ (**13**) (Fig. 8),¹⁶ which was prepared by the reaction of MgCl_2 with the clathrate of composition $\{[(\text{H}_3\text{O}) \cdot (\text{18C6})]^+ + [\text{HCl}_2]^- \}$. This complex is considered¹⁶ as a purely ionic compound with composition $\{[(\text{Mg}) \cdot (\text{18C6})]^{2+} + 2[\text{HCl}_2]^- \}$. However, the $\text{Mg}-\text{Cl}$ distances in **13** (2.428 and 2.454 Å) and in **12** (2.429 Å) are close to the sum of the covalent radii of both elements and, in our opinion, it is more reasonable to describe both compounds as molecular complexes.

Figure 8. Structure of the complex **13**.

2. Aluminium chloride

A complex with composition $\{[(\text{AlCl}_2) \cdot (\text{15C5})]^+ + [\text{AlCl}_4]^- \}$ (**14**) was produced by the reaction of anhydrous AlCl_3 with 15C5 in anhydrous ether.¹⁷ The coordination number of the aluminium atom in the cation is 7. The coordination polyhedron about the metal atom is a pentagonal bipyramid with the oxygen atoms of the crown ether molecule in the equatorial plane and the chlorine atoms in the axial positions. This type of the polyhedron and the coordination number are untypical of aluminium compounds. The $\text{Al}-\text{O}$ distances vary from 2.081 to 2.142 Å and the $\text{Al}-\text{Cl}$ distances are 2.188 and 2.210 Å. The statistically disordered crown ether molecule in **14** is located on the mirror plane (Fig. 9). The complex of AlEtCl_2 with benzo-15-crown-5 (**15**) has an analogous structure.¹⁸

Figure 9. Structure of the complex **14**.

Complete hydration of complex **14** gave a compound with composition $\{[(\text{Al}) \cdot (\text{H}_2\text{O})_6]^{3+} + (\text{15C5}) + 3\text{Cl}^- + (\text{H}_2\text{O})_4\}$ (**16**)⁷ in which the metal atom is not coordinated by the oxygen atoms of the crown ether molecule and the individual structural units are linked to each other through a complex network of $\text{OH} \cdots \text{O}$ and $\text{OH} \cdots \text{Cl}$ hydrogen bonds.

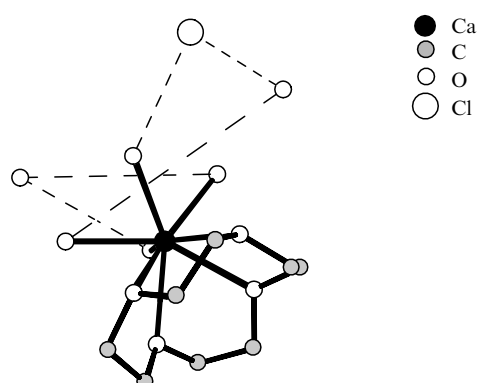
3. Silicon tetrafluoride

The only silicon-containing complex with CE known to date was prepared by the reaction of SiF_4 with 18C6.¹⁹ The compound has the composition $\{[(\text{SiF}_4) \cdot (\text{H}_2\text{O})_2] + (\text{18C6}) + (\text{H}_2\text{O})_2\}$ (**17**) and belongs to type C complexes. The silicon atom is in an octahedral environment. The isolated structural fragments are linked to each other through intermolecular $\text{OH} \cdots \text{O}$ hydrogen bonds with the participation of water and CE molecules.

IV. Systems with halides of the third-row elements

1. Calcium chloride

The reaction of crown ether 12C4 with an aqueous solution of calcium chloride afforded a compound with composition $\{[(\text{Ca}) \cdot (\text{12C4}) \cdot (\text{H}_2\text{O})_4]^{2+} + 2\text{Cl}^- + (\text{H}_2\text{O})_2\}$ (**18**).²⁰ The calcium atom is located above the mean plane of the macrocycle and is coordinated by all the four oxygen atoms of CE and the four water molecules (Fig. 10). The $\text{Ca}-\text{O}$ distances vary from 2.380 to

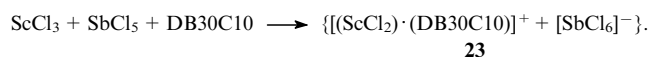
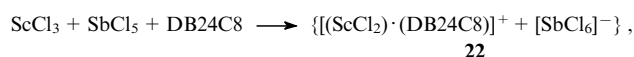
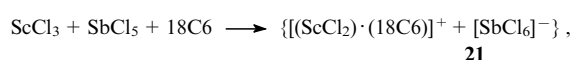
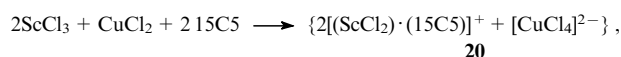
Figure 10. Structure of the complex **18**.

2.540 Å. In the crystal structure of **18**, a complex network of OH...O and OH...Cl intermolecular hydrogen bonds with the participation of all water molecules is realised.

The reaction of molten CaCl₂ with 18C6 in acetone yielded ⁷ a complex with composition $\{[(\text{Ca}) \cdot (18\text{C}6) \cdot (\text{H}_2\text{O})_2]^{2+} + 2\text{Cl}^- + (\text{H}_2\text{O})_2\}$ (**19**), which is a typical representative of type A crown compounds. The calcium atom is located exactly in the centre of the cavity of the CE molecule ($\text{Ca}-\text{O}_{\text{cr}} = 2.555\text{--}2.604$ Å) and is additionally coordinated by two water molecules ($\text{Ca}-\text{O}_{\text{w}} = 2.29$ Å) which are located above and below the mean plane of the macrocycle.

2. Scandium chloride

Data on homometallic complexes of scandium halides with CE molecules are unavailable in the literature. The structures of heterometallic halides have been studied.^{21–23} These complexes were prepared by the following reactions:



In compounds **20–23**, the scandium atom is located in the centre of the cavity of the CE molecule and has a bipyramidal coordination. The Sc–O distances vary from 2.09 to 2.30 Å.

3. Titanium chlorides

The compositions and structures of complexes of TiCl₄ with various CE reflect the general tendency of interactions between metal halides in the highest oxidation states and polyethers, which is associated with destruction of the latter and the formation of various reactive oxygen-containing fragments.

Only one complex of TiCl₄ with 12C4, which was prepared by the reaction of a mixture of TiCl₄ and SbCl₅ in acetonitrile, was reported in the literature.²⁴ This reaction yielded a complex with composition $\{[(\text{TiCl}_3) \cdot (\text{CH}_3\text{CN})_3]^+ + [\text{SbCl}_6]^{-}\}$ as an intermediate. Treatment of the latter with 12C4 in dichloromethane afforded a compound with composition $\{[(\text{TiCl})_2(\mu_2\text{-O}) \cdot (12\text{C}4)]_2^+ + [\text{SbCl}_6]^{-} + (\text{CH}_2\text{Cl}_2)\}$ (**24**). The bridging oxygen atoms in this structure occur apparently due to destruction of a portion of CE molecules. The structure of the Ti-containing fragment is shown in Fig. 11. The Ti–O_μ distances (1.81 and 1.82 Å) are intermediate between the length of the double bond in titanyl chloride and the coordination bond. The Ti–O_{cr} distances vary from 2.12 to 2.38 Å, *i.e.*, these bonds are nonequivalent. The coordination number of the Ti atom is 7. The coordination polyhedron about the metal atom is a distorted pentagonal

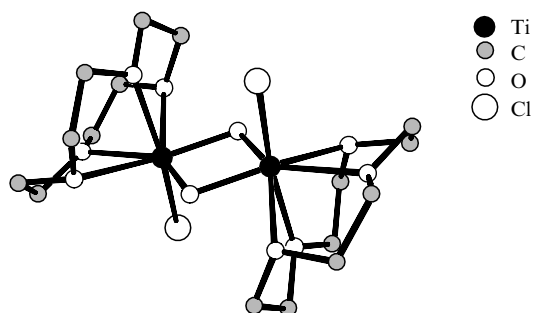


Figure 11. Structure of the $[(\text{TiCl})(\mu_2\text{-O}) \cdot (12\text{C}4)]_2^+$ fragment in the complex **24**.

bipyramid with the oxygen and chlorine atoms in the apical positions.

Apparently, analogous destruction of CE to form titanyl chloride as an intermediate occurs in the reaction of TiCl₄ with 15C5 in acetonitrile.²⁵ The resulting complex has the composition $[(\text{TiCl}) \cdot (15\text{C}5) \cdot (\mu_2\text{-O})(\text{TiCl}_3)]$ (**25**) (Fig. 12). Unlike the above-described compound, the Ti–O distances in **25** are essentially nonequivalent (1.691 and 2.014 Å), which is indicative of the predominant formation of the Ti(1)–O double bond and the Ti(2)–O coordination interaction due to the lone electron pair of the bridging oxygen atom. The Ti–O_{cr} distances vary from 2.073 to 2.140 Å. The coordination polyhedra about the Ti(1) and Ti(2) atoms are a pentagonal bipyramid and a typical octahedron, respectively.

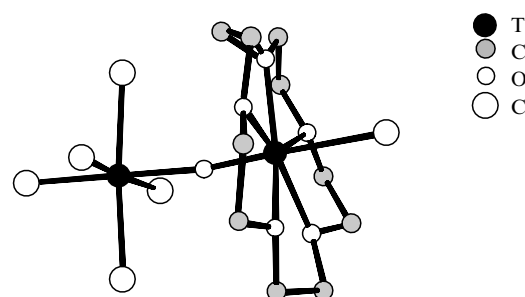


Figure 12. Structure of the complex **25**.

It was demonstrated²⁵ that destruction of CE is suppressed upon introduction of metal halides with readily ionisable M–X bonds which are not prone to autocomplexation. Thus the reaction of TiCl₄ with 15C5 in the presence of MgCl₂ in acetonitrile afforded the complex $\{[(\text{Mg}) \cdot (\text{CH}_3\text{CN})_2 \cdot (15\text{C}5)]^{2+} + [\text{TiCl}_6]^{2-}\}$ (**26**) in virtually quantitative yield. As in the compounds **9–11**, the magnesium atom in the complex **26** has a pentagonal-bipyramidal environment. The anion has a usual octahedral structure with the Ti–Cl distances varying from 2.324 to 2.354 Å. The reaction of TiCl₃ and AlCl₃ with 15C5 in tetrahydrofuran²⁵ gave a complex with composition $\{[(\text{TiCl}_2) \cdot (15\text{C}5)]^+ + [\text{AlCl}_4]^{-}\}$ (**27**). In **27**, the titanium atom is located in the centre of the cavity of the CE molecule. The Ti–O distances vary from 2.12 to 2.20 Å and Ti–Cl = 2.38 Å. The structure of the anion is analogous to that of the anion in the complex **14**.

According to the published data, the reaction of TiCl₄ with 18C6 did not lead to destruction of the CE molecule. Thus a distinct type B complex with composition $[(\text{TiCl}_4) \cdot (18\text{C}6)]$ (**28**) was prepared.²⁶ The coordination polyhedron about the titanium atom in this compound is an octahedron formed by four chlorine atoms and two oxygen atoms of the CE molecule (Ti–O = 2.125 and 2.145 Å). The CE molecule is strongly distorted (Fig. 13). The reaction of TiCl₄ with 18C6 in ethanol²⁷ afforded a type C

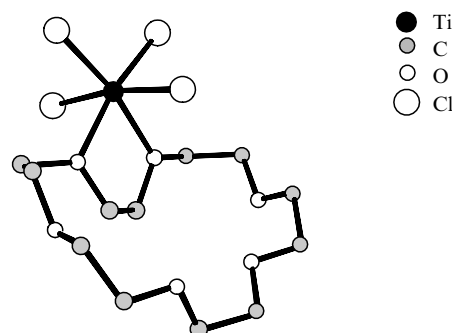


Figure 13. Structure of the complex **28**.

complex with composition $[(\text{TiCl}_3) \cdot (\text{OC}_2\text{H}_5) \cdot (\text{C}_2\text{H}_5\text{OH})_2 \cdot (18\text{C}6)_2]$ (**29**). The environment about the titanium atom is an octahedron (Fig. 14) formed by three chlorine atoms ($\text{Ti}-\text{Cl} = 2.337\text{--}2.387\text{ \AA}$), the oxygen atom of the ethoxy group ($\text{Ti}-\text{O} = 1.726\text{ \AA}$) and two coordinated ethanol molecules ($\text{Ti}-\text{O} = 2.030\text{ and }2.033\text{ \AA}$). The coordinated ethanol molecules interact with the macrocycle molecules through $\text{OH} \cdots \text{O}$ hydrogen bonds ($2.63\text{ and }2.64\text{ \AA}$).

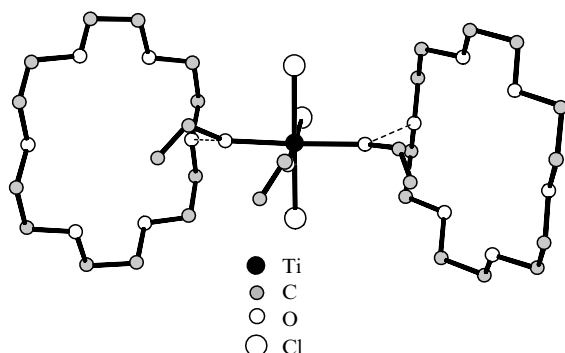


Figure 14. Structure of the complex **29**.

4. Vanadium chlorides

The reaction of VCl_4 with **15C5** in acetonitrile in the presence of water was accompanied by disproportionation of the halide to form a complex with composition $\{[(\text{V}^{\text{III}}\text{Cl}_2) \cdot (15\text{C}5)]^+ + [\text{V}^{\text{VO}}\text{Cl}_4]^- \}$ (**30**).²⁸ The coordination polyhedron about the vanadium atom in the cation is a pentagonal bipyramid formed by the five oxygen atoms of the macrocycle ($\text{V}-\text{O} = 2.08\text{--}2.11\text{ \AA}$) and the two apical chlorine atoms ($\text{V}-\text{Cl} = 2.34\text{ and }2.35\text{ \AA}$). The coordination environment about the vanadium atom in the anion is a tetragonal pyramid formed by four chlorine atoms ($\text{V}-\text{Cl} = 2.23\text{--}2.26\text{ \AA}$) and one oxygen atom ($\text{V}-\text{O} = 1.548\text{ \AA}$).

The structure of the complex prepared by the reaction of VOCl_2 with **18C6** in aqueous ethanol was reported^{29,30} to belong to type C and it is described by the formula $\{[(\text{VOCl}_2) \cdot (\text{H}_2\text{O})_2] + [(18\text{C}6) \cdot (\text{H}_2\text{O})]\}$ (**31**). The coordination polyhedron about the vanadium atom is a slightly distorted tetragonal pyramid ($\text{V}-\text{O} = 1.573\text{ \AA}$, $\text{V}-\text{O}_w = 1.964\text{ and }2.024\text{ \AA}$ and $\text{V}-\text{Cl} = 2.215\text{ and }2.362\text{ \AA}$). Both fragments of the structure are linked to each other through $\text{OH} \cdots \text{O}$ intermolecular hydrogen bonds with the participation of water and CE molecules.

5. Chromium trichloride

Presently, only one structure of the chromium-containing complex with composition $[(\text{CrCl}_3) \cdot (\text{H}_2\text{O}) \cdot (15\text{C}5)]$ (**32**) (Fig. 15) is known.³¹ This complex was prepared by the reaction of CrCl_3 with **15C5** in aqueous acetonitrile. In the monomolecular complex of type B, the coordination environment about the chromium

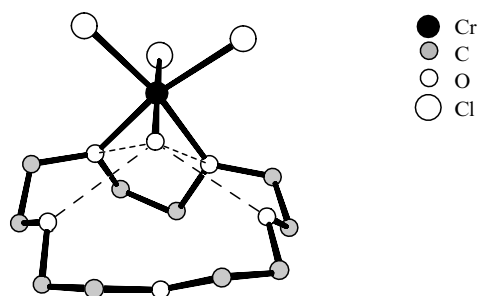


Figure 15. Structure of the complex **32**.

atom is an octahedron formed by three chlorine atoms, one oxygen atom of the water molecule and two (of five) oxygen atoms of the CE molecule ($\text{Cr}-\text{O}_{\text{cr}} = 2.05\text{--}2.10\text{ \AA}$).

6. Manganese halides

The reaction of manganese bis(tribromide) with **12C4** gave the sandwich complex $\{[(\text{Mn}) \cdot (12\text{C}4)_2]^{2+} + 2[\text{Br}_3]^- \}$ (**33**) (Fig. 16).³² The $\text{Mn}-\text{O}$ distances vary from $2.241\text{ to }2.369\text{ \AA}$.

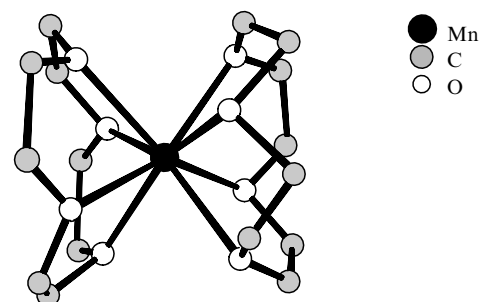
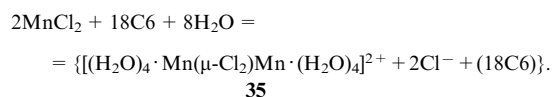


Figure 16. Structure of the $[(\text{Mn}) \cdot (12\text{C}4)_2]^{2+}$ cation in the complex **33**.

One product of the reaction of MnCl_2 with **18C6** in tetrahydrofuran is a compound with composition $\{2[(\text{H}_3\text{O}) \cdot (18\text{C}6)]^+ + [\text{MnCl}_4]^{2-} \}$ (**34**). Its formation can only be attributed to partial hydrolysis in the solution or to the use of the reagents containing water.³³ The oxonium ion in **34** is located in the centre of the cavity of the CE molecule. In the nearly regular tetrahedral anion, the $\text{Mn}-\text{Cl}$ distances vary from $2.35\text{ to }2.37\text{ \AA}$. Interestingly, hydrolysis products were not detected in the analogous reaction performed in the presence of an excess of water. In this case, the salt underwent complete ionisation and the cation was hydrated.^{34,35} The structure of the Mn-containing fragment is more complex and the CE molecule is located in the second coordination sphere.



Individual fragments of the structure **35** (Fig. 17) are linked to each other through a complex system of $\text{OH} \cdots \text{O}$ and $\text{OH} \cdots \text{Cl}$ hydrogen bonds.

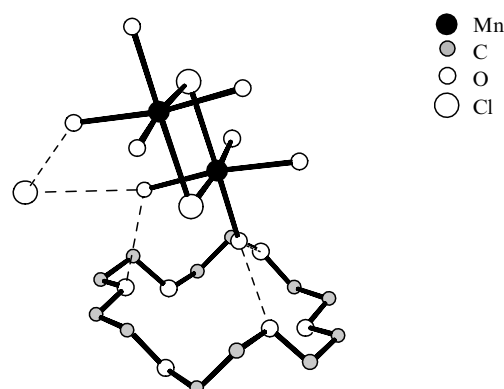


Figure 17. Structure of the $[(\text{H}_2\text{O})_4 \cdot \text{Mn}(\mu\text{-Cl}_2)\text{Mn} \cdot (\text{H}_2\text{O})_4]^{2+}$ cation in the complex **35**.

7. Iron halides

The reaction of FeBr_2 with **15C5** in dry dichloromethane afforded a complex of type A with composition $\{[(\text{FeBr}_2) \cdot (15\text{C}5)] + (\text{CH}_2\text{Cl}_2)\}$ (**36**) with the iron atom in the pentagonal-bipyramidal

environment. The Fe–O distances in the equatorial plane vary from 2.18 to 2.26 Å and the Fe–Br distances (the Br atoms are located in the apical positions) are in the range of 2.623–2.628 Å.³⁶

The reaction of FeCl₃ with 15C5 in dry tetrahydrofuran proceeded analogously to the reaction of aluminium chloride with this CE (see the preparation of **14**). The process yielded an ionic complex with composition $\{[(\text{FeCl}_2) \cdot (15\text{C}5)]^+ + [\text{FeCl}_4]^- \}$ (**37**) as the final product.³⁷ The Fe–O_{cr} distances in the cation vary from 2.112 to 2.192 Å.

The reaction of FeCl₃ or FeBr₃ with 18C6 in ordinary tetrahydrofuran containing water resembles the above-considered reaction of MnCl₂ with 18C6, *i.e.*, this reaction proceeded as hydrolysis to form type C complexes with composition $\{[\text{FeX}_4]^- + [(\text{H}_3\text{O}) \cdot (18\text{C}6)]^+ \}$ [X = Cl (**38**) or Br (**39**)]. In the resulting complexes, the oxonium ion is a ‘guest.’ The cations have a flattened tetrahedral structure.^{38,39} An analogous reaction performed in a mixture of dry tetrahydrofuran and diethyl ether afforded an unusual sandwich complex of type B with composition $\{[(\text{FeCl}) \cdot (18\text{C}6)_2]^{2+} + 2[\text{FeCl}_4]^- \}$ (**40**) (Fig. 18).⁴⁰ Crystals of this complex contain the dications $[(\text{FeCl}) \cdot (18\text{C}6)_2]^{2+}$ in which the five-coordinate iron atom exists in two equally probable orientations. The coordination environment about the iron atom in the cation is a distorted octahedron formed by two chlorine atoms [statistically disordered positions (50%)] and four of the six oxygen atoms of the CE molecule (the Fe–O_{cr} distances vary from 2.156 to 2.209 Å). The anion has a flattened tetrahedral structure.

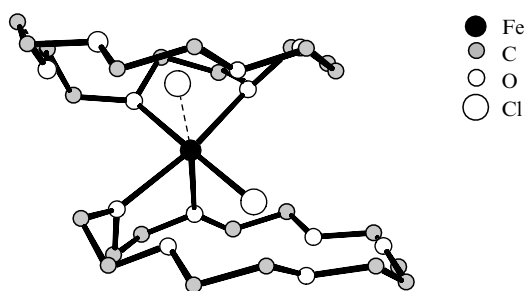


Figure 18. Structure of the $[(\text{FeCl}) \cdot (18\text{C}6)_2]^{2+}$ cation in the complex **40**.

The reaction of an equimolar mixture of FeCl₂ and FeCl₃ with 18C6 in tetrahydrofuran gave a product with an interesting structure.⁴¹ In the complex of type B, the Fe^{II} atoms form complex cations $\{2[(\text{Fe}) \cdot (\text{H}_2\text{O}) \cdot (\text{C}_4\text{H}_8\text{O}) \cdot (18\text{C}6)](\mu_2\text{-Cl}_2)\}^{2+}$ (**41**) (Fig. 19). The coordination polyhedron about the metal atom is an octahedron. The equatorial plane is formed by two chlorine atoms (Fe–Cl = 2.43–2.47 Å) and two oxygen atoms of the CE molecule (Fe–O_{cr} = 2.14–2.18 Å). The apical positions are

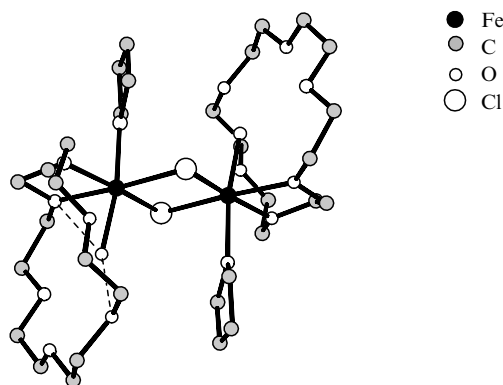


Figure 19. Structure of the cation $\{2[(\text{FeCl}) \cdot (\text{H}_2\text{O}) \cdot (\text{C}_4\text{H}_8\text{O}) \cdot (18\text{C}6) (\mu\text{-Cl}_2)]\}^{2+}$ in the complex **41**.

occupied by the oxygen atom of the water molecule (2.06 Å) and the oxygen atom of the tetrahydrofuran molecule (2.13 Å). The Fe^{III} atoms form tetrahedral anions $[\text{FeCl}_4]^-$.

8. Cobalt chlorides

The reactions of CoCl₂ with 15C5 were studied in a series of works.^{42–47} This reaction in acetonitrile always afforded the inner-cavity cation $[(\text{Co}) \cdot (\text{CH}_3\text{CN})_2 \cdot (15\text{C}5)]^{2+}$ but the composition of the anion in the complex varied from $[(\text{CoCl}_3) \cdot (\text{CH}_3\text{CN})]^-$ (**42**) and $[\text{CoCl}_4]^{2-}$ (**43**) (mononuclear tetrahedral) to $[\text{Co}_2\text{Cl}_6]^{2-}$ (**44**) (binuclear bridging) depending on the concentration of CoCl₂. The presence of water in organic solvents resulted only in hydration of the complex rather than in hydrolysis of the salt. In this case, the acetonitrile molecules located in the apical positions of the pentagonal bipyramid (the coordination polyhedron about the cobalt atom) were replaced by water molecules with retention of the structural type of the cation $[(\text{Co}) \cdot (\text{H}_2\text{O})_2 \cdot (15\text{C}5)]^{2+}$ (see Ref. 44). Only free Cl[–] ions (**45**) or tetrahedral anions $[\text{CoCl}_4]^{2-}$ (**46**) act as anions. In all the structures under consideration, the coordination polyhedron about the cobalt atom is a pentagonal bipyramid. The Co–O_{cr} distances vary from 2.07 to 2.40 Å.

The reaction of anhydrous CoCl₂ with 15C5 in ethanol yielded a complex of type A with composition $\{[(\text{Co}) \cdot (\text{EtOH})_2 \cdot (15\text{C}5)]^{2+} + [\text{CoCl}_4]^{2-} \}$ (**47**).⁴⁵ The Co–O_{Et} distances vary from 2.11 to 2.13 Å.

The reaction of CoCl₂ with 15C5 in the presence of an equimolar amount of MgCl₂ in acetonitrile afforded an inner-cavity magnesium complex with CE with composition $\{[(\text{Mg}) \cdot (\text{CH}_3\text{CN})_2 \cdot (15\text{C}5)]^{2+} + [\text{CoCl}_4]^{2-} + (\text{CH}_3\text{CN})\}$ (**48**).⁴² One product of hydration of this compound is a homometallic complex with composition $\{[(\text{Co}) \cdot (\text{H}_2\text{O})_2 \cdot (15\text{C}5)]^{2+} + 2\text{Cl}^- + (\text{H}_2\text{O})_{2.5}\}$ (**49**). The cobalt atom is in the typical pentagonal-bipyramidal coordination. The structural fragments are linked to each other through a system of OH⋯O and OH⋯Cl intermolecular hydrogen bonds.⁴²

The reaction of a mixture of cobalt chloride and copper chloride with 15C5 in acetonitrile gave a complex with composition $\{[(\text{Co}) \cdot (\text{CH}_3\text{CN})_2 \cdot (15\text{C}5)]^{2+} + [\text{Cu}_2\text{Cl}_6]^{2-} \}$ (**50**). The Co–O_{cr} distances in this compound vary from 2.103 to 2.269 Å, Co–N = 2.097 Å. Complete hydration of this complex led to changes in the composition of the cation and in the structure of the anion. The resulting compound has the composition $\{[(\text{Co}) \cdot (\text{H}_2\text{O})_2 \cdot (15\text{C}5)]^{2+} + [\text{CuCl}_4]^{2-} \}$ (**51**).

The reaction of anhydrous CoCl₂ with 18C6 in acetonitrile yielded a compound with composition $\{[(\text{Co}) \cdot (\text{CH}_3\text{CN}) \cdot (18\text{C}6)]^{2+} + [\text{CoCl}_4]^{2-} \}$ (**52**). In this complex, the cobalt atom has a rather untypical hexagonal-pyramidal coordination (the coordination number is 7). The metal atom is coordinated to all the six oxygen atoms of the CE molecule (Co–O_{cr} = 2.26 Å) and to the nitrogen atom (Co–N = 1.83 Å) and deviates from the mean plane through the oxygen atoms by 0.5 Å. The values of the torsion angles indicate that the CE molecule is highly strained.⁴⁵

The reaction of CoCl₂ · 6H₂O with 18C6 in acetone afforded a complex with composition $\{[(\text{Co}) \cdot (\text{H}_2\text{O})_6]^{2+} + [\text{CoCl}_4]^{2-} + (18\text{C}6) + [(\text{CH}_3)_2\text{CO}]\}$ (**53**). All structural units of this complex are linked to each other through a branched system of OH⋯O and OH⋯Cl hydrogen bonds.⁴⁸

The reaction of a mixture of CoCl₂ and BaCl₂ with 18C6 gave a compound $\{[(\text{Ba}) \cdot (\text{H}_2\text{O})_2 \cdot (18\text{C}6)]^{2+} + [\text{CoCl}_4]^{2-} \}$ (**54**).⁴⁹

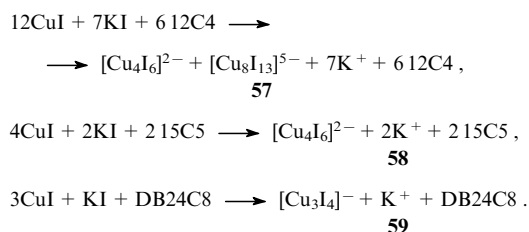
9. Nickel chloride

The reaction of anhydrous NiCl₂ and NaCl with 15C5 gave a complex with composition $\{2[(\text{Na}) \cdot (15\text{C}5)]^+ + [\text{NiCl}_4]^{2-} \}$ (**55**) in which the tetrahedral anion and the complex cation are linked through an Na⋯Cl interaction (2.65 Å).⁵⁰

The reaction of nickel chloride dihydrate with 18C6 in methanol afforded a compound $\{[(\text{H}_2\text{O})_4 \cdot \text{Ni}(\mu\text{-Cl}_2)\text{Ni}(\text{H}_2\text{O})_4]^{2+} + (18\text{C}6) + 2\text{Cl}^- \}$ (**56**) the structure and composition of which are analogous to those of the manganese complex **35**.⁵¹

10. Copper halides

The products of reactions of a mixture of monovalent copper iodide and KI with various CE in acetone were studied by Rath and Holt.⁵² Complexes containing potassium cations, CE molecules (dibenzo-24-crown-8, DB24C8, or dibenzo-18-crown-6, DB18C6) and $[\text{Cu}_x\text{I}_y]^{n-}$ anions of different compositions were prepared according to the following reactions:



The reaction of CuI with DB18C6 in acetonitrile gave a molecular complex of composition $\{[(\text{Cu}_4\text{I}_4) \cdot (\text{CH}_3\text{CN})_4] + (\text{DB18C6})\}$ (**60**) with fragments that are not linked to each other.⁵³

Only one structure of a monomolecular complex of CuCl_2 with 12C4 (**61**) (Fig. 20) has been reported.⁵⁴ In this complex, the copper atom has an octahedral coordination formed by four oxygen atoms of the CE molecule and two chlorine atoms ($\text{Cu}-\text{O}_{\text{cr}} = 2.113\text{--}2.403\text{ \AA}$ and $\text{Cu}-\text{Cl} = 2.214\text{--}2.228\text{ \AA}$).

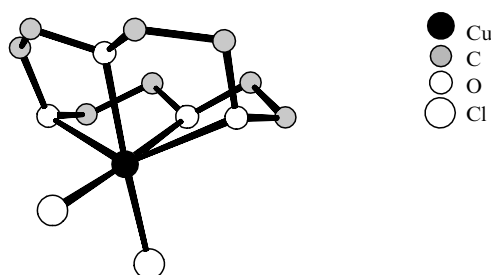
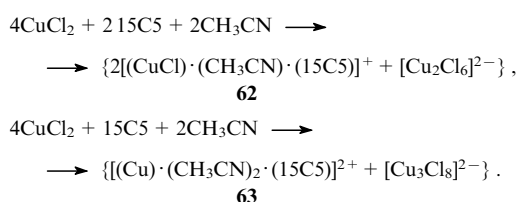


Figure 20. Structure of the complex **61**.

The reaction of CuCl_2 with 15C5 in acetonitrile was studied in several works.^{55–57} Ionic complexes of the type $\{[(\text{Cu}) \cdot (\text{CH}_3\text{CN})_{2-x} \cdot \text{Cl}_x \cdot (\text{15C5})] + \text{A}\}$, where $x = 0$ or 1 and A is an anion in which the coordination environment about the copper atom is a pentagonal bipyramid, were synthesised. The following complexes were obtained depending on the halide : CE : solvent ratio:



The $\text{Cu}-\text{O}$ distances in these compounds vary from 2.16 to 2.34 Å and the $\text{Cu}-\text{N}$ distances are in the range of 1.95–1.99 Å. In the complex **63**, the anion exists as an infinite chain of alternating tetragonal-bipyramidal and tetragonal-pyramidal fragments linked through bridging chlorine atoms (Fig. 21). The $\text{Cu}-\text{Cl}$ distances are in the range of 2.255–2.787 Å. Hydration of compounds **62** and **63** with water vapour resulted in the removal of the CE molecules from the coordination sphere of the metal atom and in the change in the type of the complex from A to C.⁵⁷ In this case, compounds with compositions $\{[(\text{Cu}) \cdot (\text{H}_2\text{O})_4]^{2+} + [(\text{Cu}_3\text{Cl}_8) \cdot (\text{H}_2\text{O})_2]^{2-} + (\text{15C5})_2\}$ (**64**) and $\{2[(\text{CuCl}_2) \cdot (\text{H}_2\text{O})_2] + (\text{15C5})\}$ (**65**) were formed along with $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$. Separate fragments in **64** and **65** are linked to each other through $\text{OH}_w \cdots \text{O}_{\text{cr}}$ hydrogen bonds (Figs 22 and 23, respectively).

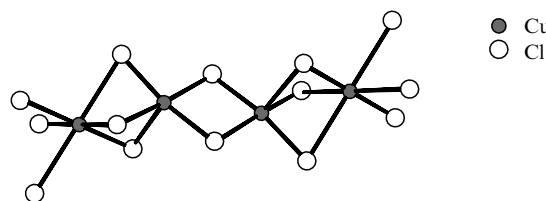


Figure 21. Structure of the $[\text{Cu}_3\text{Cl}_8]^{2-}$ anion in the complex **63**.

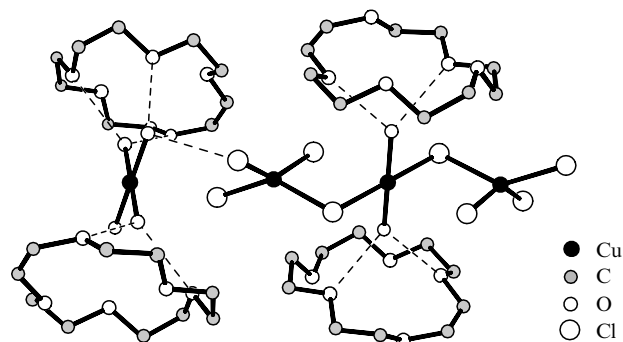


Figure 22. Structure of the complex **64**.

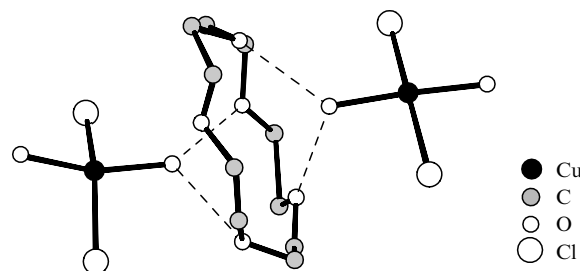
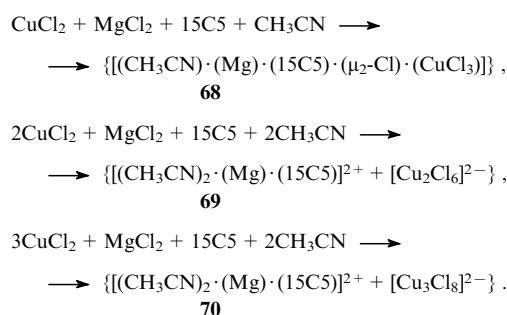


Figure 23. Structure of the complex **65**.

The reaction of anhydrous CuCl_2 with 15C5 in aqueous methanol gave a complex of type C with composition $\{[(\text{CuCl}_2) \cdot (\text{H}_2\text{O})_2 \cdot (\text{CH}_3\text{OH})] + (\text{15C5})\}$ (**66**).⁵⁸ The coordination environment about the copper atom is a square pyramid. In the crystal structure of the complex, $\text{OH} \cdots \text{O}$ intermolecular hydrogen bonds with the participation of water, methanol and CE molecules are realised. The reaction of CuBr_2 with 15C5 yielded a complex with composition $\{[(\text{H}_2\text{O})_2 \cdot (\text{CuBr}_2)] + (\text{15C5})\}$ (**67**). The coordination polyhedron about the copper atom is a strongly flattened tetrahedron.⁵⁹

The structures of a number of products which were formed in the reactions of a mixture of CuCl_2 and MgCl_2 with 15C5 in acetonitrile where the reagents were taken in different ratios and at various concentrations were reported.⁶⁰



The structure **68** consists of monomolecular fragments (Fig. 24), while structures **69** and **70** are ionic. In all the three compounds, the magnesium atom is located in the centre of the cavity of the CE molecule and has a pentagonal-bipyramidal

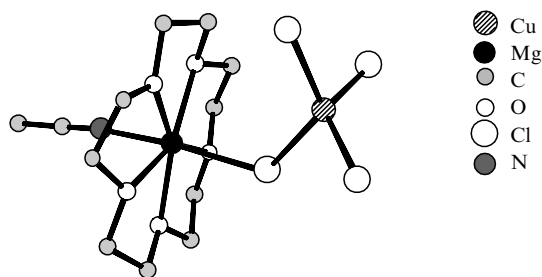
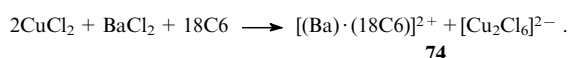
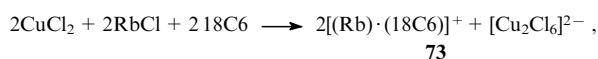


Figure 24. Structure of the complex 68.

coordination. In compound **70**, the chain anion is analogous to that observed in the structure **63**. Hydration of compounds **68–70** with water vapour gave complexes with compositions $\{[(\text{H}_2\text{O})_2 \cdot (\text{Mg}) \cdot (15\text{C}5)]^{2+} + [\text{CuCl}_4]^{2-}\}$ (**71**) and $\{[(\text{Cu}_3\text{Cl}_8) \cdot (\text{H}_2\text{O})_2]^{2-} + [(\text{Mg}) \cdot (\text{H}_2\text{O})_6]^{2+} + (15\text{C}5)_2\}$ (**72**). The structure of the cation in **71** is analogous to that in **11**. The metal atom in the cation of **72** has an octahedral coordination. The central copper atom in the anion has an octahedral coordination formed by two oxygen atoms of the water molecules and four chlorine atoms. The terminal copper atoms have a tetrahedral environment. The fragments are linked to each other through $\text{OH}_w \cdots \text{O}_{\text{cr}}$ and $\text{OH}_w \cdots \text{Cl}$ hydrogen bonds.

The reactions of copper chloride with 18C6 in the presence of halides of alkali or alkaline-earth metals gave complexes in which the metal atoms are coordinated by CE molecules and the copper atoms form the $[\text{Cu}_2\text{Cl}_6]^{2-}$ anions.⁶¹



The product of the reaction of CuCl_2 with benzo-15-crown-5 (B15C5) in chloroform was also structurally characterised.⁶² The product has the composition $\{[(\text{CuCl}_2) \cdot (\text{B15C5})] + (\text{CHCl}_3)\}$ (**75**). The copper atom is located in the centre of the cavity of the CE molecule and has a pentagonal-bipyramidal coordination. This reaction in acetonitrile in the presence of NaCl gave a complex $\{2[(\text{Na}) \cdot (\text{B15C5})]^+ + [\text{Cu}_2\text{Cl}_6]^{2-}\}$ (**76**).⁶³ An analogous product with composition $\{2[(\text{Na}) \cdot (\text{DB18C6})]^+ + [\text{Cu}_2\text{Cl}_6]^{2-}\}$ (**77**) was formed when DB18C6 was used as a polyether.⁶³ The reaction with KCl and naphtho-15-crown-5 (N15C5) yielded a compound with a similar composition, $\{2[(\text{K}) \cdot (\text{N15C5})]^+ + [\text{Cu}_2\text{Cl}_6]^{2-} + (\text{H}_2\text{O})\}$ (**78**), containing a water molecule of crystallisation.⁶⁴

11. Zinc halides

The reactions of anhydrous ZnCl_2 with 15C5 in different solvents gave complexes of type A of the general formula $\{[(\text{Zn}) \cdot (\text{L}_1) \cdot (\text{L}_2) \cdot (15\text{C}5)]^{2+} + [\text{Zn}_2\text{Cl}_6]^{2-}\}$, where $\text{L}_1 = \text{Cl}$ and $\text{L}_2 = (\text{CH}_3)_2\text{CO}$ (**79**), $\text{L}_1 = \text{Cl}$ and $\text{L}_2 = \text{H}_2\text{O}$ (**80**) (both prepared in acetone), $\text{L}_1 = \text{L}_2 = \text{C}_4\text{H}_8\text{O}$ (**81**) (in tetrahydrofuran) and $\text{L}_1 = \text{L}_2 = \text{CH}_3\text{CN}$ (**82**) (in acetonitrile).^{65,66} In all the structures under consideration, the zinc atom is located in the cavity of the CE molecule and has a pentagonal-bipyramidal coordination. The $\text{Zn}-\text{O}_{\text{cr}}$ distances vary from 2.13 to 2.27 Å.

The reaction of zinc chloride dihydrate with 15C5 in methanol yielded a typical complex of type C with composition $\{[(\text{H}_2\text{O})_2 \cdot (\text{ZnCl}_2)] + (15\text{C}5)\}$ (**83**).⁶⁷ In this complex, the zinc atom has a tetrahedral coordination. The structural fragments are linked to each other through $\text{OH} \cdots \text{O}$ hydrogen bonds.

In going from 15C5 to 18C6, the compositions and structures of zinc chloride complexes become more diversified. Thus the reaction in tetrahydrofuran^{66,68} gave a complex of type B with composition $[(\text{H}_2\text{O}) \cdot (\text{ZnCl}_2) \cdot (18\text{C6})]$ (**84**). The coordination poly-

hedron about the zinc atom is a tetrahedron formed by two chlorine atoms ($\text{Zn}-\text{Cl} = 2.20$ and 2.23 Å), one water molecule ($\text{Zn}-\text{O}_w = 1.97$ Å) and one oxygen atom of the CE molecule ($\text{Zn}-\text{O}_{\text{cr}} = 2.08$ Å). The water molecule, in turn, forms an intramolecular hydrogen bond with another O_{cr} atom (2.77 Å) resulting in strong distortion of the macrocycle (Fig. 25).

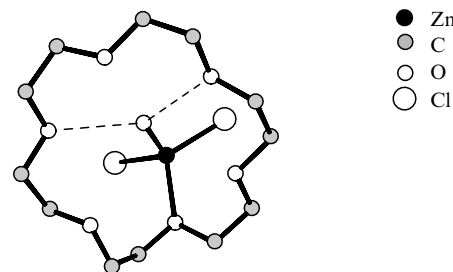


Figure 25. Structure of the complex 84.

The reaction of ZnCl_2 with 18C6 in diethyl ether afforded a complex of type B with composition $\{2(\text{H}_2\text{O})_2 \cdot (\text{ZnCl}) \cdot (18\text{C6})\}^+ + [\text{Zn}_2\text{Cl}_6]^{2-}$ (**85**).⁶⁹ The zinc atom is coordinated by one chlorine atom, one oxygen atom of the water molecule and three (of six) oxygen atoms of the CE molecule. Recrystallisation of this compound from a mixture of acetone and CCl_4 gave a complex of type C with composition $\{[(\text{Zn}) \cdot (\text{H}_2\text{O})_6]^{2+} + 2[(\text{ZnCl}_3) \cdot (\text{H}_2\text{O})]^- + (18\text{C6}) + [(\text{CH}_3)_2\text{CO}]\}$ (**86**). In the crystal structure of this complex, an extensive system of intermolecular hydrogen bonds exists. The reaction of ZnCl_2 with 18C6 in tetrahydrofuran yielded a product with composition $\{[\text{ZnCl}_4]^{2-} + 2[(\text{H}_3\text{O}) \cdot (18\text{C6})]^- \}$ (**87**) with the oxonium ion occupying the centre of the cavity of the CE molecule.³² Under analogous conditions, the reaction of ZnI_2 with 18C6 afforded the compound $\{[(\text{H}_2\text{O})_2 \cdot (\text{ZnI}_2)] + (18\text{C6})_2 + (\text{H}_2\text{O})\}$ (**88**) in which the tetrahedral zinc-containing fragments are located between two CE molecules and are bound to the CE molecules through $\text{OH} \cdots \text{O}$ hydrogen bonds (Fig. 26).

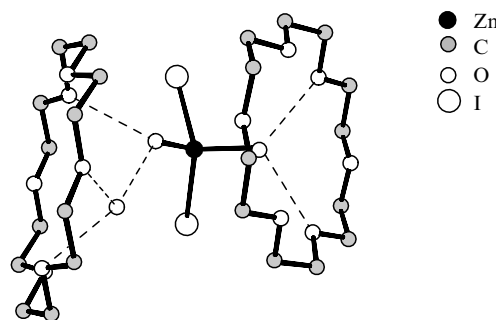


Figure 26. Structure of the complex 88.

12. Gallium halides

It was shown⁷⁰ that the complexes prepared by reactions of gallium halides with 15C5 have the composition $\{[(\text{GaX}_2) \cdot (15\text{C}5)]^+ + [\text{GaX}_4]^- \}$, where $\text{X} = \text{Cl}$ (**89**) or Br (**90**). These complexes are isostructural to the aluminium complex **14**.

The reaction of GaCl_3 with 18C6 in acetonitrile afforded the compounds $\{[\text{GaCl}_4]^- + [(\text{H}_3\text{O}) \cdot (18\text{C6})]^+ \}$ (**91**) with the oxonium ion occupying the centre of the CE molecule. The structure of this complex is analogous to that of the above-described manganese complex **34**.

13. Arsenic halides

The structures of the molecular complexes $[(\text{AsCl}_3) \cdot (12\text{C}4)]$ (**92**) (Fig. 27) and $[(\text{AsCl}_3) \cdot (15\text{C}5)]$ (**93**) were reported.⁷¹ The $\text{As} \cdots \text{O}_{\text{cr}}$ distances in these compounds vary from 2.776 to 2.915 Å and from 2.944 to 3.156 Å, respectively, which are only slightly smaller than the sum of the van der Waals radii. In general, a complex of arsenic bromide with 15C5 has an analogous structure.⁷² However, the $\text{As} \cdots \text{O}$ bonds in the latter complex are nonequivalent: four bonds vary from 3.12 to 3.29 Å and the fifth bond is substantially longer (3.85 Å).

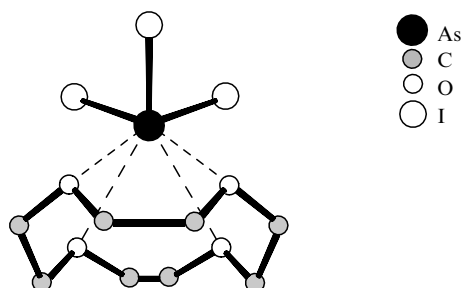


Figure 27. Structure of the complex **92**.

V. Systems with halides of the fourth-row elements

1. Zirconium tetrachloride

The reactions of metal halides in the highest oxidation states with CE were accompanied by destruction of the latter. The reaction of ZrCl_4 with 18C6 in tetrahydrofuran is a typical example.⁷³ The resulting product (Fig. 28) has the composition $\{[(\text{ZrCl}_5) \cdot (\text{C}_4\text{H}_8\text{O})]^- + [(\text{ZrCl}_2) \cdot (\text{O}_4\text{C}_8\text{H}_{16}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{Cl})]^+\}$ (**94**). The $\text{Zr} \cdots \text{O}$ distances (1.93 and 2.24–2.33 Å) in the cation indicate that both covalent and coordination interactions exist between the zirconium and oxygen atoms.

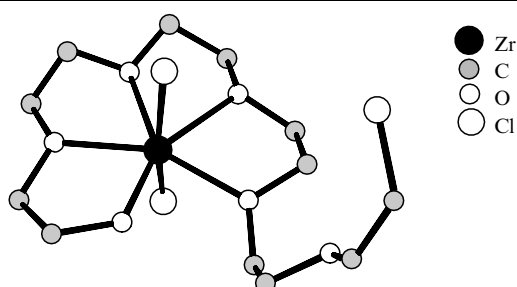


Figure 28. Structure of $[(\text{ZrCl}_2) \cdot (\text{O}_4\text{C}_8\text{H}_{16}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{Cl})]^+$ cation in the complex **94**.

2. Molybdenum halides

The reaction of MoCl_5 with 15C5 in 1,2-dimethoxyethane (L) in the presence of sodium silicide was accompanied by reduction of Mo^{V} to Mo^{IV} (see Ref. 74). The resulting complex of type C has the composition $\{[(\text{MoCl}_4) \cdot (\text{L})]^- + (15\text{C}5)\}$ (**95**). The coordination polyhedron about the molybdenum atom is a distorted octahedron. The $\text{Mo} \cdots \text{O}_{\text{cr}}$ distances vary from 2.14 to 2.18 Å.

The reaction of MoCl_5 with 15C5 in acetonitrile in the presence of AlCl_3 gave the compound $\{[(\text{MoOCl}_4) \cdot (\text{CH}_3\text{CN})]^- + [(\text{AlCl}_2) \cdot (15\text{C}5)]^+ + (\text{CH}_3\text{CN})\}$ (**96**). It was assumed⁷⁵ that the oxychloride was formed as a result of decomposition of the CE molecule under the action of the strong Lewis acid, *viz.*, MoCl_5 . The coordination polyhedron about the molybdenum atom in the

anion of **96** is an octahedron. The structure of the cation of **96** is analogous to that of the complex **14**.

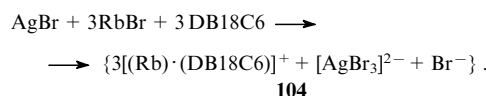
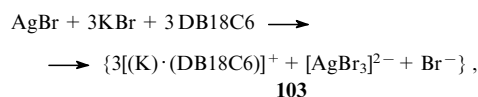
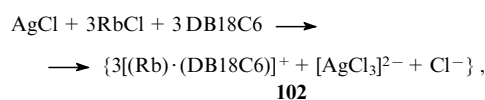
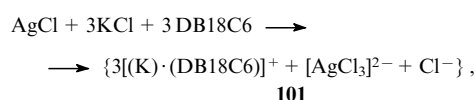
The reactions of molybdenum oxychloride $\text{Mo}^{\text{V}}\text{OCl}_3$ with 12C4 or 18C6 yielded complexes containing the octahedral cations $[(\text{MoOCl}_4) \cdot (\text{H}_2\text{O})]^-$ and the oxonium-containing cations of the type $[(\text{H}_3\text{O}) \cdot (\text{CE})]^+$, *viz.*, $\{[(\text{MoOCl}_4) \cdot (\text{H}_2\text{O})]^- + [(\text{H}_3\text{O}) \cdot (12\text{C}4)]^+\}$ (**97**) and $\{[(\text{MoOCl}_4) \cdot (\text{H}_2\text{O})]^- + [(\text{H}_3\text{O}) \cdot (18\text{C}6)]^+\}$ (**98**), respectively.^{76,77} The $\text{Mo} \cdots \text{O}$ and $\text{Mo} \cdots \text{O}_{\text{w}}$ distances in these complexes are 1.641 (1.654) and 2.285 (2.355) Å, respectively. Separate structural fragments are linked to each other through a system of $\text{OH} \cdots \text{O}$ and $\text{OH} \cdots \text{Cl}$ hydrogen bonds. The reaction with MoOBr_3 gave a complex with an analogous structure $\{[(\text{MoOBr}_3) \cdot (\text{H}_2\text{O})]^- + [(\text{H}_3\text{O}) \cdot (18\text{C}6)]^+\}$ (**99**).⁷⁸

3. Palladium chloride

The reaction of PdCl_2 with 18C6 in a tetrahydrofuran solution of hydrochloric acid afforded a binuclear complex $\{[\text{Pd}_2\text{Cl}_6]^{2-} + 2[(\text{H}_3\text{O}) \cdot (18\text{C}6)]^+\}$ (**100**) of type C.³⁸ The palladium atoms in the planar anion have a square coordination. The $\text{Pd} \cdots \text{Cl}$ distances are 2.326 Å (for the terminal bond) and 2.668 Å (for the bridging bond).

4. Silver halides

The reactions of silver halides with DB18C6 in dimethylformamide in the presence of alkali metal halides were studied by Helgesson and Jagner.⁷⁹



In all cases, complexes containing planar anions of silver halides were detected (Fig. 29).

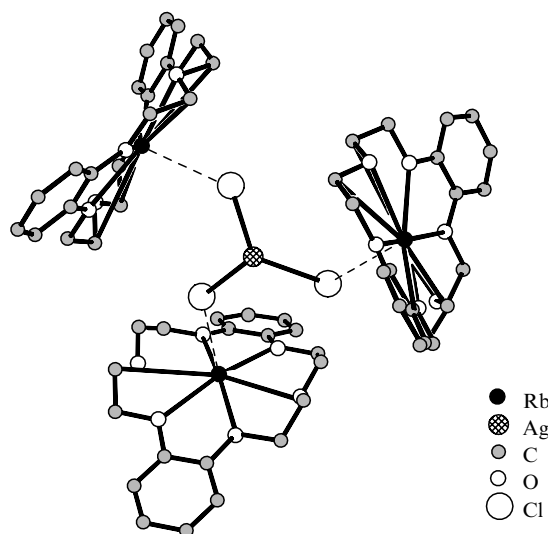


Figure 29. Structure of the complex **102**.

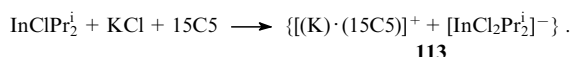
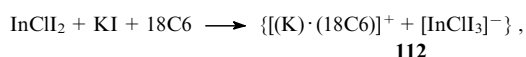
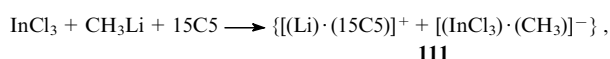
5. Cadmium halides

The reactions of cadmium halides with 18C6 gave typical complexes of type A with composition $[(\text{CdCl}_2) \cdot (18\text{C}6)]$ (**105**), $[(\text{CdBr}_2) \cdot (18\text{C}6)]$ (**106**) and $[(\text{CdI}_2) \cdot (18\text{C}6)]$ (**107**) in which the cadmium atom is located in the centre of the cavity of the CE molecule and has a hexagonal-bipyramidal coordination.^{80,81} The Cd–O_{cr} distances in the complexes vary from 2.36 to 2.75 Å.

6. Indium halides

The reactions of indium(III) halide hydrates with 15C5 or 18C6 always yielded complexes of type C in which direct In–O_{cr} contacts were absent. Thus the reaction of $\text{InCl}_3 \cdot 4\text{H}_2\text{O}$ with 15C5 gave the complex $\{[(\text{InCl}_3) \cdot (\text{H}_2\text{O})_2] + (15\text{C}5)\}$ (**108**).⁸² The coordination environment about the indium atom in this complex is a slightly distorted trigonal bipyramid. The In–O_w distances are in the range of 2.201–2.218 Å. The fragments are linked to each other through O_wH···O_{cr} hydrogen bonds. An analogous reaction with 18C6 afforded the complex $\{[(\text{InCl}_3) \cdot (\text{H}_2\text{O})_3] + (18\text{C}6)\}$ (**109**). In this compound, the indium atom has an octahedral environment. The In–O_w distances vary from 2.23 to 2.25 Å.

The reaction of InCl_3 with 18C6 in tetrahydrofuran afforded the compound $\{[\text{InCl}_4]^- + [(\text{H}_3\text{O}) \cdot (18\text{C}6)]^+\}$ (**110**) isostructural to the complex **38**.³⁸ The formation of the tetrahedral anions of the same type was also observed in the reactions of indium mixed halides with alkali metal halides and alkyl derivatives.^{83–85}



7. Tin chlorides

Only one example of complexation of SnCl_2 with CE (18C6) in methanol saturated with hydrogen chloride is documented.⁸⁶ This reaction gave the complex $\{[(\text{SnCl}) \cdot (18\text{C}6)]^+ + [\text{SnCl}_3]^- \}$ (**114**) with a very unusual structure (Fig. 30). The tin atom in the cation has a nontypical hexagonal-pyramidal coordination with the Sn–O distances varying from 2.59 to 2.88 Å. The tin atom in the anion has a pyramidal coordination and is located in the mean plane of the base of the pyramid. Oxidation of SnCl_2 in aqueous methanol containing 15C5 with atmospheric oxygen at 120 K yielded the complex of type C with composition $\{[(\text{Sn}^{\text{IV}}\text{Cl}_4) \cdot (\text{H}_2\text{O})_2] + [15\text{C}5]\}$ (**115**).⁸⁶ The coordination polyhedron about the tin atom is an octahedron. The Sn–O_w distances vary from 2.107 to 2.125 Å. The fragments in this compound are linked to each other through O_wH···O_{cr} hydrogen bonds.

The reaction of SnCl_4 with 15C5 in acetonitrile resulted in decomposition of the CE molecule.⁸⁸ In this case, two C–O bonds were cleaved, one –CH₂–CH₂– unit was eliminated in the form of dichloroethane and two tin atoms were μ_2 -coordinated by two

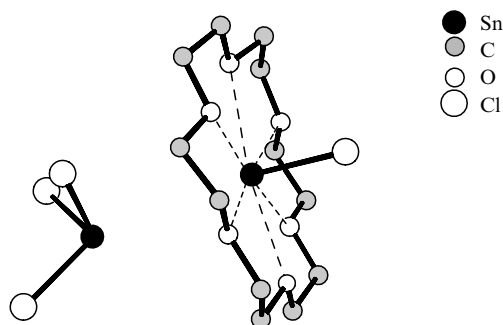


Figure 30. Structure of the complex **114**.

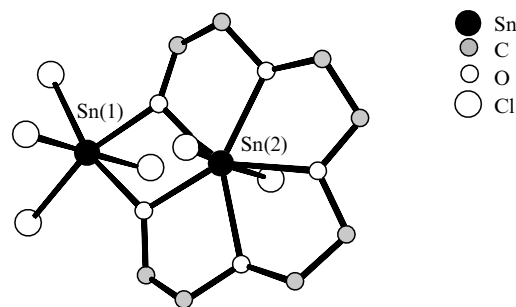


Figure 31. Structure of the complex **116**.

terminal oxygen atoms (Fig. 31). The resulting complex has the composition $\{[(\text{SnCl}_4) \cdot (\text{O}_5\text{C}_8\text{H}_{16}\text{SnCl}_2)] + (\text{CH}_3\text{CN})\}$ (**116**). The coordination environment about the Sn(1) atom is a pentagonal bipyramid. The Sn(1)–O_{cr} coordination bonds are in the range of 2.237–2.239 Å. The Sn(1)–O_μ covalent bond is 2.074 Å. The Sn(2) atom has an octahedral coordination with the Sn(2)–O_μ distances of 2.149 Å.

The reaction of SnCl_4 with 18C6 in chloroform gave a complex of type C with composition $\{[(\text{SnCl}_4) \cdot (\text{H}_2\text{O})_2] + (18\text{C}6) + (\text{CHCl}_3) + (\text{H}_2\text{O})\}$ (**117**).^{89,90} The octahedral tin-containing fragment is linked to the CE molecule through O_wH···O_{cr} hydrogen bonds. In addition, there are H-bonds between the coordinated water molecules and the water molecules of crystallisation.

8. Antimony halides

The complex $[(\text{SbCl}_3) \cdot (12\text{C}4)]$ (**118**)^{71,91} has a structure analogous to that of the complex **92**. The reaction of a mixture of SbCl_3 and SbCl_5 with 12C4 in acetonitrile gave a compound with composition $\{[(\text{Sb}^{\text{III}}) \cdot (12\text{C}4)_2]^{3+} + 3[\text{Sb}^{\text{V}}\text{Cl}_6]^- + (\text{CH}_3\text{CN})\}$ (**119**).⁹² The Sb–O_{cr} distances in the sandwich cation vary from 2.325 to 2.530 Å.

The reaction of SbCl_3 with 15C5 afforded the monomolecular complex $[(\text{SbCl}_3) \cdot (15\text{C}5)]$ (**120**).⁹³ The pyramidal SbCl_3 molecule is hanging over the mean plane of the CE molecule and the lone electron pair of the antimony atom is directed toward the polyether molecule. The Sb–O_{cr} distances vary from 2.787 to 2.997 Å. The reaction of SbBr_3 with 15C5 and the reaction of SbCl_3 with DB18C6 in chloroform afforded analogous structures [**121**⁹⁴ and **122** (Fig. 32), respectively].[†]

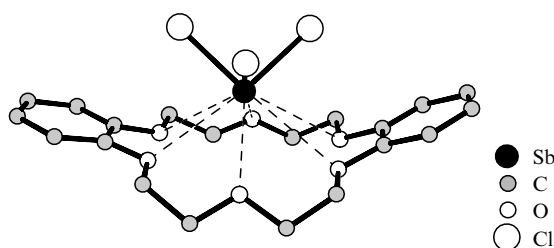


Figure 32. Structure of the complex **122**.

The reaction of a mixture of tri- and pentavalent antimony chlorides with 18C6 in acetonitrile afforded a compound with composition $\{[(\text{Sb}^{\text{III}}\text{Cl}_2) \cdot (18\text{C}6)]^+ + [\text{SbCl}_6]^- \}$ (**123**)⁹⁵ in which the antimony(III) atom is coordinated by two chlorine atoms and only two oxygen atoms of the CE molecule. The coordination polyhedron about this atom (taking into account the lone electron pair) is a trigonal bipyramid. The anion in the complex **123** has the typical octahedral structure.

[†] V K Belsky. Unpublished data.

9. Tellurium tetrachloride

The reaction of TeCl_4 with a mixture of SbCl_5 and 15C5 gave a bimetallic ionic complex with composition $\{[(\text{TeCl}_3) \cdot (15\text{C}5)]^+ + [\text{SbCl}_6]^- \}$ (**124**). The $\text{Te}-\text{O}_{\text{cr}}$ distances vary from 2.66 to 2.79 Å.⁹⁶

VI. Systems with halides of the fifth-row elements

1. Barium bromide

Only one structure of the complex formed by the reaction of barium bromide hydrate with 15C5 was reported in the literature.⁹⁷ The resulting compound has the composition $\{[(\text{Ba}) \cdot (15\text{C}5)_2]^{2+} + 2\text{Br}^- + (\text{H}_2\text{O})_2\}$ (**125**). The barium ion is located in the centre of the sandwich formed by CE molecules. The $\text{Ba} \cdots \text{O}$ distances are in the range of 2.749–2.880 Å. In the crystal, the Br^- anions and the water molecules are involved in the formation of a network of $\text{OH} \cdots \text{Br}$ intermolecular hydrogen bonds (3.326–3.493 Å).

2. Lanthanide and yttrium halides

The structures of complexes of lanthanide halide hydrates with 12C4, which were crystallised from a mixture of methanol with acetonitrile, are known.^{98,99} Compounds of three different structural types were obtained depending on the nature of the metal atom and the reaction temperature. In the case of lanthanide and yttrium chlorides, the compositions and structures of the resulting complexes are similar, viz., $\{[(\text{Ln}) \cdot (\text{H}_2\text{O})_5 \cdot (12\text{C}4)]^{3+} + 3\text{Cl}^- + (\text{H}_2\text{O})_2\}$, where $\text{Ln} = \text{Ce}$ (**126**) (Fig. 33), Nd (**127**), Sm (**128**), Eu (**129**), Gd (**130**), Dy (**131**), Y (**132**), Ho (**133**), Er (**134**) or Yb (**135**). In these complexes, the coordination environment about the metal atom is a monocapped tetragonal antiprism formed by four oxygen atoms of the CE molecule and five oxygen atoms of the water molecules ($\text{Ln}-\text{O}_{\text{cr}} = 2.42\text{--}2.63$ Å and $\text{Ln}-\text{O}_{\text{w}} = 2.23\text{--}2.51$ Å). All water molecules (both coordinated and of crystallisation) and chloride ions are involved in the formation of a complex system of $\text{OH} \cdots \text{Cl}$ intermolecular hydrogen bonds.

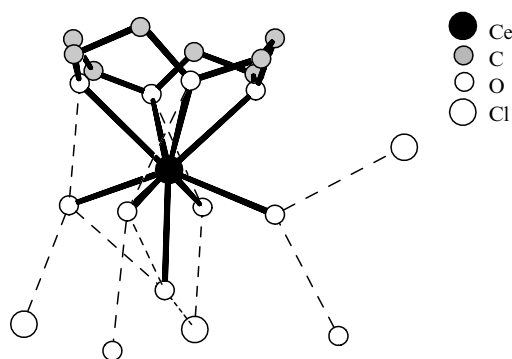


Figure 33. Structure of the complex **126**.

In complexes with composition $\{[(\text{H}_2\text{O})_2 \cdot (\text{LnCl}_2) \cdot (12\text{C}4)]^+ + \text{Cl}^-\}$, where $\text{Ln} = \text{Ho}$ (**136**), Er (**137**), Tm (**138**), Yb (**139**) or Lu (**140**) (Fig. 34), the coordination environment about the metal atom is a bicapped trigonal prism formed by four oxygen atoms of the CE molecule, two oxygen atoms of the water molecules and two chlorine atoms. The structural fragments are linked to each other through a system of $\text{OH} \cdots \text{Cl}$ hydrogen bonds.

The reaction of yttrium chloride with 12C4 afforded a complex with composition $\{[(\text{H}_2\text{O}) \cdot (\text{YCl}_2) \cdot (\text{CH}_3\text{OH}) \cdot (12\text{C}4)]^+ + \text{Cl}^-\}$ (**141**) in which one water molecule is replaced by the methanol molecule. Though the yttrium atom retains the coordination number of 8, it has a different coordination environment (a square antiprism, Fig. 35).

The praseodymium complexes with compositions $\{[(\text{H}_2\text{O}) \cdot (\text{PrCl}_3) \cdot (12\text{C}4)] + (12\text{C}4) + (\text{CH}_3\text{OH})\}$ (**142**) and $\{[(\text{CH}_3\text{OH}) \cdot (\text{PrCl}_3) \cdot (12\text{C}4)]\}$ (**143**) were also described in the literature.¹⁰⁰ In both structures, the coordination environment

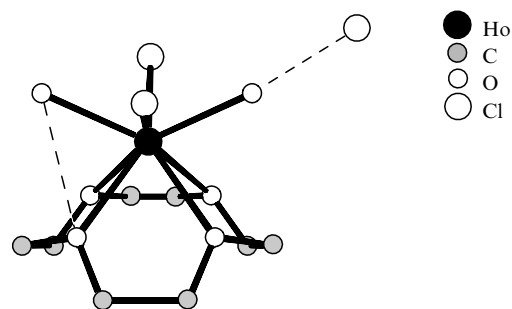


Figure 34. Structure of the complex **136**.

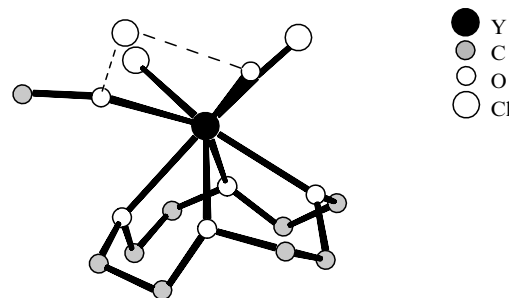


Figure 35. Structure of the complex **141**.

about the metal atom is a tetragonal antiprism with $\text{Pr}-\text{O}_{\text{cr}} = 2.56\text{--}2.63$ Å, $\text{Pr}-\text{OCH}_3\text{OH} = 2.51$ Å and $\text{Pr}-\text{O}_{\text{w}} = 2.48$ Å. In the complex **142**, the structural fragments are linked to each other through $\text{O}_{\text{w}}\text{H} \cdots \text{O}_{\text{cr}}$ hydrogen bonds (Fig. 36).

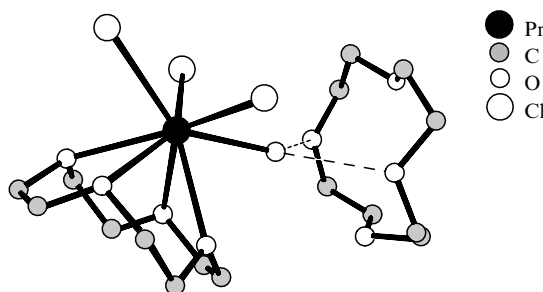
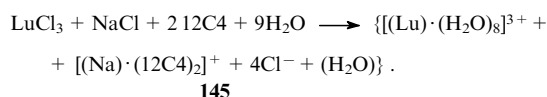
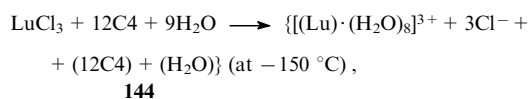


Figure 36. Structure of the complex **142**.

Complete hydration of complexes of lutetium chloride with 12C4 gave eight-coordinate (square antiprism) octa-aqualutetium ions.^{101, 102}



The reactions of LnCl_3 with 15C5 generally gave complexes of two types. The complexes of the first type, viz., $\{[(\text{LnCl}_3) \cdot (15\text{C}5)]\}$, were formed when anhydrous chlorides of praseodymium (**146**), neodymium (**147**) or samarium (**148**) were used.^{103, 104} The structures of these complexes are analogous to those of trihalides of Group V elements (see, for example, structure **93**). The pyramidal LnCl_3 molecule is located above the mean plane of the CE molecule. The $\text{Ln}-\text{O}_{\text{cr}}$ distances vary from 2.50 to 2.75 Å. The stabilities of these complexes were calculated by the INDO method.¹⁰⁵

Complexes of the second type have the composition $\{[(Ln) \cdot (H_2O)_8]^{3+} + (15C5) + 3Cl^- + (H_2O)_n\}$. These compounds were obtained by the reactions with metal chloride hydrates in aqueous solvents or by hydration of lanthanide salts with water vapour. The complexes with $Ln = Y$ (**149**), Gd (**150**) and Lu (**151**) were prepared.^{106–109} In all cases, the coordination polyhedron about the metal atom is a distorted dodecahedron. Complex systems of $OH \cdots O$ and $OH \cdots Cl$ hydrogen bonds are observed in all the structures under consideration.

Products of complexation of chlorides of rare-earth elements with 18C6 are characterised by different types of crystal structures.^{110,111} The reactions performed in a 1 : 3 mixture of methanol and acetonitrile afforded complexes with compositions $\{[(H_2O)_2 \cdot (LnCl) \cdot (18C6)]^{2+} + 2Cl^- + (H_2O)_2\}$, where $Ln = Nd$ (**152**), Sm (**153**), Gd (**154**), Tb (**155**), Pr (**156**) or Eu (**157**). The metal atom is coordinated by six oxygen atoms of the CE molecule, one chlorine atom (located 'above' the mean plane of CE) and two water molecules (located 'below' the mean plane of CE) (Fig. 37).

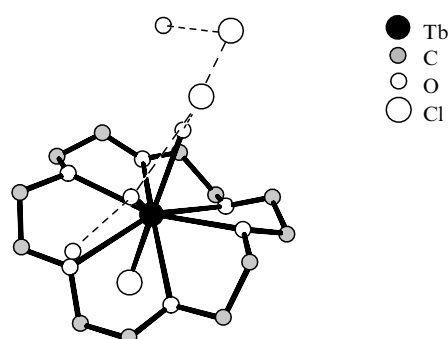


Figure 37. Structure of the complex **155**.

The $Ln-O_{cr}$ and $Ln-O_w$ distances are in the ranges of 2.53–2.55 and 2.36–2.45 Å, respectively. In all cases, the coordination polyhedron about the lanthanide atom is a tricapped trigonal prism. The lanthanide atoms have the same coordination in another type of complexes in which one coordinated water molecule is replaced by the chlorine atom or the methanol molecule:¹¹¹ $\{[(CH_3OH) \cdot (LaCl_2) \cdot (18C6)]^+ + Cl^- + (H_2O)_{1.5}\}$ (**158**), $\{[(H_2O) \cdot (LaCl_2) \cdot (18C6)]^+ + Cl^-\}$ (**159**) and $\{[(H_2O) \cdot (CeCl_2) \cdot (18C6)]^+ + Cl^- + (H_2O)_2\}$ (**160**).

An anhydrous lanthanum complex $[(LaCl_3) \cdot (18C6)]$ (**161**) was prepared by crystallisation at 70 °C.¹¹¹ The coordination polyhedron in the complex **161** is also similar to a tricapped trigonal prism (formed by six oxygen atoms of the CE molecule and three chlorine atoms).

The addition of the salting-out reagent, $LiCl$, to a solution of $[(GdCl_3) \cdot (H_2O)_6 + (18C6)]$ in methanol afforded a compound with a more complex composition, $\{[GdCl_6]^{3-} + 3[(H_2O) \cdot (GdCl_2) \cdot (18C6)]^+ + 2[CH_3OH]\}$ (**162**).¹¹¹ The chlorine atoms and water molecules in the cation are statistically disordered. The structure of the complex **162** is analogous to those of compounds **159** and **160**.

The reactions of lanthanide chloride hexahydrates $LnCl_3 \cdot 6H_2O$ with 18C6 in a methanol:acetonitrile mixture under argon¹¹² gave complexes with composition $\{[(H_2O)_7 \cdot (Ln) \cdot (CH_3OH)]^{3+} + 2[(H_2O)_2 \cdot (LnCl) \cdot (18C6)]^{2+} + 7Cl^- + (H_2O)_2\}$, where $Ln = Y$ (**163**) or Dy (**164**) (X-ray data were collected at –150 °C). The structures of the double-charged cations are analogous to those observed in the complexes **152**–**157**. The trivalent cation has an octahedral environment. All the water and methanol molecules and noncoordinated chloride ions are involved in intermolecular hydrogen bonding.

In addition, two more types of complexes of $DyCl_3$ with 18C6 were reported. One of them was formed in acetonitrile and has the

composition $\{[(Dy) \cdot (H_2O)_8]^{3+} + (18C6) + 3Cl^-\}$ (**165**).¹¹³ The coordination polyhedron about the dysprosium atom is a bicapped trigonal prism. In a complex with triethylene glycol (L) with composition $\{[(DyCl_3) \cdot (L)] + (18C6)\}$ (**166**), the dysprosium atom has a pentagonal-bipyramidal environment.¹¹⁴

3. Tantalum chlorides

As mentioned above, the reaction of CE with strong Lewis acids (halides of metals in the highest oxidation states) are often accompanied by opening and decomposition of the macrocycle to produce large amounts of water, hydrogen chloride (due to hydrolysis), $-O-CH_2-CH_2-O-$ fragments and products of their interactions. The products of the reaction of anhydrous $TaCl_5$ with 15C5 have been studied most thoroughly.¹¹⁵ The reaction in dry acetonitrile afforded a mixture of several compounds. Thus crystals of an ionic complex with composition $\{[(TaCl_2) \cdot (C_8H_{16}O_5)]^+ + [TaCl_6]^- \}$ (**167**) were isolated at room temperature. The structure of the cation of this compound (Fig. 38) is analogous to that of the complex **116**. The Ta(1) is located in the centre of the mean plane formed by five oxygen atoms of the CE molecule. However, as in the case of the complex **116**, the metal atom is bound to three oxygen atoms [O(1), O(4) and O(4a)] through donor-acceptor bonds ($Ta-O = 2.24-2.27$ Å) and to two oxygen atoms [O(7) and O(7a)] through covalent bonds ($Ta-O = 1.89$ Å).

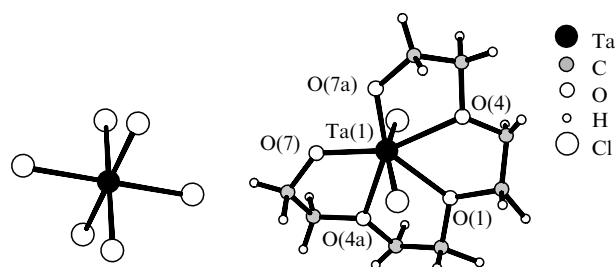


Figure 38. Structure of the complex **167**.

The coordination polyhedron about the tantalum atom is a slightly distorted pentagonal bipyramid. The $Cl-Ta-Cl$ angle is 162°.

Heating of the reaction mixture to 35–40 °C afforded a complex with composition $\{[TaCl_6]^- + [(H_3O) \cdot (18C6)]^+\}$ (**168**).¹¹⁵ The structure of the cation in this compound is analogous to those, for example, of the complexes **34**, **87** and **91**. The appearance of a new CE (18C6) in the $TaCl_5-15C5-CH_3CN$ system was attributed to processes of profound destruction of 15C5, chain extension of the open-chain polyether and closure of the latter. Apparently, these processes are accompanied by the formation of water molecules and hydrolysis of $TaCl_5$ as follows from the presence of the oxonium ion in the complex **168** and the concurrent formation of complexes with compositions $\{[(H_2Cl) \cdot (15C5)_2]^+ + [TaCl_6]^- \}$ (**169**) and $\{[(15C5) \cdot (CH_3C(Cl)=NH_2)]^+ + [TaCl_6]^- \}$ (**170**). The fragments in the cation of the last-mentioned compound are linked to each other through $NH \cdots O$ hydrogen bonds (Fig. 39).

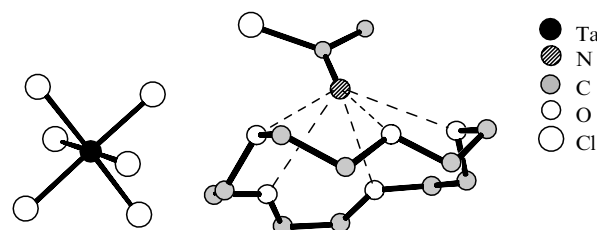


Figure 39. Structure of the complex **170**.

Introduction of an additional component, namely, a tertiary amine or a quaternary ammonium salt, into the TaCl_5 –15C5–acetonitrile system afforded the complex $\{[(\text{C}_2\text{H}_5)_3\text{NH} \cdot (15\text{C}5)]^+ + [\text{TaCl}_6]^- \}$ (**171**) in which the fragments of the cation interact through $\text{NH} \cdots \text{O}$ hydrogen bonds and a complex tantalum oxychloride with composition $\{[\text{Ta}_3\text{O}_3\text{Cl}_{12}]^{3-} + 3[\text{N}(\text{CH}_3)_4]^+ + (\text{CH}_3\text{CN})\}$ (**172**), which contains no CE molecules. The structure of the cation in the complex **172** is shown in Fig. 40.

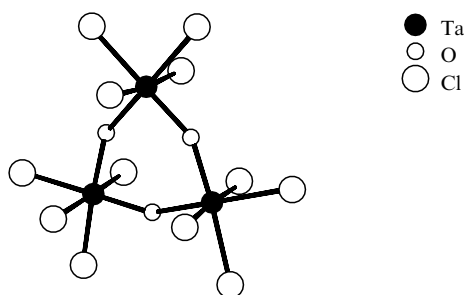


Figure 40. Structure of the $\text{Ta}_3\text{O}_3\text{Cl}_{12}$ fragment in the complex **172**.

The reaction of TaCl_5 with 15C5 in acetonitrile in the presence of LiCl gave complexes in which the lithium atom is a 'guest' for the CE molecule and the tantalum atom forms anions of different compositions depending on the ratio of halide molecules.¹¹⁶ Two products with compositions $\{[(\text{TaCl}_5)_2\text{O}]^{2-} + 2[(\text{Li}) \cdot (\text{CH}_3\text{CN}) \cdot (15\text{C}5)]^+ \}$ (**173**) (Fig. 41) and $\{[\text{TaCl}_6]^- + [(\text{Li}) \cdot (\text{CH}_3\text{CN}) \cdot (15\text{C}5)]^+ \}$ (**174**) were identified. The structures of the cations in both compounds are identical. The lithium atom has a pentagonal-pyramidal coordination and deviates from the mean plane through the oxygen atoms of the CE molecule by 0.45 Å. The $\text{Li} - \text{O}_{\text{cr}}$ distances vary from 2.08 to 2.39 Å. The $\text{Li} - \text{N}$ distance is 2.11 Å.

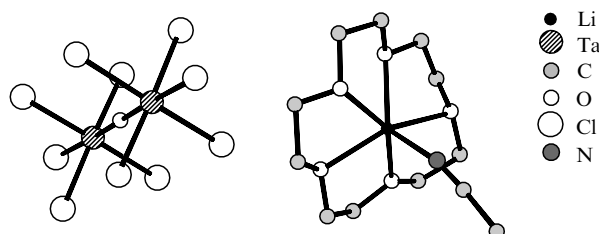


Figure 41. Structure of the complex **173**.

4. Rhenium halides

The reactions of ReOCl_3 and ReOBr_3 with 12C4 and 18C6 in the presence of water gave complexes with compositions $\{[(\text{ReOX}_4) \cdot (\text{H}_2\text{O})]^- + [(\text{H}_3\text{O}) \cdot (12\text{C}4)]^+ \}$, where $\text{X} = \text{Cl}$ (**175**) and Br (**176**), respectively. The reaction of ReOCl_2 with 18C6 yielded the complex $\{[(\text{ReOCl}_4) \cdot (\text{H}_2\text{O})]^- + [(\text{H}_3\text{O}) \cdot (18\text{C}6)]^+ \}$ (**177**).^{76,117} The structures of the anions in the compounds **175**–**177** are analogous to that in the complex **98**.

The reaction of a mixture of ReCl_4 and LiCl with 12C4 in acetonitrile afforded a product with composition $\{(\text{ReCl}_5) \cdot (\text{CH}_3\text{CN})\}^- + [(\text{Li}) \cdot (12\text{C}4)_2]^+ + [(\text{CH}_3\text{CN})]$ (**178**) containing the octahedral anion.¹¹⁷

5. Gold trichloride

The reaction of a mixture of gold trichloride and potassium chloride with 15C5 yielded a compound with composition $\{[(\text{K}) \cdot (15\text{C}5)_2]^+ + [\text{AuCl}_4]^- \}$ (**178**) containing the tetrahedral anion $[\text{AuCl}_4]^-$.

6. Mercury halides

The reactions of HgCl_2 and HgBr_2 with 18C6 gave typical complexes of type A with composition $[(\text{HgX}_2) \cdot (18\text{C}6)]$, where $\text{X} = \text{Cl}$ (**180**) and Br (**181**), respectively. The mercury atom is located in the cavity of the CE molecule and has a hexagonal-bipyramidal coordination. The $\text{Hg} - \text{O}_{\text{cr}}$ distances vary from 2.31 to 2.86 Å.^{81,118}

7. Thallium halides

The reaction of a mixture of TlCl and SbCl_5 with 12C4 afforded a bimolecular complex with composition $\{[\text{SbCl}_6]^- + [(\text{Tl}) \cdot (12\text{C}4)_2]^+ \}$ (**182**).¹¹⁹ The thallium atom in the sandwich cation is located between two CE molecules. The $\text{Tl} - \text{O}_{\text{cr}}$ distances vary from 2.865 to 2.904 Å. The reaction of an equimolar mixture of TlBr_3 and RbBr with 15C5 yielded a complex with composition $\{[\text{TlBr}_4]^- + [(\text{Rb}) \cdot (15\text{C}5)_2]^+ \}$ (**183**) with the thallium atom in the tetrahedral anion and the rubidium atom in the sandwich cation.⁴⁹

The reactions of mixtures of TiX and TiX_3 with 18C6 in the presence of copper or manganese dihalides gave complexes with the analogous composition $\{4[(\text{Ti}^{\text{I}}) \cdot (18\text{C}6)]^+ + 2[\text{Ti}^{\text{III}}\text{X}_4]^- + [\text{MX}_4]^{2-} \}$, where $\text{M} = \text{Cu}$ and $\text{X} = \text{Cl}$ (**184**) or Br (**185**); or $\text{M} = \text{Mn}$, $\text{X} = \text{Cl}$ (**186**).^{49,61,120} In all the structures, the thallium(I) atom deviates from the mean plane through the oxygen atoms of the CE molecule by ~ 0.9 Å. The $\text{Tl} - \text{O}_{\text{cr}}$ distances vary from 2.93 to 3.01 Å.

8. Lead halides

The reaction of lead dibromide with 18C6 in a hot aqueous solution gave a complex of type A with composition $\{[(\text{PbBr}_2) \cdot (18\text{C}6)] + (\text{H}_2\text{O})\}$ (**187**). The coordination number of the lead atom is 8 (the $\text{Pb} - \text{O}_{\text{cr}}$ distances with the six oxygen atoms of the CE molecule vary from 2.77 to 2.80 Å; $\text{Pb} - \text{Br} = 2.924$ and 2.927 Å).¹²¹ In the crystal, the complex molecules are linked to each other through $\text{OH} \cdots \text{Br}$ intermolecular hydrogen bonds (3.37 Å) with the participation of water molecules. The complexes $[(\text{PbI}_2) \cdot (18\text{C}6)]$ (**188**)¹²² and $[(\text{PbCl}_2) \cdot (\text{DCHex}18\text{C}6)]$, where $\text{DCHex}18\text{C}6$ is dicyclohexyl-18-crown-6, (**189**)¹²³ have analogous structures. The reaction of a 1 : 2 mixture of PbCl_2 and SbCl_5 with 18C6 in acetonitrile afforded a compound with composition $\{[(\text{CH}_3\text{CN})_3 \cdot (\text{Pb}) \cdot (18\text{C}6)]^{2+} + 2[\text{SbCl}_6]^- \}$ (**190**) in which the lead atom is also located in the centre of the CE cavity and is additionally coordinated by three acetonitrile molecules (one molecule is located 'above' the mean plane of the macrocycle and two molecules are located 'below' this plane).¹²⁴

9. Bismuth halides

Complexes of BiCl_3 with 12C4 (**191**) and of BiBr_3 with 12C4 (**192**) are structurally similar to the corresponding arsenic complex (**92**).^{125,126} A 1 : 1 mixture of BiCl_3 and SbCl_3 reacted with 12C4 in acetonitrile to yield a product with composition $\{[(\text{Bi}) \cdot (12\text{C}4)_2]^{3+} + 3[\text{SbCl}_6]^- + [\text{CH}_3\text{CN}]\}$ (**193**),⁹² which is isostructural to the antimony complex **119**.

The reaction of a 1 : 1 mixture of BiCl_3 and SbCl_5 with 15C5 in acetonitrile afforded the complex $\{[(\text{CH}_3\text{CN}) \cdot (\text{BiCl}_2) \cdot (15\text{C}5)]^+ + [\text{SbCl}_6]^- \}$ (**194**) in which the $[(\text{BiCl}_2) \cdot (\text{CH}_3\text{CN})]$ fragment is located above the mean plane through the oxygen atoms of the CE molecule.¹²⁷ The analogous reaction of a 1 : 2 mixture of tri- and pentachlorides of bismuth and antimony with 18C6 gave a product with composition $\{[(\text{CH}_3\text{CN})_2 \cdot (\text{BiCl}) \cdot (18\text{C}6)]^{2+} + 2[\text{SbCl}_6]^- \}$ (**195**) in which the bismuth atom is coordinated by one chlorine atom, two nitrogen atoms and four (of six) oxygen atoms of the CE molecule.¹²⁷

VII. Systems with actinide halides

The reaction of uranium(VI) oxychloride with 12C4 in tetrahydrofuran containing water yielded a compound with composition $\{[(\text{H}_2\text{O})_2 \cdot (\text{UO}_2\text{Cl}_2) \cdot (12\text{C}4)] + [12\text{C}4]\}$ (**196**).^{128,129} The coordination environment about the uranium atom is a pentagonal bipyramid formed by two oxygen atoms of the water molecules

(U–O_w = 2.41 Å), two chlorine atoms (U–Cl = 2.68–2.71 Å), two oxygen atoms of the uranyl fragment (U–O = 1.76 Å) and one oxygen atom of the CE molecule (U–O_{cr} = 2.55 Å) (Fig. 42).

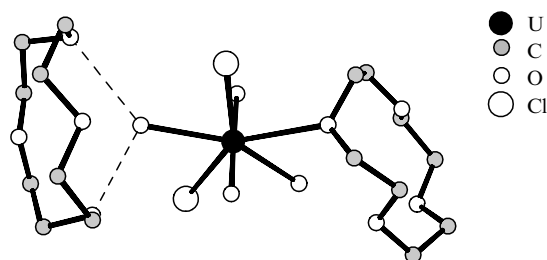
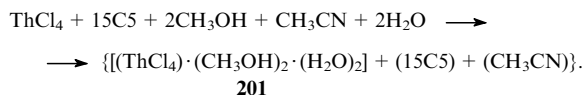
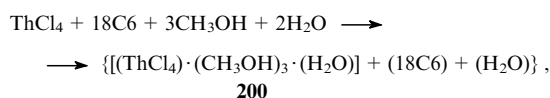
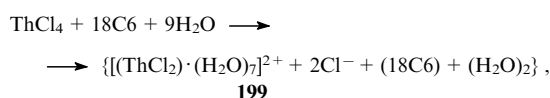


Figure 42. Structure of the complex **196**.

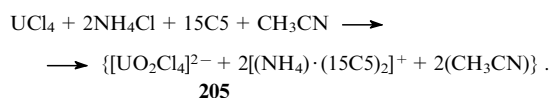
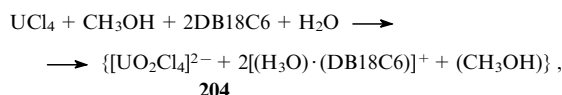
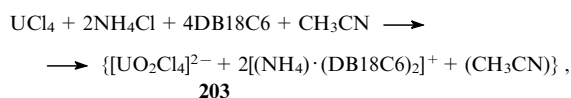
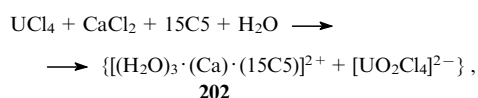
The reaction of uranyl chloride with 12C4 in the presence of NaCl afforded the complex $\{[\text{UO}_2\text{Cl}_4]^{2-} + 2[(\text{Na}) \cdot (12\text{C}4)]^+\}$ (**197**) containing the octahedral anion.^{130, 131} The reaction of uranyl chloride with benzo-15-crown-5 (B15C5) proceeded analogously to form a complex with composition $\{[\text{UO}_2\text{Cl}_4]^{2-} + 2[(\text{Na}) \cdot (\text{B}15\text{C}5)]^+\}$ (**198**).¹³²

Thorium tetrachlorides reacted with various CE in solvents containing water to produce complexes of type C in which the thorium atom is not directly bound to oxygen atoms of the CE molecules.^{133–135}



The coordination polyhedron about the thorium atom in the complexes **199**, **200** and **201** is a tricapped trigonal prism, a square antiprism and a distorted dodecahedron, respectively.

The reactions of UCl_4 with crown ethers 15C5, DB18C6 and DCHex18C6 in air proceeded with oxidation of U^{4+} to U^{6+} (see Refs 131 and 136–138).

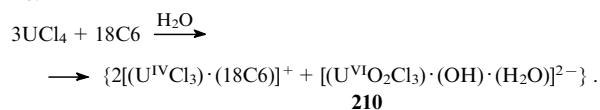


In the absence of air, the reaction of UCl_4 with B15C5 in the presence of NH_4Cl afforded the octahedral anion $[\text{UCl}_6]^{2-}$ and the cation $[(\text{NH}_4) \cdot (\text{B}15\text{C}5)]^+$ (**206**).¹³¹ The reaction of uranium tetrachloride with DCHex18C6 gave compounds with compositions $\{[\text{UCl}_6]^{2-} + 2[(\text{H}_3\text{O}) \cdot (\text{DCHex}18\text{C}6)]^+\}$ (**207**)¹³⁷ and $\{[\text{UCl}_6]^{2-} + 2[(\text{UCl}_3) \cdot (\text{DCHex}18\text{C}6)]^+\}$ (**208**)¹³⁹ depending on the reaction conditions. The coordination number of the uranium

atom in the cation of **208** is equal to 9. The metal atom is coordinated by three chlorine atoms and all the six oxygen atoms of the CE molecule.

The reaction of a 1 : 1 mixture of UCl_4 and NH_4Cl with 18C6 in acetonitrile yielded a compound with composition $\{[\text{UCl}_6]^{2-} + 2[(\text{NH}_4) \cdot (18\text{C}6)]^+ + (\text{CH}_3\text{CN})_2\}$ (**209**).¹⁴⁰

An interesting example of a redox process that occurred in the reaction of UCl_4 with 18C6 in tetrahydrofuran was reported.¹⁴¹ The reaction product contained the uranium(IV) and uranium(VI) atoms.



The uranium(VI) atom in the anion has a pentagonal-bipyramidal environment and the uranium(IV) atom in the cation is coordinated by all the six oxygen atoms of the CE molecule (U–O_{cr} = 2.48–2.61 Å) and three chlorine atoms.

VIII. Conclusions

To date, crown compounds of the majority of metal and semi-metal halides in the highest oxidation states have been prepared and structurally characterised. However, data on the structures of this class of compounds with metal halides in the lowest oxidation states are virtually unavailable. As has been mentioned in the Introduction, the structures of the great majority of crown compounds can be actually classed into three major types, *viz.*, A, B and C, and their variations. Homonuclear molecular complexes of crown ethers with halides of semimetals, such as As, Sb and Bi, as well as complexes, the nature of bonding in which is still not clearly understood, should be assigned to exceptions or to the individual type D.

The geometrical correspondence between the dimension of the metal atom (d_m) and the dimension of the cavity (d_c) of the crown ether molecule is a necessary but not nearly sufficient condition for the formation of inner-cavity crown compounds. The principle of this correspondence virtually forbids the synthesis of these compounds only if $d_m > d_c$. Moderate-sized metal atoms in the cavity are displaced toward two or three oxygen atoms or find alternative possibilities for the formation of complexes (see, for example, complexation of halides of lithium, beryllium, metals of the arsenic subgroup and lanthanides).^{142, 143} In these cases, the metal atoms are generally located outside the cavity of the CE molecule. It should be noted that unusual and nontypical coordination numbers of metal atoms located in the cavity of the CE molecule (for example, of the aluminium atom in the complex with the crown ether 15C5) should not be regarded as a violation of the well-known structural principles because the above-mentioned deviations of the metal atoms are induced by the macrocyclic nature of the polyethers.

Apparently, the possibility of ionisation and/or autocomplexation of a salt in a solution should be regarded as a prerequisite for the preparation of crown-ether compounds containing the metal atom in the cavity. All the above-considered inner-cavity crown compounds were prepared in solvents of the donor type. Since the processes of ionisation and autocomplexation in these solvents occur with difficulty, complexes with metal halides in the lowest oxidation states are very poorly studied. It should be noted that these metals generally form rather stable polymeric structures.

Acceptors of halide ions are introduced into salt solutions in order to direct the reactions toward inner-cavity complexes. However, in these cases the reactions always afford hetero- or homonuclear different-valence ionic complexes in which the inner-cavity cation is formed by the metal ion with the lower affinity for the halogen atom (a weaker Lewis acid). In this respect, the conversion of the complexes based on SbX_3 from type D to type A in the presence of SbX_5 is a prominent example.

The introduction of a versatile solvent, *viz.*, water, into the reaction system prevents, as a rule, the formation of inner-cavity

crown compounds or causes their destruction, *i.e.*, leads to the passage from type A to type B or C in which the fragments are linked to each other through a system of hydrogen bonds. We are aware of only three examples where the metal atoms remain in the cavity of the macrocycle in the presence of water, *viz.*, the complexes prepared by the reactions of 15C5 with CoCl_2 (see Ref. 42) and with MgCl_2 (See Ref. 14) and by the reaction of CaCl_2 with 18C6.⁷

The presence of water in a salt–CE–organic solvent system sharply changes the character of interactions between the components. In this case, the process involves either hydration of the cation accompanied by displacement of molecules of the organic solvent from the coordination sphere of this cation or hydrolysis accompanied by the appearance of hydrogen halide, oxonium ions, oxides, hydroxides and a number of other products in the solution. However, the reasons for the appearance of water in the reaction zone have not been a matter of discussion in the majority of works. Undoubtedly, the experiments performed with the use of crystal hydrates or ordinary (not dehydrated) solvents are quite understandable the more so that hydrated compounds are formed under these conditions in rather high yields.

The instances where the reactions which were carried out with the use of anhydrous solvents and thoroughly dehydrated salts afforded single crystals of hydrated complexes are not so unambiguous. Since the yields of these salts were no more than 5%–8% (see, for example, Refs 7, 14 and 41), hydration of salts may be attributed to residual traces of moisture in the initial compounds and in solvents as well as to the anomalous hydrophilicity of salts of some divalent metals.

Finally, the appearance of water in reactions of crown ethers with some anhydrous metal halides in the highest oxidation states, for example, with MoCl_5 ⁷⁵ and TaCl_5 ,^{115, 116} is still unclear. The complexes prepared by these reactions never have and apparently cannot have the structures of classical intra-cavity crown compounds because these structures can be formed only if the charge of the cation is no less than $3+$, which is observed in none of the above-described structures. However, these reactions always afforded a wide range of various compounds, including hydrolysis products in yields of up to 20%–30%. These yields are substantially larger than those calculated taking into account all possible sources of residual moisture that could exist in the reaction zone. In this connection, we believe that hydrolysis can be explained only by profound decomposition of the polyether molecule accompanied by the formation of large amounts of water. In this case, residual moisture, which is introduced into the reaction zone with the initial compounds and the solvent, can act as an initiator of cleavage of the macrocycle. Taking into account the above-mentioned characteristic features of the salt behaviour, not only the results of experiments on extraction and separation of metal halides (and, apparently, compounds of other types as well) with the use of crown ethers but also the ideology of these studies are highly questionable.

Reactions of solvation and complexation are the major subject matter of coordination chemistry. However, these reactions are explicitly and implicitly involved in many processes which are far from this field of chemistry. In this respect, the chemistry of macrocyclic compounds (in particular its structural aspect) is undeniably helpful in developing general model concepts of interactions between components of complex systems which can be used in various divisions of chemistry.

For example, products of intercalation of salts of the acceptor type (generally, metal halides, Lewis acids) into the interlayer space of graphite (the so-called intercalation graphite compounds, IGC) are known. Most of these products are compounds formed by metal halides MX_n which are intercalated into graphite only in the presence of free halogen or metal halides in the highest oxidation states M^*X_m (hetero-IGC). If the graphite network is considered as a polyligand, this behaviour of salts MX_n is readily explained from the standpoint of formation of heterocrown compounds, *i.e.*, on the assumption that ionisation, autocomplex-

ation and, finally, intercalation of ionic salts of the type $\{[\text{M}^*\text{X}_{m-1}]^+[\text{MX}_{n+1}]^-\}$ or $\{[\text{X}^+[\text{MX}_{n+1}]^-\}$ into the interlayer space occur.

Yet another example is associated with the chemistry of Ziegler–Natta catalytic systems applied onto mineral supports whose surface layers, in principle, can be considered as polyligands. It is known that introduction of magnesium salts, for example, of MgCl_2 , into catalysts $\text{AlRR}'\text{R}''\text{--TiXX}'\text{X}''$, where $\text{R} = \text{Alk}$, $\text{R}' = \text{H}$, $\text{R}'' = \text{Hal}$; $\text{X} = \text{Hal}$, $\text{X}' = \text{Alk}$, $\text{X}'' = \text{C}_5\text{H}_5$, *etc.*, increases their activity in polymerisation of alkenes by several orders of magnitude. Aluminium and titanium salts can form both cationic and anionic components of complexes, while magnesium is involved only in cations of CE complexes. Therefore, magnesium efficiently competes with the first two metals in formation of cations thus causing them to form anions. One would expect that, like MgCl_2 , salts of other metals which can undergo ionisation and are not prone to autocomplexation (for example, ScCl_3), are efficient promoters of polymerisation.

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The chemistry of furazans fused to six- and seven-membered heterocycles with one heteroatom

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Abstract. The data on the synthesis and properties of furazan derivatives fused with pyridine, pyran, thiopyran, azepine and thiepine rings are surveyed and described systematically. The bibliography includes 85 references.

I. Introduction

Furazan (1,2,5-oxadiazole) derivatives are heterocyclic compounds of a non-natural origin. The first representatives of furazans were synthesised more than a hundred years ago. The subsequent development of the chemistry of this class of compound has been stimulated both by the diversity of their chemical transformations and by a number of their interesting properties, which provide the possibility of using them in medicine, agriculture and some fields of engineering.

In this decade alone, the peculiar behaviour of furazans and their *N*-oxides (furoxans) and the large body of information, which permanently extends as a result of studies of numerous groups of researchers, have led to the publication of several reviews^{1–10} and monographs.^{11,12}

Fused systems consisting of two or more heterocycles, of which at least one heterocycle is a furazan ring, deserve close attention both from the theoretical viewpoint and due to the possible application of these compounds as intermediates in synthesis. Some derivatives of this class have been proposed as herbicides, rubber modifiers, liquid crystals, luminescent dyes and explosives.

Systems in which a furazan ring is fused to a five-membered heterocycle have been considered in a review.⁶ The present review is devoted to the least studied derivatives, furazans fused to six- and seven-membered heterocycles with one heteroatom.

II. Furazan ring as a fragment of a bicyclic system

Furazan can be regarded as a hetero-analogue of cyclopentadiene. On passing from electron-releasing cyclopentadiene to electron-withdrawing furazan, chemical properties are virtually reversed. One can say that furazan is a sort of antipode of cyclopentadiene.

Successive replacement of carbon atoms by heteroatoms results in redistribution of electron density and in enhancement of π -acceptor properties of the system in the following series: cyclopentadiene, furan, isoxazole, furazan.

In all of these rings, electronic effects of substituents are transferred solely through the (hetero)diene system of bonds.¹³ The CH_2 group (in cyclopentadiene) and oxygen atoms (in the other three rings) act as a sort of insulator for this transfer. As a consequence, the degrees of aromaticity of these four cyclic systems are approximately equal.

Compound				
Aromaticity index (<i>I</i>) ¹⁴	45	43	47	43

It should be noted that the degree of bond order fixation in the heterodiene system of furazan is extremely high; derivatives of this heterocycles are not susceptible to annular-group tautomerism.

The chain consisting of three heteroatoms, present in the furazan molecule, accounts for the substantial electron-withdrawing properties of this heterocycle.^{15–17} The Taft induction constants σ^* of 4-*R*-furazanyl groups (as substituents) fall in the range 2.55–2.88 (these values correspond to *R* = NH_2 and *R* = NO_2 , respectively).¹⁸ For comparison, the σ^* value of the 3-furyl group is 0.62. The well-known electron-withdrawing picryl group, 2,4,6-(NO_2)₃ C_6H_2 has a σ^* value of only 1.62. The following substituents are characterised by σ^* constants close to that of furazan: $\text{CH} = \text{C}(\text{CN})_2$ ($\sigma^* = 2.56$), CF_3 ($\sigma^* = 2.6$); $\text{CBr}(\text{NO}_2)_2$ ($\sigma^* = 2.8$); 5-tetrazolyl group ($\sigma^* = 2.82$); nitrile group ($\sigma^* = 3.25$).¹⁹

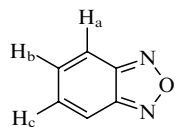
The reactivity of annelated furazan derivatives is also significantly affected by the nature of the second ring — its size, the number of heteroatoms and their type and positions. A typical feature of annelated furazans is bond order fixation over the whole contour of the bicyclic system. It is known that the degree of delocalisation of π electrons in benzoannelated heterocycles can be estimated using the Gunther method²⁰ based on the ratio of spin-spin coupling constants, J_{bc}/J_{ab} . When the bonds are fully

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equivalent, as in benzene, this ratio is equal to unity, whereas completely localised bonds correspond to a ratio of 0.5. According to ^1H NMR spectroscopy, the J_{bc}/J_{ab} ratio for benzofurazan is 0.706; in other words the bonds are substantially localised.²¹

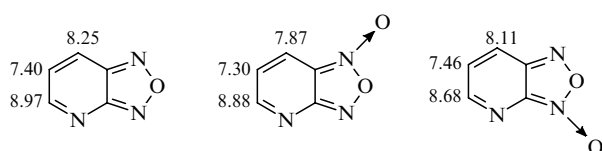


The replacement of one $=\text{CH}-$ unit in the benzene molecule by an isoelectronic fragment, $=\text{N}-$, is known to result in a less uniform distribution of electron density and more pronounced localisation.¹⁴ In fact, on passing from benzofurazan to furazano[3,4-*b*]pyridine, the spin-spin coupling constant for protons a, b changes only slightly ($J = 9.34$ Hz for benzofurazan²² and $J = 9.00$ Hz for furazanopyridine²³), whereas the constant for protons b, c changes more significantly ($J = 6.50$ and 3.70 Hz, respectively). Evidently, this points to a decrease in the order of the b-c bond and, hence, to an increase in the degree of localisation upon the replacement of the $=\text{CH}-$ fragment by $=\text{N}-$.

On passing from benzene to pyridine and then from benzofurazan²² to furazanopyridine,²³ the ^1H NMR signal shifts downfield, which is also due to a decrease in the electron density in this series. However, it should be mentioned that the influence of the furazan ring is still weaker than that of two *ortho*-nitro groups.

Compound					
δ , ppm	7.27	7.46	7.96	8.25	8.92

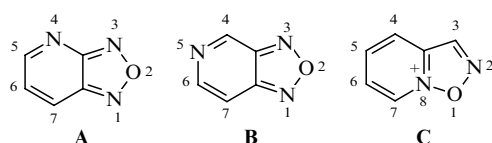
The *N*-oxide fragment acts as a resonance electron-releasing group of medium strength;¹⁴ therefore, on passing to the *N*-oxide, furoxanopyridine, the electron-withdrawing influence of the furazan ring becomes weaker. In particular, the signals of the protons at C(7) in the ^1H NMR spectra of both isomers of furoxanopyridine are shifted upfield in relation to corresponding signal in the spectrum of furazanopyridine.²³



Theoretical calculations²⁴ and polarographic studies^{25–29} have also been used to describe the influence of the furazan ring on the properties of molecules incorporating it. Acid–base properties of some annelated furazan derivatives have also been studied.³⁰

III. Furazanopyridines

Derivatives of all three possible types of bicyclic systems based on furazan and pyridine rings — furazano[3,4-*b*]pyridine (**A**), furazano[3,4-*c*]pyridine (**B**) and furazano[3,4-*a*]pyridine (**C**) — have been described in the literature.

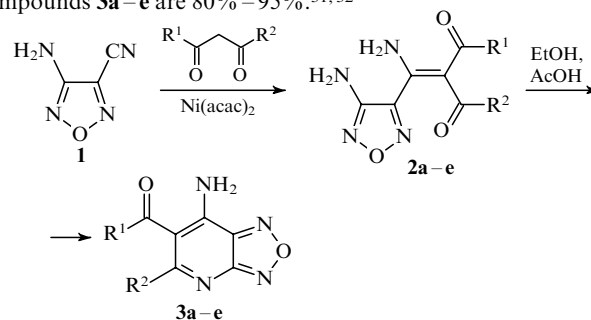


1. Furazano[3,4-*b*]pyridine

The heterocyclic system of furazano[3,4-*b*]pyridine (**A**) is also referred to as 1,2,5-oxadiazolo[3,4-*b*]pyridine and the correspond-

ing 1(3)-oxides are also called furoxano[3,4-*b*]pyridines and pyridofuroxans.

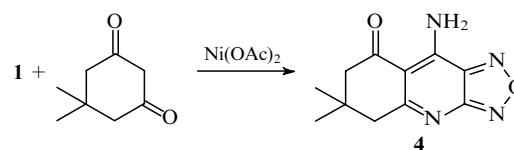
Derivatives of the bicyclic system **A** can be obtained from both furazan and pyridine synthons. Thus the reaction of 3-amino-furazan-4-carbonitrile **1** with β -dicarbonyl compounds in the presence of a catalytic amount of nickel acetylacetonate gives rise to labile enamines **2a–e**. On heating with acetic acid in ethanol, they undergo intramolecular condensation to give the corresponding amino-derivatives **3a–e**. The overall yields of the compounds **3a–e** are 80%–95%.^{31, 32}



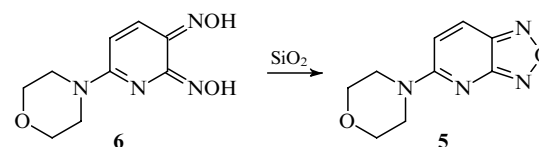
$\text{R}^1 = \text{R}^2 = \text{Me}$ (**a**); $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Ph}$ (**b**); $\text{R}^1 = \text{R}^2 = \text{Ph}$ (**c**);
 $\text{R}^1 = \text{OEt}$, $\text{R}^2 = \text{Me}$ (**d**); $\text{R}^1 = \text{OEt}$, $\text{R}^2 = \text{Ph}$ (**e**).

Even in the case where $\text{R}^1 \neq \text{R}^2$, as in the compound **2b**, the reaction occurs regioselectively giving only one product **3b** in which the more bulky substituent is attached directly to the pyridine ring.

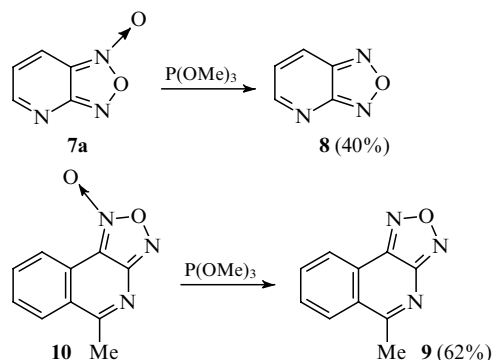
The reaction of the nitrile **1** with dimedone in the presence of nickel acetate affords tricyclic compound **4** in 67% yield. In this case, the intermediate enamine was not isolated.³²



Dehydration of 1,2-dioximes (glyoximes) is used most widely for the synthesis of furazans.^{1, 6} An unusual version of dehydration has been employed in order to prepare furazan **5**. 2,3-Dihydroxyiminopyridine **6** adsorbed on silica gel undergoes spontaneous dehydration over a period of 12 h to give the compound **5** in 14% yield.³³



Readily available furoxanopyridine **7a** can be reduced to the corresponding furazan **8** by a short-term heating to 100 °C in trimethyl phosphite.²³ Benzo-annelated derivative **9** can be obtained in a similar way from the furoxan **10**.³⁴



The above furazanopyridines have been synthesised only recently. Meanwhile, the 1(3)-oxides of furazanopyridines of type **A** (furoxans) were first prepared more than 40 years ago.³⁵ The synthesis of these compounds is based on the ability of *o*-azido nitro aromatic compounds to undergo thermally induced intramolecular cyclocondensation. The mechanism of this transformation has been studied comprehensively by measuring the kinetics of this reaction for benzene derivatives.¹¹ It is believed that an oxygen atom of the nitro group attacks a nitrogen atom of the azide group. Cyclisation can be represented as electron transfer occurring synchronously with elimination of a nitrogen molecule.

Thus heating of tetrazolopyridine **11a**, which is formed upon treatment of chloropyridine **12a** with sodium azide, in dichlorobenzene leads to elimination of a nitrogen molecule from the intermediate azide **13a** and closure of the furoxan ring yielding the bicyclic compound **7a**.³⁵ Later it has been shown that the compound **7a** is formed in approximately the same yield when thermolysis is carried out in some other solvents or without a solvent (Table 1).

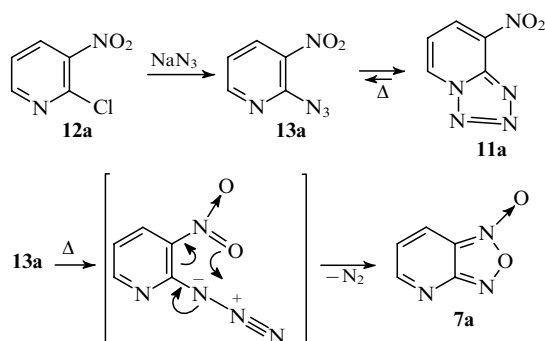
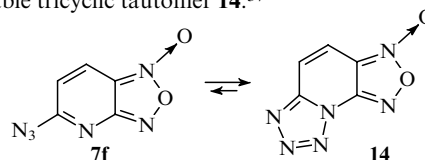


Table 1. Synthesis of furoxano[3,4-*b*]pyridines **7a–i** by thermolysis of the corresponding tetrazolopyridines **11a–i**.

Compound	R ¹	R ²	Solvent	Temperature/ °C	Time/h	Yield (%)	Ref.
11a	H	H	none	170	0.03	97	35
			PhOPh	175		75	36
			PhMe	110		96	37
			none	130	0.66	—	38
11b	H	Me	dioxane	Δ		97	39
			none	155	0.03	93	40
11c	H	COOH	none	161	0.03	86	40
11d	H	COOMe	"	106	0.03	97	40
11e	H	NO ₂	"	130		—	37
			"	95	0.03	—	38
11f	N ₃	H	PhMe	95		92	37
			MeCN	82	4	88	37
			C ₆ H ₆	80	4	85	37
11g	NPPH ₃	H	PhMe	110		75	37
11h	NHPic ^a		NO ₂	AcOH	118	—	—
11i	NH ₂	NO ₂	C ₆ H ₆	80	1.5	95	42, 43

This reaction is general. The presence of any substituents, especially electron-withdrawing ones, in the initial nitrotetrazolopyridines **11a–i** facilitates their transformation into tautomeric 2-azido-3-nitropyridines and is thus favourable for the formation of the furoxan ring upon thermolysis (see Table 1).

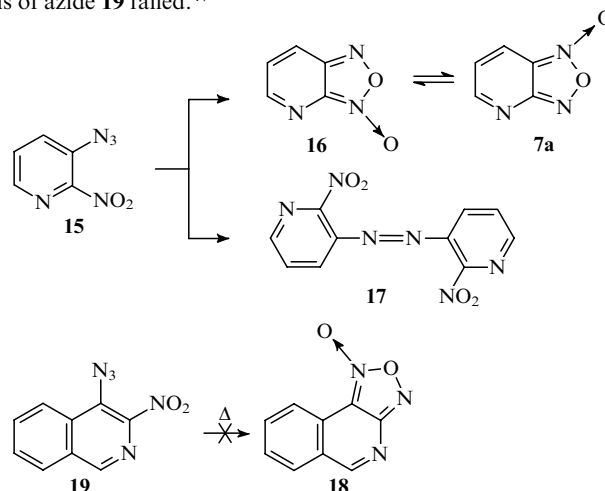
It should be noted that furoxanopyridine **7f** exists as the more stable tricyclic tautomer **14**.³⁷



A particular modification of this method is the reaction of 2-chloro-3,5-dinitropyridine with sodium azide in the presence of phase transfer catalysts in dichloroethane followed by keeping the reaction mixture at 60 °C. The furoxanopyridine **7e** is prepared in this way in 92% yield without isolation of the intermediate azide or tetrazolopyridine.⁴⁴

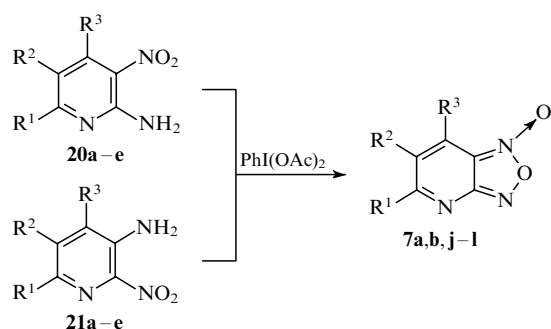
The thermolysis of azide **15**, isomeric to azide **13a**, gives the furoxanopyridine **7a**, which is thermodynamically more stable than isomer **16**.^{45, 46} It is noteworthy that for the azide **15**, azido-tetrazole tautomerism is impossible, and in this case, the solvent determines not only the yield of the bicyclic compound **7a** but also the reaction pathway itself. A similar situation is observed in the transformation of *o*-azidonitrobenzenes into benzofuroxans.¹¹ Thus at 87 °C in decalin, the yield of the compound **7a** is 94%, while in ethanol, it is equal to 80%. Thermolysis of the azide **15** in *o*-dichlorobenzene or acetic anhydride does not give a furoxan derivative but yields instead azo compound **17**.⁴⁶

An attempt to synthesise isoquinolinofuroxan **18** by thermolysis of azide **19** failed.⁴⁷

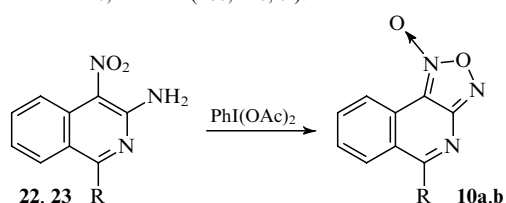


Yet another method for the synthesis of furoxano-[3,4-*b*]pyridines consists in oxidative condensation of 2(3)-amino-3(2)-nitropyridines. The most widely used oxidant which permits successful preparation of this bicyclic system is diacetoxy-λ³-iodanylbenzene.^{34, 36, 39, 48, 49} In fact, when amines **20a–e** or isomeric amines **21a–e**, or bicyclic amines **22** and **23** are merely stirred with this reagent in acetic acid, acetone or benzene at room temperature or at 50–60 °C, the corresponding furoxans **7** or **10a,b** are formed in 70%–90% yields.

The use of sodium hypochlorite as the oxidant in the synthesis of furoxano[3,4-*b*]pyridine derivatives usually does not lead to the desired products, unlike its use in the synthesis of benzofuroxans¹¹ from the corresponding *o*-amino nitro compounds.³⁶ Only one example of successful employment of this oxidant in the reaction in question is known. On treatment with sodium hypochlorite in a methanolic solution of KOH, the amine **23** undergoes

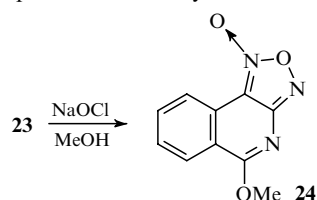


$\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ (**a**); $\text{R}^1 = \text{R}^3 = \text{H}$, $\text{R}^2 = \text{Me}$ (**b**); $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{Me}$ (**20c**, **21c**, **7j**); $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{R}^3 = \text{H}$ (**20d**, **21d**, **7k**); $\text{R}^1 = \text{R}^3 = \text{Me}$, $\text{R}^2 = \text{H}$ (**20e**, **21e**, **7l**).

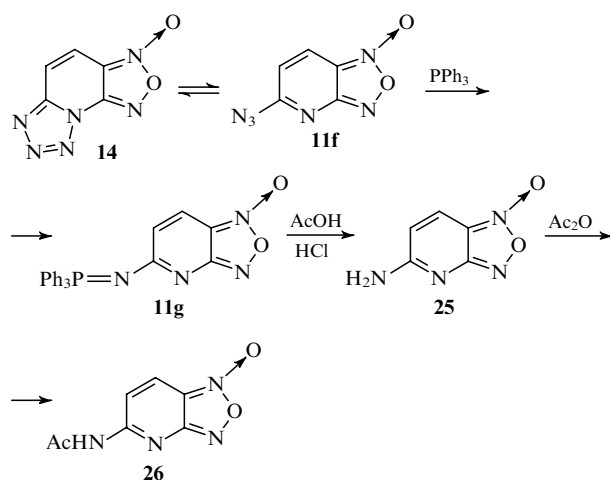


$\text{R} = \text{Me}$ (**22**, **10a**), $\text{OC}_6\text{H}_4\text{Cl-}p$ (**23**, **10b**).

oxidative condensation with simultaneous replacement of the *p*-chlorophenoxy group by a methoxy group to give tricyclic compound **24** in 64% yield.³⁴

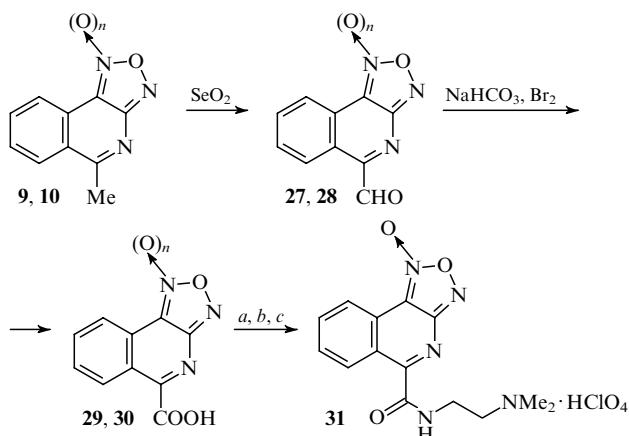


Furazano[3,4-*b*]pyridines enter into two types of reactions. The first type comprises transformations that do not affect the bicyclic cage of the initial molecule. Reactions in which this cage is destroyed belong to the second type. The first type of reactions includes transformations of the functional groups present in the pyridine moiety of the molecule. Thus refluxing of the tetrazole **14** in ethanol in the presence of triphenylphosphine results in the formation of the iminophosphorane **11g** in 90% yield. Hydrolysis of this product occurs quantitatively and affords amine **25**, which is readily acylated with acetic anhydride to give amide **26**.³⁷



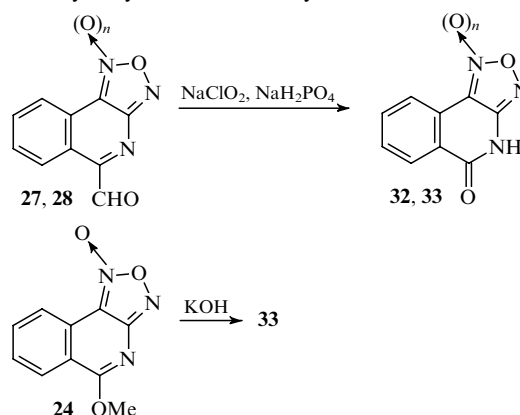
Refluxing of the tricyclic compounds **9** ($n = 0$) or **10** ($n = 1$) with selenium dioxide in dioxane is accompanied by oxidation of the methyl group. This gives aldehydes **27** and **28** in 56% and 75% yields, respectively.³⁴ Further oxidation of these products with bromine in a solution of sodium bicarbonate in aqueous butanol

gives rise to the corresponding acids **29** (yield 72%) and **30** (yield 65%). The acid **30** was converted into amide **31**.³⁴



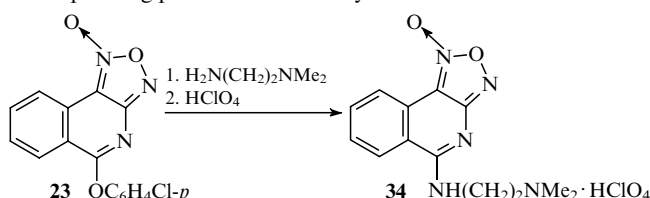
(a) Et_3N , BuOCOCl ; (b) $\text{H}_2\text{N}(\text{CH}_2)_2\text{NMe}_2$; (c) HClO_4 ; $n = 0$ (**9**, **27**, **29**), $n = 1$ (**10**, **28**, **30**).

Interestingly, when sodium chlorite is employed as the oxidant in this reaction, the acid is not formed but instead the aldehyde group is eliminated and the C(5) atom in the ring is oxidised. The corresponding isoquinolinones **32** and **33** are produced in 75% – 79% yields. The compound **33** (yield 54%) can also be obtained by alkaline hydrolysis of the methoxy-derivative **24**.



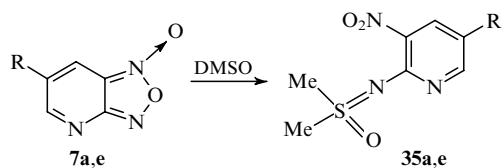
$n = 0$ (**27**, **32**), 1 (**28**, **33**).

Treatment of the *N*-oxide **23** with excess (*N,N*-dimethylamino)ethylamine at 75 °C leads to substitution of the *p*-chlorophenoxy group. The resulting amine **34** was isolated as the corresponding perchlorate in 42% yield.³⁴

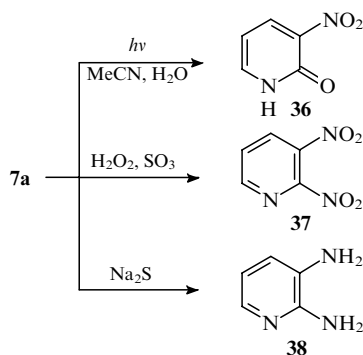


The second type of reaction typical of furazano[3,4-*b*]pyridine derivatives is transformation of the furoxan ring. For example, when the bicyclic derivatives **7a,e** are heated in dimethyl sulfoxide, retro-cleavage of the furoxan ring at the *N*–*O* bond occurs giving rise to a nitro group and a nitrene. The nitrene reacts with the solvent yielding sulfimine *S*-oxides **35a,e**.³⁸ Irradiation of the *N*-oxide **7a** with a UV lamp in aqueous acetonitrile for 30 h affords nitropyridone **36** in 18% yield.³³ The furoxan **7a** is not oxidised with *m*-chloroperbenzoic acid. However, treatment of **7a** with concentrated hydrogen peroxide in oleum results in oxidation of the furoxan ring giving 2,3-dinitropyridine **37** in 60% yield. No products resulting from the oxidation of the pyridine nitrogen

atom were detected. An additional nitro group present in the initial furoxan, for example in **7e**, makes the furoxan ring resistant to oxidation.³⁷

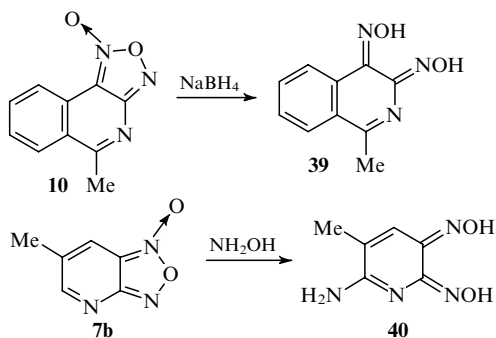


R = H (**a**), NO₂ (**e**).

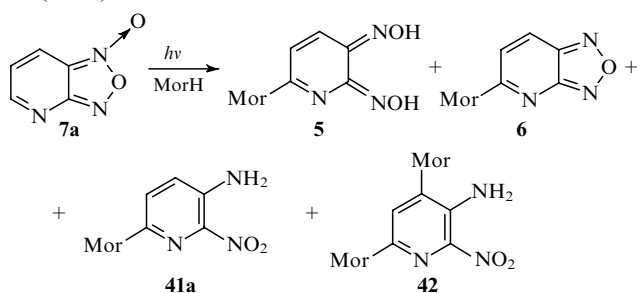


Diamine **38** has been obtained in 17% yield on treatment of the furoxan **7a** with sodium sulfide. It was suggested that the furazan **8a** could also arise in this reaction; however, it was not isolated in this study.³⁵

On treatment with sodium borohydride at 50 °C in methanol, the furoxanisoquinoline **10** is reduced to give glyoxime **39** in a low yield.³⁴ The reduction of a furoxan ring giving two oxime groups occurs more efficiently under the action of hydroxylamine. Thus the reaction of the *N*-oxide **7b** with hydroxylamine affords glyoxime **40** in 54% yield. It should be noted that in addition to the reduction of the furoxan moiety, this reaction involves amination of the pyridine ring.⁴⁰



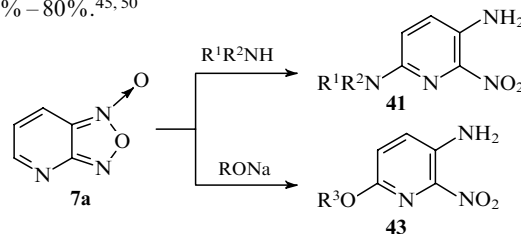
Photolysis of the compound **7a** ($\lambda = 254$ nm) carried out for 15 h in dichloromethane in the presence of morpholine under argon at room temperature gives a series of morpholine-containing products such as the glyoxime **6** (5%), the furazan **5** (9%), monomorpholypyridine **41a** (0.3%) and bis(morpholyl)pyridine **42** (0.3%).³³



Mor is morpholin-1-yl.

However, the compound **41** as well as a large number of its analogues can be prepared in a higher yield by conventional nucleophilic substitution. Treatment of the compound **7a** with *N*- and *O*-nucleophiles in water or ethanol at 18–25 °C induces opening of the furoxan ring accompanied by nucleophilic substitution of the hydrogen atom at C(6) in the pyridine ring.

This reaction has been used to prepare a group of diverse 3-amino-2-nitropyridines **41** and **43**. The yields of the products are 70%–80%.^{45,50}

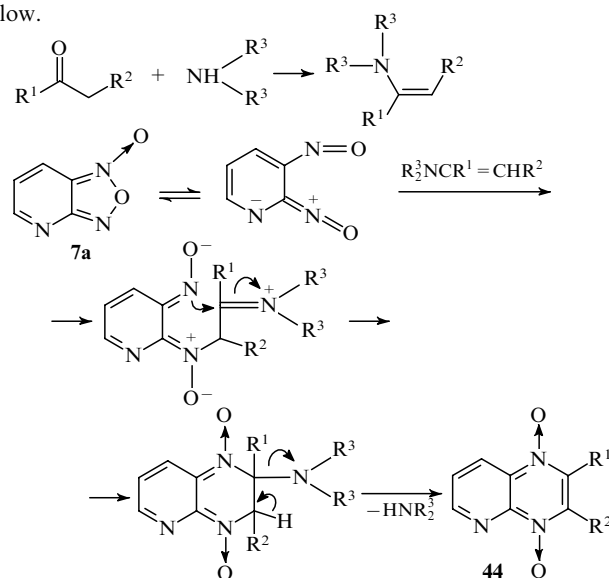


$R^1 - R^2 = (CH_2)_2O(CH_2)_2, (CH_2)_2NH(CH_2)_2, (CH_2)_4$;

$R^1 = R^2 = H, Me, Et$; $R^1 = H$; $R^2 = Me, Et, Bu$; $R^3 = H, Me, Et$.

It is noteworthy that aminonitropyridines such as **41** and **43** as well as some other products of transformation of furoxanopyridines are potential precursors of polyfunctional derivatives of the same bicyclic system (which can be synthesised, for example, by oxidation). Unfortunately, this line of research is not represented in original publications.

The reaction of furoxanopyridines and amines in the presence of carbonyl compounds having an α -methylene unit follows a totally different pathway. In this case, the so-called Beirut reaction occurs,¹¹ in which enamine formed in the reaction medium functions as the active nucleophile, attacking the furoxan ring rather than the C(6) atom of the pyridine ring. The amine merely catalyses this transformation and is not incorporated in the reaction products, which are azaquinoxaline bis-*N,N'*-oxides **44**.^{39,51,52} The mechanism proposed for this process is presented below.



R^1	Me	Me	H	Pr ⁱ	Me
R^2	Me	H	Me	H	CO ₂ Me
R^1	CO ₂ Me	Me	Me	H	CH(OMe) ₂
R^2	Me	CONMe ₂	CH ₂ CO ₂ Me	CH(OMe) ₂	H

Unlike benzofuroxans, the furoxanopyridine **7a** gives rise to the Beirut reaction products in low yields (20%–30%). The standard procedure is very simple and consists in stirring the furoxan **7a** with excess carbonyl compound in ethanol in the presence of an amine (ammonia, morpholine, pyrrolidine, *etc.*) or sodium acetate. The resulting azaquinoxaline bis-*N,N'*-oxides **44** are of interest for pharmacology.

Detailed analysis of the ^1H and ^{13}C NMR spectra has provided full assignment of all the ^{13}C and ^1H signals for furazano[3,4-*b*]pyridine derivatives.^{23,31,37} NMR spectroscopy is especially useful for the investigation of isomeric *N*-oxides of this bicyclic system.^{23,49} The acid–base properties of the compound **7h** have been estimated based on the data of potentiometric titration in various solvents.⁴¹ X-Ray diffraction analysis of the bicyclic furazan **3a**³¹ and the tricyclic furoxan **14**³⁷ has shown that the bond lengths and bond angles in these compounds are close to the standard values. Kinetic studies led to the assumption that the initial events in the thermal decomposition of the compounds **7e** and **7i** and benzofuroxan and pyridine *N*-oxide derivatives are similar. These reactions were assumed to involve the formation of three-membered activated intermediates of the oxaziridine type.^{53–55}

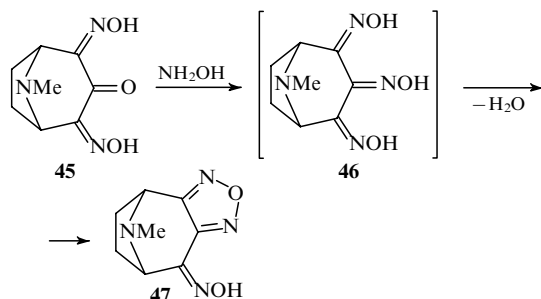
The furoxan **7a** has been patented as a modifier (vulcaniser) for unsaturated polymers.^{56–59} Nitro-derivatives of this bicyclic system are thermally stable explosives.^{42,53,54} Biological studies have shown that some furazanoquinoxalines exert moderate inhibitory effect on c-AMP-dependent protein kinase.⁶⁰

2. Furazano[3,4-*c*]pyridines

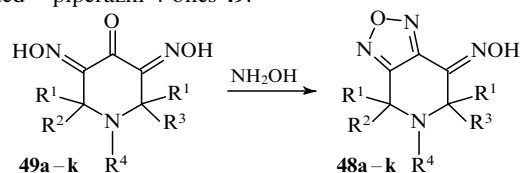
Derivatives of furazano[3,4-*c*]pyridine (**B**) are also referred to as 1,2,5-oxadiazolo[3,4-*c*]pyridines, and the corresponding *N*-oxides are also called furoxano[3,4-*c*]pyridines.

The methods used to synthesise this class of compounds are more diverse, while the procedures employed to prepare the *N*-oxides largely resemble those outlined above.

The first representative of furazano[3,4-*c*]pyridines — cage furazan **47** — was prepared 100 years ago by treatment of α,α' -dihydroxyiminotropinone hydrochloride **45** with an alkaline solution of hydroxylamine. Obviously, the reaction starts with oximation of the free carbonyl group, which is followed by dehydration of two neighbouring oxime groups in the trioxime **46** thus formed. Compound **47** was isolated in 90% yield.⁶¹



A series of fused furazan derivatives **48** have been obtained in high yields from 2,2,6,6-tetrasubstituted⁶² and 2,6-disubstituted⁶³ piperazin-4-ones **49**.

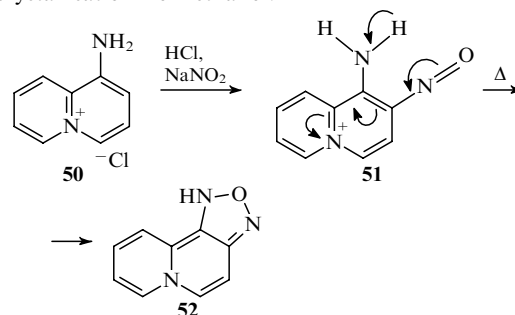


Compounds 48 and 49	R ¹	R ²	R ³	R ⁴
a	Me	Me	Me	H
b	Me	Me	Me	OH
c	H	Me	Me	Me
d	H	Me	Me	H
e	H	Me	Me	Bu ^t
f	H	Ph	Ph	Me
g	H	Ph	Me	Me
h	H	Me	Me	OMe
i	H	H		Ph

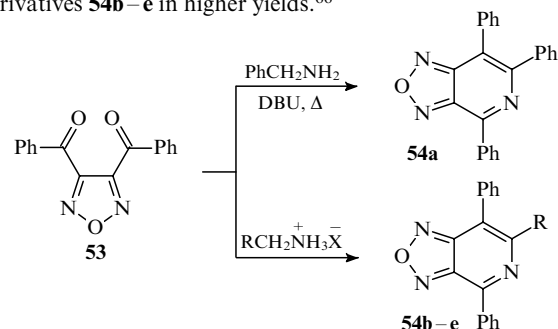
Compounds 48 and 49	R ¹	R ²	R ³	R ⁴
j	H	H	H	Bu ^t
k	H	H	H	H

When asymmetrical initial compounds are used, for example **49g,i**, mixtures of isomers are produced.

Nitrosation of quinolinizinium salt **50** with sodium nitrite in 2 M hydrochloric acid affords *o*-amino nitroso compound **51**, which was reported⁶⁴ to be converted into tricyclic derivative **52** during recrystallisation from ethanol.

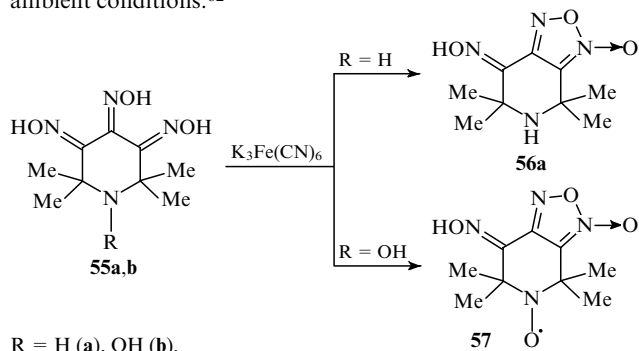


Furazano[3,4-*c*]pyridine derivatives have also been synthesised from furazan precursors. Thus condensation of 3,4-dibenzoylfurazan **53** with benzylamine in boiling toluene catalysed by diazabicycloundecene (DBU) results in the formation of compound **54a** in 13% yield.⁶⁵ However, condensation of dibenzoylfurazan with salts of amines having electron-withdrawing substituents at the α -carbon atom is more efficient and gives derivatives **54b–e** in higher yields.⁶⁶



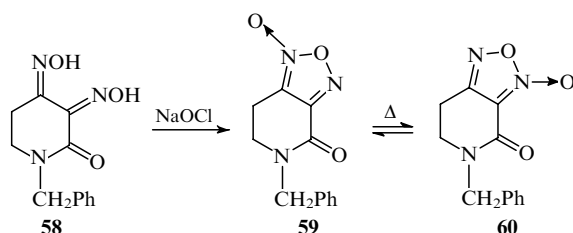
Compound	R	X	Yield (%)
54b	CO ₂ Et	Cl	41
54c	CO ₂ Me	Cl	45
54d	CN	HSO ₄	73
54e	COPh	Cl	44

The reaction of trioxime **55a** with potassium ferricyanide occurs as oxidative cyclocondensation of two neighbouring oxime groups yielding furoxan **56a**. A similar treatment of the trioxime **55b** is accompanied by oxidation of the hydroxylamine function and gives rise to the furoxan nitroxide **57** stable under ambient conditions.⁶²

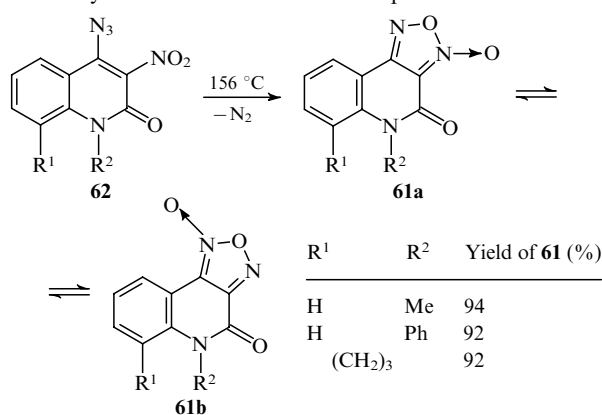


R = H (**a**), OH (**b**).

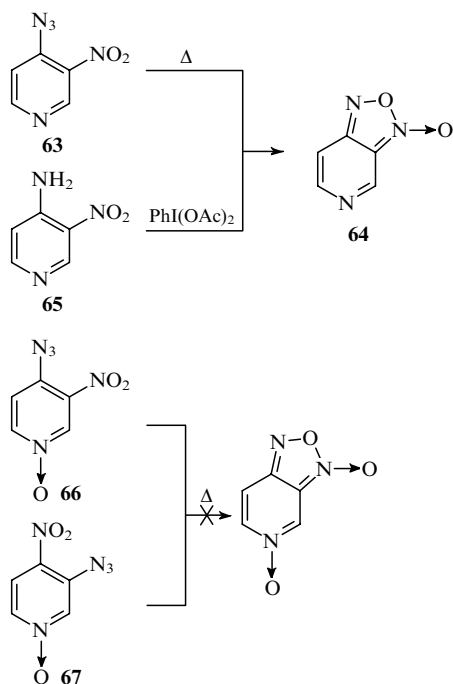
Oxidation of an alkaline solution of cyclic glyoxime **58** with sodium hypochlorite involves closure of the furoxan ring and gives lactam **59** in 87% yield.⁶⁷ On heating in toluene, this product partly rearranges to the isomeric 3-oxide **60**. The rearrangement gives a mixture of the isomers **59** and **60** in 1 : 4 ratio.



Benzoannulated analogues of the lactams **59** and **60**, for example **61**, have been synthesised by thermolysis of 4-azido-3-nitroquinolones **62** in boiling bromobenzene. The compounds **61** exist as unseparable mixtures of 3-oxides (**61a**) and 1-oxides (**61b**); this is clearly manifested in the ¹H NMR spectra.⁶⁸



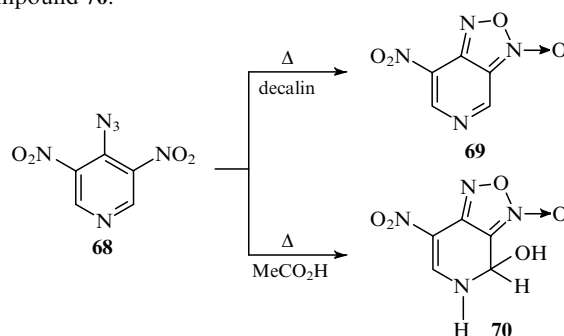
Thermolysis of 4-azido-3-nitropyridine **63** in boiling ethanol or decalin at 80 °C gives furoxan **64** in 74% and 95% yields, respectively.⁴⁶ It is worth noting that the earlier attempts to perform this reaction in boiling toluene have failed.⁶⁹



When amine **65** is oxidised with diacetoxy- λ^3 -iodanylbenzene, only traces of the *N*-oxide **64** are detected; when sodium hypochlorite is used as the oxidant, the product **64** is not formed at all.³⁶

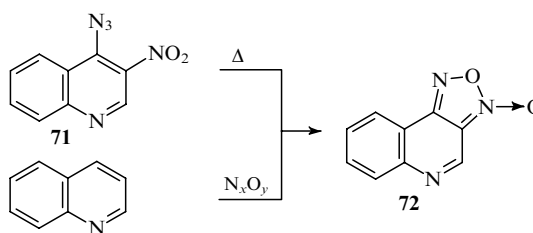
The attempts to annelate a furoxan ring to pyridine *N*-oxides have been unsuccessful. Thus thermolysis of *N*-oxides **66** and **67** gave only high-melting compounds, the structures of which were not identified.⁶⁹

An additional nitro group present in the initial azidonitropyridine facilitates the formation of the furoxan ring. In this case, an unusual solvent effect is manifested. Thermolysis of compound **68** in decalin gives furoxan **69** in 97% yield.⁴⁶ When the process is carried out in benzene, the yield becomes 45% to 70%, the reaction product being produced as a complex with the solvent. The same reaction performed in acetic acid gives rise to hydrated compound **70**.⁶⁹

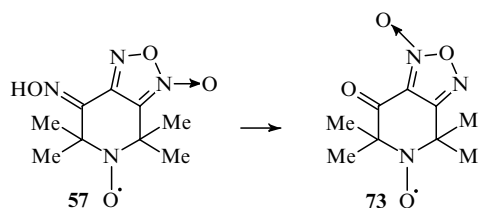


Being an analogue of dinitrobenzofuroxan,¹¹ the compound **69** might also exhibit superelectrophilic properties. However, no studies considering its reactivity from this viewpoint have been reported to date.

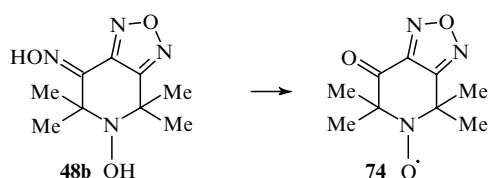
On heating in decalin, 4-azido-3-nitroquinoline **71** is smoothly converted into furoxan **72** in 94% yield.^{46,47} The same compound is formed as a minor product, together with 3-nitroquinoline, when quinoline is treated with nitrogen oxides.⁷⁰



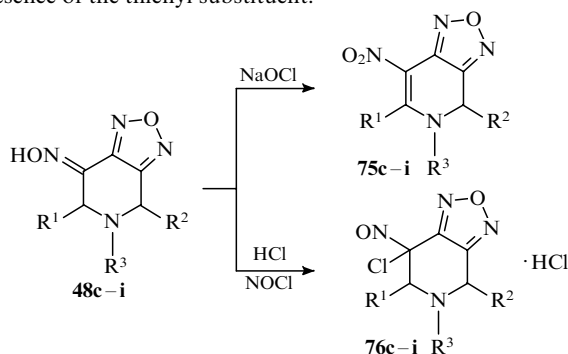
Since the electron-withdrawing furazan ring in furazano[3,4-*c*]pyridines is separated from the pyridine nitrogen, the N atom exhibits basic properties; hence, these compounds can form salts with acids.⁶⁹ Compounds in which the pyridine ring is hydrogenated show the highest basicity.⁶¹ Conversely, the nitro derivative **69** is an acid; it forms salts with bases, hydrazine and transition metal cations and charge transfer complexes with naphthalene derivatives and pyrene (no data about the structure of complexes formed by **69** are presented in the study cited).⁶⁹ The oximes **47** and **48** can be acylated on treatment with acyl chlorides in the presence of bases according to a conventional procedure.^{61,63} Deoxygenation of the nitroxide **57** is accompanied by simultaneous migration of the *N*-oxide oxygen atom in the furoxan ring to give ketone **73**.⁶²



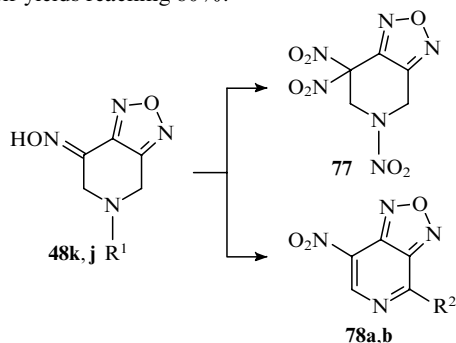
Oxidation of hydroxylamino oxime **48b** is accompanied by deoxygenation with generation of a radical site.⁶² The furazan nitroxide **74** thus formed is stable under ambient conditions.



Treatment of the oximes **48c–i** with sodium hypochlorite in alkaline solutions affords nitro derivatives of dihydrogenated bicyclic compounds **75c–i**. However, the yields of these products are normally relatively low (12%–43%). The oximes **48c–i** are chlorinated with nitrosyl chloride in organic solvents to give chloro nitroso compounds, which have been isolated as salts **76c–h** in 60%–70% yields. The reaction of the compound **48i** with nitrosyl chloride affords the chloro nitroso derivative **76i**, its yield being only 7%, due to the side reactions caused by the presence of the thienyl substituent.⁶³

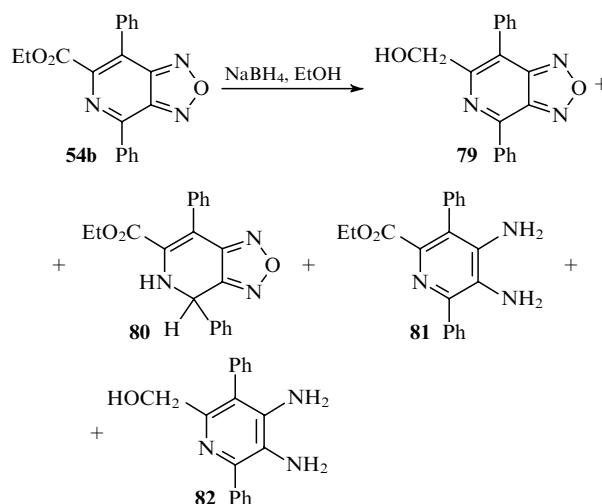


Nitration of the bicyclic compounds **48k** ($R^1 = R^2 = R^3 = H$) and **48j** ($R^1 = R^2 = H, R^3 = Bu^t$) with N_2O_4 , N_2O_5 , BF_4NO_2 or a mixture of HNO_3 with sulfuric or trifluoroacetic acid either gives trinitro derivative **77** or involves aromatisation giving rise to mono (**78a**) or di-nitro compound (**78b**). The reaction can be directed at the predominant formation of either of the products, their yields reaching 80%.⁶³

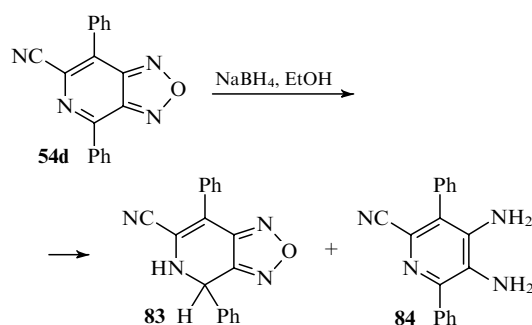


$R^1 = H$ (**48k**), Bu^t (**48j**); $R^2 = H$ (**78a**), NO_2 (**78b**).

The reduction of the compound **54b** with sodium borohydride involves three reaction sites — the ester group (to give hydroxymethyl derivative **79**), the pyridine ring (with the formation of dihydro derivative **80**) and the N–O bond (this leads to cleavage of the furazan ring resulting in the formation of diamines **81** and **82**). Depending on the reaction conditions (ratio of the reactants, temperature, reaction duration), a mixture of compounds enriched in a particular reduction product can be obtained.⁷¹ The yields of individual compounds are rather low. When $LiAlH_4$ is used as the reducing agent, the reaction carried out at room temperature affords alcohol **79** in 62% yield.



Only two types of products can be formed in a similar reaction of the cyano derivative **54d**. Stirring this compound with sodium borohydride in ethanol for 1 h at 20 °C gives furazan **83** in 65% yield and diamine **84** in a yield of only 4%. If the reaction mixture is refluxed for 10 min, the diamine **84** becomes the sole reaction product (yield 79%).⁷¹



Treatment of the dihydro derivatives **80** and **83** with NaOH in ethanol (1.5 h, 20 °C) or with DBU in benzene (4 h) induces oxidative aromatisation giving rise to the compounds **54b,d** in good yields.⁷¹

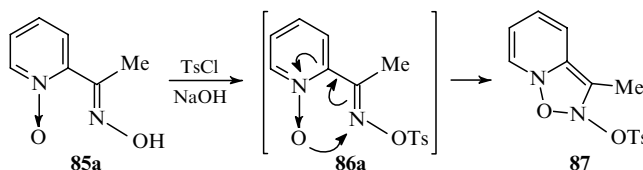
The structures of furazano[3,4-*c*] pyridine derivatives have been studied by mass spectrometry,^{72,73} IR⁷¹ and NMR⁶⁷ spectroscopy and UV spectrometry.⁷¹

The compound **54d** has been patented as a luminescent dye.⁷⁴

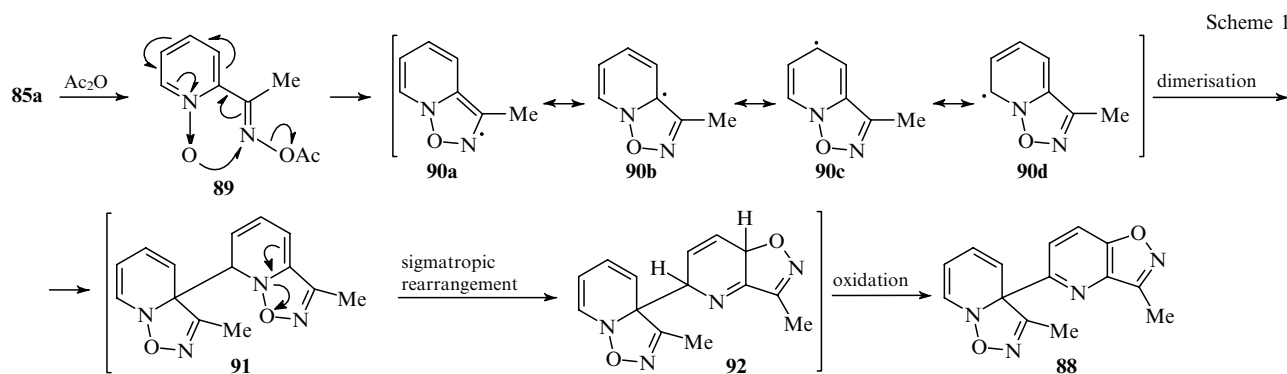
3. Furazano[2,3-*a*]pyridines

Furazano[2,3-*a*]pyridines (**C**) are also referred to as 1,2,5-oxadiazolo[2,3-*a*]pyridines.

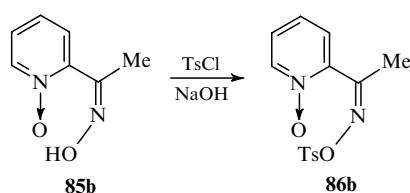
The only method for the synthesis of these compounds known to date is based on pyridine precursors. The reaction of the *E*-oxime of 2-acetylpyridine *N*-oxide **85a** with toluene-*p*-sulfonyl chloride in the presence of alkali leads on closure to a furazan ring and gives the bicyclic derivative **87** in 67% yield.⁷⁵



Presumably, this transformation involves the intermediate formation of the tosylate **86a**. A similar reaction of the corresponding *Z*-isomer **85b** does not give a bicyclic product but stops at the stage of formation of the tosylate **86b**.

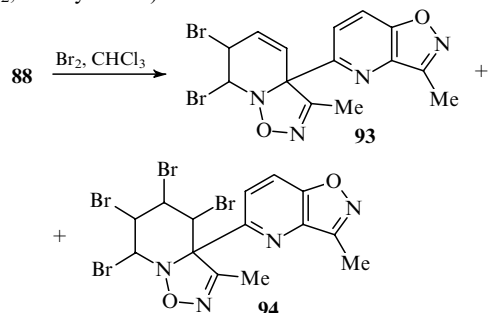


Treatment of the *E*- and *Z*-isomers of the methylquinolyl and methylisoquinolyl ketoxime *N*-oxides did not result in closure to give a furazan ring.⁷⁶

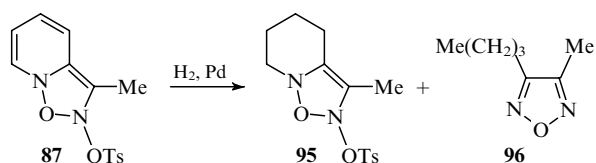


Heating of the *E*-isomer **85a** in acetic anhydride at 130 °C for 2 h affords furazan derivative **88** in 88% yield. At temperatures below 100 °C, the reaction stops at the stage of formation of acetyl derivative **89**. The *Z*-isomer **85b** is not converted into a furazan derivative even at high temperatures. The compound **88** is formed by a radical mechanism. This was confirmed experimentally by conducting the reaction in the presence of radical sources or radical traps. The course of the reaction can be described by a scheme with intermediates **90–92** (Scheme 1).⁷⁷

The compound **88** remains unchanged when refluxed with 20% hydrochloric acid or alkali. However, it is readily brominated in chloroform to give a mixture of di- (**93**) and tetra-brominated (**94**) compounds in 52% and 33% yields, respectively. On refluxing in ether for 4 h, the compound **94** eliminates a bromine molecule, being quantitatively converted into the dibromide **93**.⁷⁷ The dimer **88** is stable against catalytic hydrogenation (H₂, Raney nickel).⁷⁷



The tosylate **87** is reduced with hydrogen over Pd to give, depending on the reaction conditions, either hydrogenated bicyclic compound **95** (in a yield of up to 25%) or monocyclic furazan **96** (in a yield of up to 89%).⁷⁵

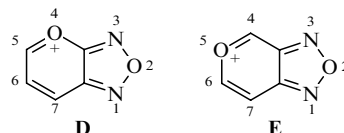


The structure of these derivatives, which are unusual for the furazan series, was established based on thorough analysis of their

¹H NMR, ¹³C NMR, UV, IR and mass spectra; 2D NMR techniques have also been used for this purpose.^{75,77}

IV. Furazanopyrans

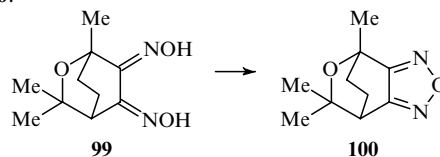
Of the two theoretically possible types of bicyclic compounds comprising furazan and pyran rings (**D** and **E**), only furazano-[3,4-*c*]pyran derivatives (type **E**) are known.



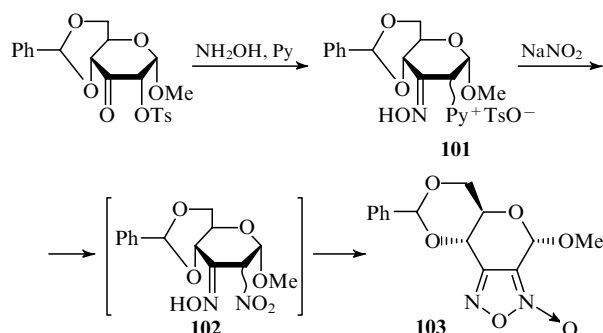
Furazano[3,4-*c*]pyran derivatives can be obtained both from furazan and pyran synthons. Thus treatment of furazan-3-carboxylic acid **97** with acetic anhydride or dicyclohexylcarbodiimide (DCC) induces intramolecular esterification. This gives lactone **98** in 80%–85% yield.⁷⁸



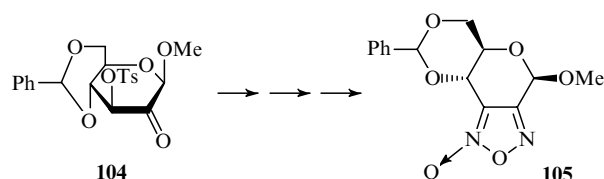
Dehydration of glyoxime **99** is accompanied by the formation of a furazan ring. This reaction gives cage furazan compound **100**.⁷⁹



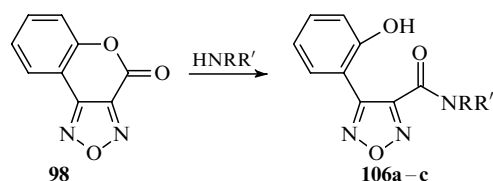
Refluxing of the pyridinium salt **101**, containing a carbohydrate fragment, with sodium nitrite in the presence of pyridine in aqueous THF leads to furoxan **103**, which is formed in 58% yield, apparently, *via* the intermediate formation of nitro derivative **102**.⁸⁰



The isomeric furoxan **105** can be prepared by successive treatment of 2-keto-D-glucopyranoside **104** with hydroxylamine in aqueous pyridine and with a solution of sodium nitrite in aqueous dioxane followed by keeping the reaction mixture for 3 h at 90 °C. The yield of the furoxan **105** is 40%.⁸⁰

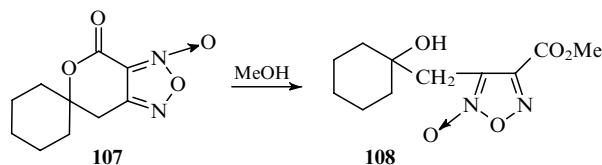


Data on the reactivity of furazano[3,4-*c*]pyran derivatives are very scarce. It is only known that the lactone ring in the compound **98** can be opened by amines to give amides of furazan-3-carboxylic acid **106**.⁷⁸



R = R' = Me (**a**), Et (**b**); R = H, R' = Ph (**c**).

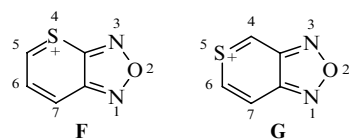
Spirocyclic lactone **107** is cleaved on treatment with methanol, being thus converted into monocyclic furazan derivative **108**.⁸¹



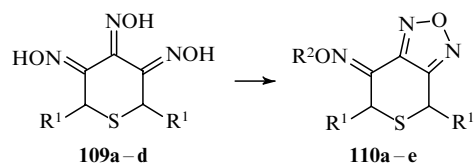
Compounds of this group have been characterised by the data of IR and UV spectroscopy and mass spectrometry.⁸⁰

V. Furazanothiopyrans

Two types of furazanothiopyrans can be conceived, furazano[3,4-*b*]thiopyrans (**F**) and furazano[3,4-*c*]thiopyrans (**G**). However, no derivatives of structure **F** are known.



Only one study concerning furazano[3,4-*c*]thiopyran derivatives has been published.⁶³ The dehydration of trioximes **109a-d** induced by heating with alkali or DCC is accompanied by closure to give a furazan ring, resulting in the formation of oximes **109a-d** in 67%–85% yields. The formation of a furazan ring with simultaneous acylation of the third oxime group was observed when trioximes **109b** and **109d** were treated with acetic anhydride. The acetates of bicyclic oximes **110d** and **110e** were isolated in 88%–93% yields.⁶³

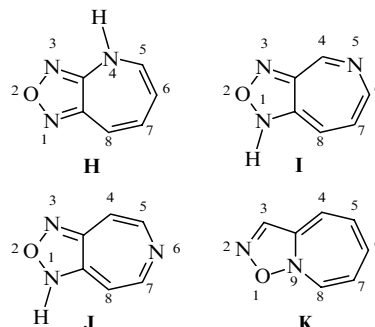


R¹ = R² = H (**a**); R¹ = Ph, R² = H (**b**); R¹ = Me, R² = H (**c**); R¹ = 2-furyl, R² = H (**109d**), Ac (**110d**); R¹ = Ph, R² = Ac (**110e**).

No data concerning the reactivity of this bicyclic system can be found in the literature.

VI. Furazanoazepines

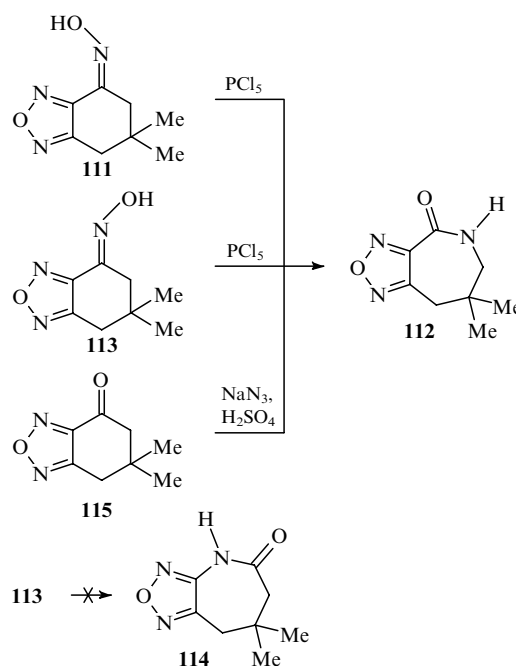
Four types of annelation of furazan and azepine rings (**H**, **I**, **J** and **K**) are possible.



Only few derivatives of furazano[3,4-*c*]azepine (**I**) have now been described.

The heterocyclic system of furazano[3,4-*c*]azepine has been mentioned in the literature as 1,2,5-oxadiazolo[3,4-*c*]azepine.

The Beckmann rearrangement of *Z*-oxime **111** in the presence of PCl_5 in ether at 20 °C gives rise to azepin-4-one **112** (yield 29%). Treatment of *E*-oxime **113** under similar conditions gives the same product **112** in a yield of only 5%. The main bulk of the initial compound is converted into a polymer rather than into the expected isomeric azepine **114**.⁸²



Azepine **112** is also formed upon the Curtius rearrangement of ketone **115**, induced by treatment with sodium azide in a mixture of chloroform and sulfuric acid. Note that the Curtius rearrangement gives the azepine **112** in a higher yield (55%) than the Beckmann rearrangement.⁸³

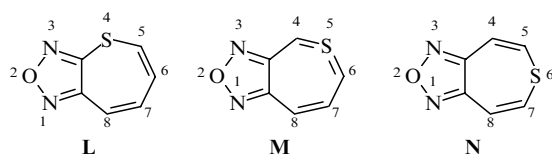
The reaction of **112** with acetyl chloride in the presence of sodium hydride in toluene gives the corresponding N-acetylation product in 67% yield.⁸²

The structure of this azepine has been confirmed by the data of its IR, ¹H NMR and mass spectra.

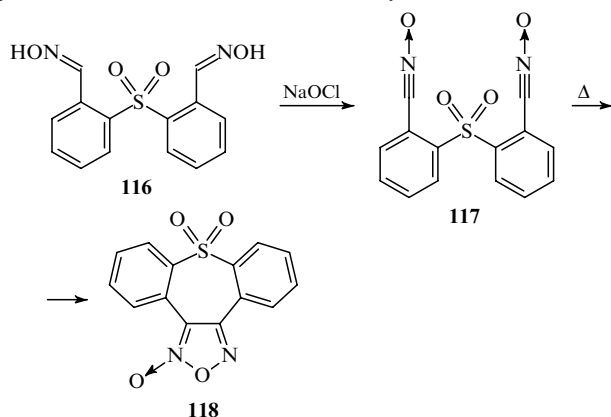
The azepine **112** exhibits moderate antimicrobial activity.⁸³

VII. Furazanothiepinines

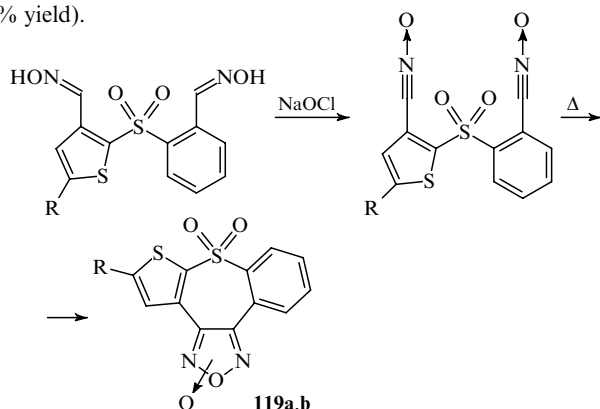
Of the three types of annelation of a furazan ring to a thiopine ring possible theoretically (**L**, **M** and **N**), only type **N** derivatives, furazano[3,4-*d*]thiepinines, have been synthesised.



Heating of a benzene solution of bis-*N,N*-oxide **117**, prepared by treatment of dioxime **116** with an alkaline solution of sodium hypochlorite, affords furoxan **118** in 90% yield.⁸⁴



Thieno-annelated compounds **119a,b** have been synthesised in a similar way.⁸⁵ However, the replacement of a benzene ring in the initial molecule by a thiophene ring results in somewhat lower yields of the corresponding tetracyclic compounds **119a,b** (72%–74% yield).



R = H (**a**), Me (**b**).

Furoxans **119a,b** exist as unseparable mixtures of isomers.

VIII. Conclusion

The data presented in this review demonstrate on the one hand, the great synthetic potential of the class of compounds considered and, on the other hand, the scarcity of investigations along this line. The latter is apparently due to the facts that the required initial compounds are relatively difficult to obtain and that the methods for their transformations are not adequately developed. Meanwhile, some existing efficient methods for the construction of the title bicyclic systems have not yet found wide use. We hope that systematisation of the published data presented in this review will serve as the basis for the further development of this field of chemistry.

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Reactions of halophosphines with conjugated heterodienes

E Ya Levina, A M Kibardin

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Abstract. Data on reactions of halophosphines $\text{P}(\text{H})\text{X}_3$, $-\text{P}(\text{H})\text{X}_2$, and $>\text{P}(\text{H})\text{X}$ with hetero-1,3-dienes resulting mostly in the formation of phosphorus-containing heterocycles are generalised and systematised. The influence of the nature, the number and positions of heteroatoms (O, N) in the heterodiene system, and of the nature of the substituents at the phosphorus atom on the reaction pathways and mechanisms is analysed. The bibliography includes 155 references.

I. Introduction

Reactions of tricoordinate phosphorus derivatives with diene systems is an important route to cyclic phosphorus-containing compounds, first of all following the $[4+1]$ -cycloaddition mechanism. In this regard, reactions of halophosphines (HP) $\text{P}(\text{H})\text{X}_3$, $-\text{P}(\text{H})\text{X}_2$, and $>\text{P}(\text{H})\text{X}$ are most numerous. Their reactions with 1,3-dienes containing no heteroatoms are well studied. The reaction of $[4+1]$ -cycloaddition of HP to 1,3-dienes was discovered by McCormack in 1953^{1,2} and most intensively studied in the 1960's and early 1970's simultaneously by several groups of investigators. Reactions of HP with conjugated dienes have been adequately covered in reviews^{3,4} and monographs.^{5–7} Despite a wide variety of compounds obtained, they all belong to phosphol-2(3)-enes ($[4+1]$ -cycloaddition reaction), to polymers or oligomers containing a phosphorus atom in the chain (1,4-addition reaction), or to the products of cyclisation occurring with retention of the system of conjugated bonds. The studies in this field^{8,9} reported after publication of a book by Quin⁶ in 1981 contain no radically new data, except for a series of studies dedicated to investigation of reactions of 1,3-dienes with HP of the X_2CHPX_2 ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) type in the presence of triethylamine.^{10–16} Under the action of excess triethylamine, this type of HP undergo dehydrohalogenation to form unstable phosphathenes $\text{XP}=\text{CX}_2$. The latter enter *in situ* into the Diels–Alder reaction with dienes following the $[4+2]$ -cycloaddition mechanism to give aromatic compounds, viz., 2-halophosphorinines containing a

dicoordinate phosphorus atom, *via* intermediate six-membered 1,2,2-trihalo-1,2,3,6-tetrahydrophosphorinines.

The study of reactions of HP addition to hetero-1,3-dienes was begun by Conant¹⁷ in 1917 taking unsaturated carbonyl compounds as an example and is being developed successfully at present. These reactions are very diverse and result in the formation of not only five-, but also six-membered rings, and open-chain structures as well. Recently, the range of heterodienes under study has been considerably extended, which has led, in particular, to obtaining of novel classes of phosphorus-containing heterocycles, which are not only of theoretical, but also of considerable practical interest.

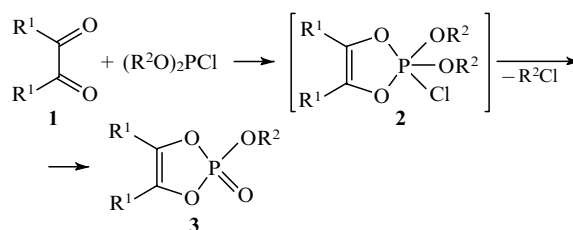
The aim of the present review is to systematise the available information on the reactions of HP with heterodienes and to reveal peculiarities of the influence of heteroatoms in the diene system on the direction and mechanisms of these reactions. We do not discuss here the reactions of compounds that formally contain a heterodiene system, if one or both double bonds of a diene are fragments of arene or heteroarene systems.

II. Reactions with oxadienes

1. Reactions with α -dicarbonyl compounds

Investigation of the reactions of P(III) derivatives with α -dicarbonyl compounds was carried out almost simultaneously with the study of analogous reactions of dienic hydrocarbons. However, it should be noted that in most cases it was phosphites that have been used as dienophiles, whereas reactions with HP have been the subject of an insignificant number of publications; moreover, all of them involved α -diketones only.

Like dienic hydrocarbons, α -diketones **1** react with dialkylphosphorochloridites by the $[4+1]$ -cycloaddition mechanism to form adducts **2** containing a pentacoordinate phosphorus atom. Further elimination of alkyl chloride from the adducts **2** according to the mechanism of the second stage of the Arbuzov reaction (see Refs 18, 19) gives 2-alkoxy-2-oxo-1,3,2-dioxaphospholes **3**.^{20,21}



$\text{R}^1 = \text{Me}, \text{Ph}; \text{R}^2 = \text{Et}, \text{Pr}^n, \text{Bu}^i, \text{Bu}^n.$

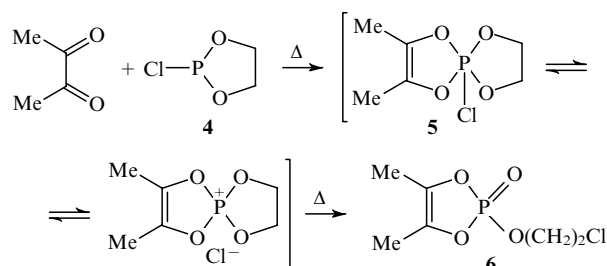
E Ya Levina, A M Kibardin A E Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Centre of Russian Academy of Sciences, ul. Acad. Arbuzova 8, 420083 Kazan, Russian Federation, Fax (7-843) 275 22 53. Tel. (7-843) 276 73 34. E-mail: lina@iopc.kcn.ru (E Ya Levina)

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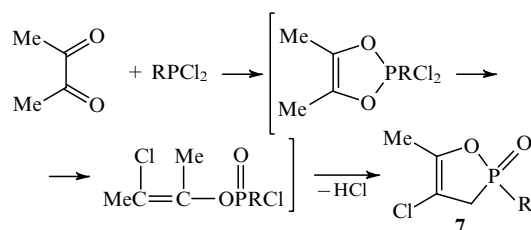
Uspekhi Khimii 68 (2) 167–183 (1999); translated by A M Raevsky

Dialkyl phosphorochloridites are less reactive than trialkyl phosphites and phosphoramidites.^{20–22} It is believed²² that the closure of the dioxaphosphole ring occurs as a result of a concerted or almost concerted passage of the lone electron pair of the phosphorus atom to the conjugated π -system of the α -diketone and transfer of the π -electrons of this system to orbitals of the phosphorus atom.

The reaction of 2-chloro-1,3,2-dioxaphospholane (**4**) with biacetyl occurs to give initially spiroposphorane **5** containing a P(V)–Cl bond and is followed by its conversion into 4,5-dimethyl-2-oxo-2-(2-chloroethoxy)-1,3,2-dioxaphosphole (**6**) by the mechanism of the second stage of the Arbuzov reaction.²³

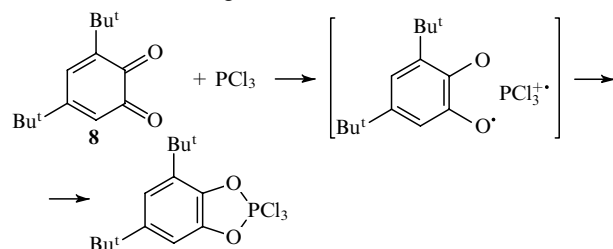


Biacetyl reacts with dichlorophosphines in a different way, viz., with the formation of 4-chloro-3*H*-5-methyl-2-oxo-1,2-oxaphosphole **7**, following a mechanism involving recyclisation.^{24,25}



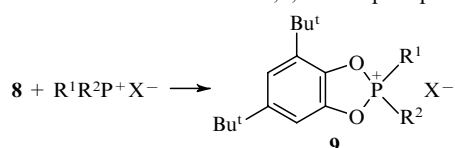
R = Me, Et, Ph.

A phosphorane-type product of [4 + 1]-cycloaddition is obtained in the reaction of phosphorus trichloride with 3,5-di-*tert*-butyl-*o*-quinone (**8**).²⁶ Based on detection of signals in the EPR spectra recorded during this reaction, it was argued²⁶ that its mechanism involves a stage of one-electron transfer.



Similar signals in the EPR spectra were also observed in the reactions of PCl₃ with *o*-chloranil, *o*-naphthoquinone, and 9,10-phenanthrenequinone; however, the final products have not been isolated.²⁶ It should be noted that the appearance of paramagnetic intermediates, detected by the EPR technique, in the reaction mixture is not the unambiguous evidence for the formation of the final phosphorane as a result of one-electron transfer.

Phosphenium salts, which are closest analogues of HP, react with *o*-quinone **8** similarly to HP, following the [4 + 1]-cycloaddition mechanism to form 1,3,2-dioxaphospholenium salts **9**.²⁷



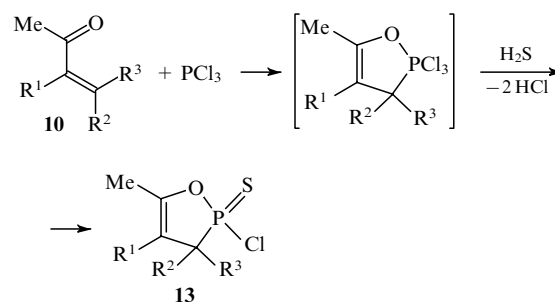
R¹ = Pr₂N; R² = Cl, N = PPh₃; R¹, R² = Alk;
R¹–R² = MeN(CH₂)₂NMe; X = AlCl₄, CF₃SO₃.

In the reactions with phosphenium salts the *o*-quinone **8** behaves analogously to 1,3-dienes.^{28–30} At the same time, (Pr₂N)₂PCl in which the phosphorus atom is less electrophilic than in the phosphenium cation, does not enter into this reaction.²⁷

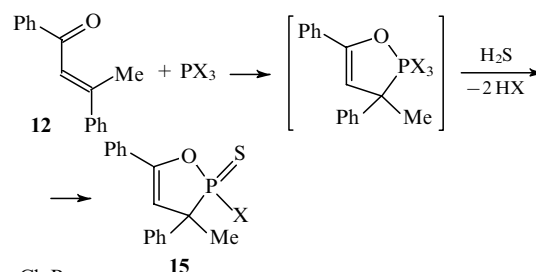
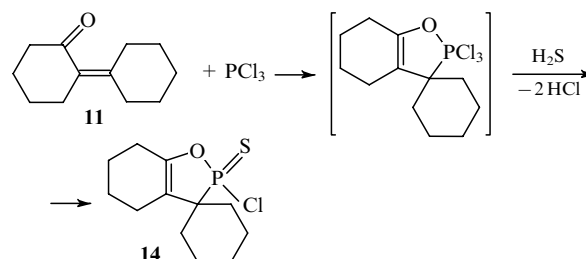
Thus, as in the case of dienic hydrocarbons, symmetric heterodiene systems of diketones and *o*-quinone add a phosphorus-containing dienophile at positions 1 and 4 with the formation of a cycloadduct containing a pentacoordinate phosphorus atom in the first stage. The final reaction products are derivatives of 1,3,2-dioxaphospholes or 3*H*-1,2-oxaphospholes. No indications of the existence of intermediate bipolar ions were found. The intermediate **2** was detected by ³¹P NMR spectroscopy.²²

2. Reactions with α,β -unsaturated carbonyl compounds

Mesityl oxide and benzylideneacetophenone were the first 1,3-heterodienes used to study the reactions with HP taking PCl₃ and PBr₃ as an example.¹⁸ The assumption that the reactions with phosphorus trihalides follow the [4 + 1]-cycloaddition mechanism with the formation of five-membered cycles, viz., 3*H*-1,2-oxaphospholes,¹⁷ was confirmed in further studies. A brief summary of the results obtained in these earlier studies has been reviewed,³ so we do not discuss them here. After the review³ was published, it was established that passage of hydrogen sulfide through a mixture of phosphorus trihalide and α,β -unsaturated ketones **10–12** afforded 3*H*-1,2-oxaphosphole sulfides **13–15** in good yields.^{31,32} This is evidence in favour of [4 + 1]-cycloaddition.

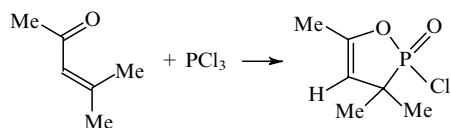


R¹, R², R³ = H, Me.

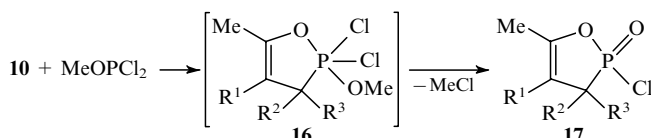


X = Cl, Br.

It was also shown later that heating phosphorus trichloride and mesityl oxide in a sealed tube in the absence of a solvent gave 2-chloro-3,3,5-trimethyl-2-oxo-3*H*-1,2-oxaphosphole.³³ We believe that the formation of this compound can be explained by the replacement of two chlorine atoms in the intermediate [4 + 1]-cycloaddition product by the carbonyl oxygen atom of the second mesityl oxide molecule.

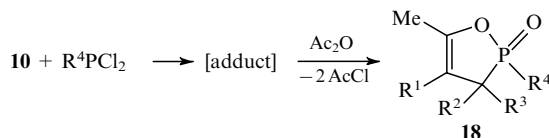


The reactions of methyl phosphorodichloridite with ketones **10** also follow the Diels–Alder reaction mechanism, subsequent elimination of methyl chloride from the adduct **16** results in 2-chloro-2-oxo-3*H*-1,2-oxaphospholes **17**.³⁴



$\text{R}^1, \text{R}^2, \text{R}^3 = \text{H}, \text{Me}$.

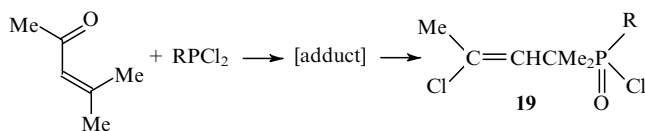
Reactions of dichlorophosphines with α,β -unsaturated ketones **10** in acetic anhydride give first the adducts of the type **16** and then 3*H*-1,2-oxaphospholes **18**.^{35–37}



$\text{R}^1, \text{R}^2, \text{R}^3 = \text{H}, \text{Me}; \text{R}^4 = \text{Et}, \text{Ph}, 2\text{-thienyl}$.

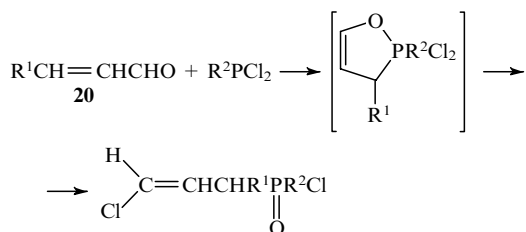
Benzylideneacetone and phenyl(dichloro)phosphine do not enter into this reaction in acetic anhydride.³⁵

However, the reactions of dichlorophosphines and phenyl phosphorodichloridites with mesityl oxide (heating in sealed tubes in the absence of a solvent) afford acyclic β,γ -unsaturated phosphorus acid chlorides **19** in which the coordination number of P atom is 4. The latter result from a ring–chain isomerisation of the adducts of the type **16** initially formed in the Diels–Alder reaction.³³



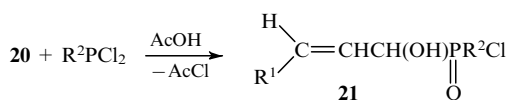
$\text{R} = \text{Me}, \text{Et}, \text{Ph}, \text{PhO}$.

Analogous products are obtained in the reaction of dichlorophosphines with α,β -unsaturated aldehydes **20**. In this case the reaction occurs under milder conditions (in solution).³⁸



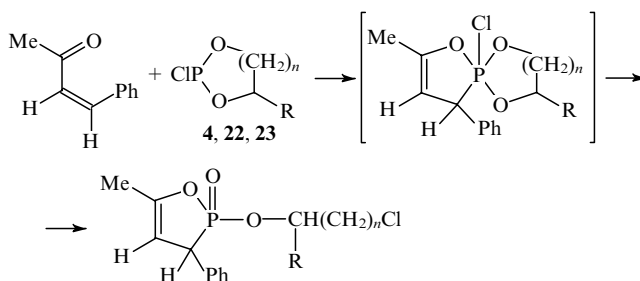
$\text{R}^1 = \text{Me}, \text{H}; \text{R}^2 = \text{Et}, \text{Ph}$.

Aldehydes **20** react with phenyl(dichloro)phosphine or PCl_3 in acetic acid to give α -hydroxy- β,γ -unsaturated phosphorus acid dichlorides **21** in which the coordination number of the P atom is 4.³⁸



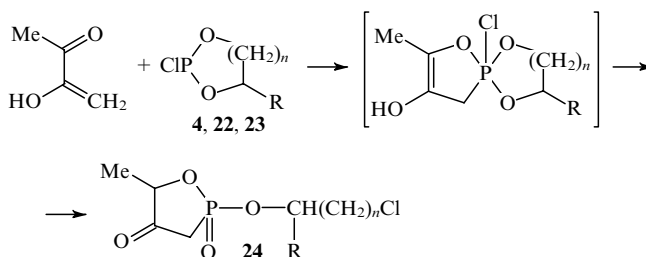
$\text{R}^1 = \text{Et}, \text{Ph}; \text{R}^2 = \text{Ph}, \text{Cl}$.

Compounds **4**, **22** and **23** react with α,β -unsaturated ketones **10** (heterodienes) by mechanisms involving cycloaddition followed by dealkylation, which is analogous to the second stage of the Arbuzov rearrangement. This results in the formation of 3*H*-1,2-oxaphosphole derivatives,^{39,40} as is shown below taking the reaction with benzylideneacetone as an example.

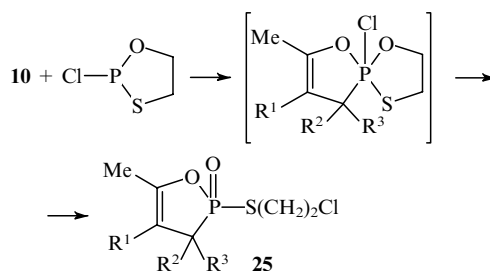


4: $\text{R} = \text{H}, n = 1$; **22**: $\text{R} = \text{Me}, n = 1$; **23**: $\text{R} = \text{H}, \text{Me}, n = 2$.

As was mentioned in Section II.1, biacetyl reacts with phospholane **4** following a conventional mechanism of cycloaddition to the $\text{O}=\text{C}-\text{C}=\text{O}$ bond system. However, it was reported⁴¹ that the reactions of biacetyl with compounds **4**, **22** and **23** under virtually the same conditions resulted in the formation of quite different products, viz., 1,2-oxaphospholan-4-ones **24**. This was rationalised by a [4 + 1]-cycloaddition of compounds **4**, **22** and **23** to the enol form of biacetyl as the heterodiene.



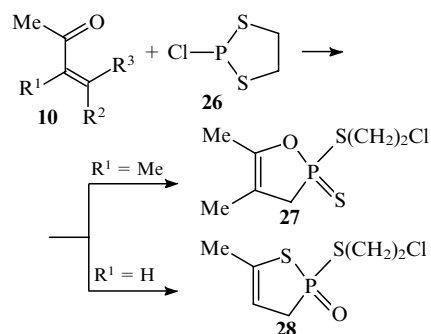
Condensation of ketones **10** with 2-chloro-1,3,2-oxathiaphospholane occurs analogously to the reaction with compound **4**. The second stage of the Arbuzov rearrangement of the intermediate adduct occurs with the cleavage of the C–O bond (not the C–S bond, as in the reaction with butadiene) to give derivatives of 2-oxo-3*H*-1,2-oxaphospholes **25** containing the P–S bond.⁴²



$\text{R}^1, \text{R}^2, \text{R}^3 = \text{H}, \text{Me}$.

The structure of the final product of reaction between 2-chloro-1,3,2-dithiaphospholane (**26**) and ketones **10** ($\text{R}^1 = \text{H}, \text{Me}; \text{R}^2 = \text{R}^3 = \text{H}$) is determined by the nature of the substituent R^1 . 2-Thioxo-3*H*-1,2-oxaphosphole **27** and 2-oxo-3*H*-1,2-thiaphosphole **28** are respectively formed at $\text{R}^1 = \text{Me}$ and H .⁴³

The reaction of compound **26** with ketone **10** ($\text{R}^1 = \text{H}$) occurs either with the rearrangement of an intermediate adduct or with the initial formation of thioxo derivative of the type **27**, which after the Pishchimuka rearrangement⁴⁴ is converted into the phosphoryl compound **28**.



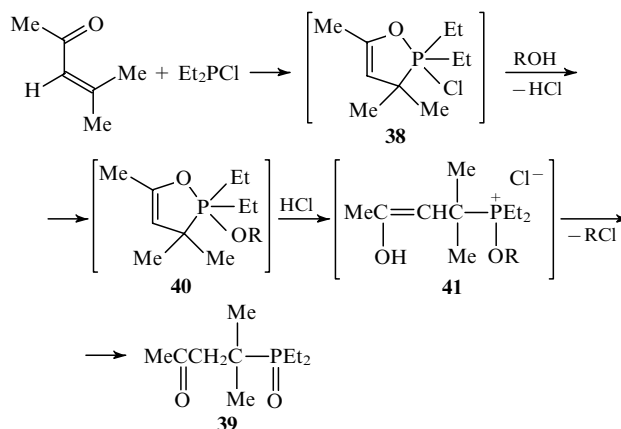
$R^1 = \text{H, Me}; R^2 = R^3 = \text{H}.$

Alkylphosphonochloridothioites **30** react with ketones **10** in a similar way; however, in this case, alkyl halide is eliminated from the intermediate [4 + 1]-cycloaddition product **29** to give 2-ethyl(-phenyl)-2-thioxo-3*H*-1,2-oxaphospholes **31** (Scheme 1, route *a*).⁴⁵ In the presence of proton-donor reagents (acetic acid or water) this reaction results in the formation of *S*-alkyl phosphinothioates **32**⁴⁶ (Scheme 1, route *b*). The formation of products **32** is explained as follows.⁴⁶ The ambident ion **33** formed in the first reaction stage as a result of nucleophilic C-addition of alkylphosphonochloridothioite **30** to the unsaturated ketone **10** reacts with acetic acid⁴⁶ to give an intermediate acyclic adduct **34**. The latter undergoes the Arbuzov rearrangement with the elimination of acyl chloride and the formation of the final product **32**. If the reaction is performed in the presence of water, alkylphosphonochloridothioite **30** is initially hydrolysed into the corresponding acid **35**, which then is added to the ketone **10** to give the ester **32** (Scheme 1, route *c*).

We believe that it is possible to combine the routes *a*, *b* and *c* into a unified scheme assuming that betaine **33** can be a common intermediate to routes *a* and *b* and that in the presence of water the process can follow not only route *c*, but also route *b* (the latter can be considered as a route common to any proton-donor reagents). Under the action of proton-donor reagents, the halogen atom in the phosphorane **29** can be replaced by an OX group to form a product **36**. The latter adds hydrogen halide to give an ion **34**,

which is in equilibrium with an ion **37**, and then the final product **32**.

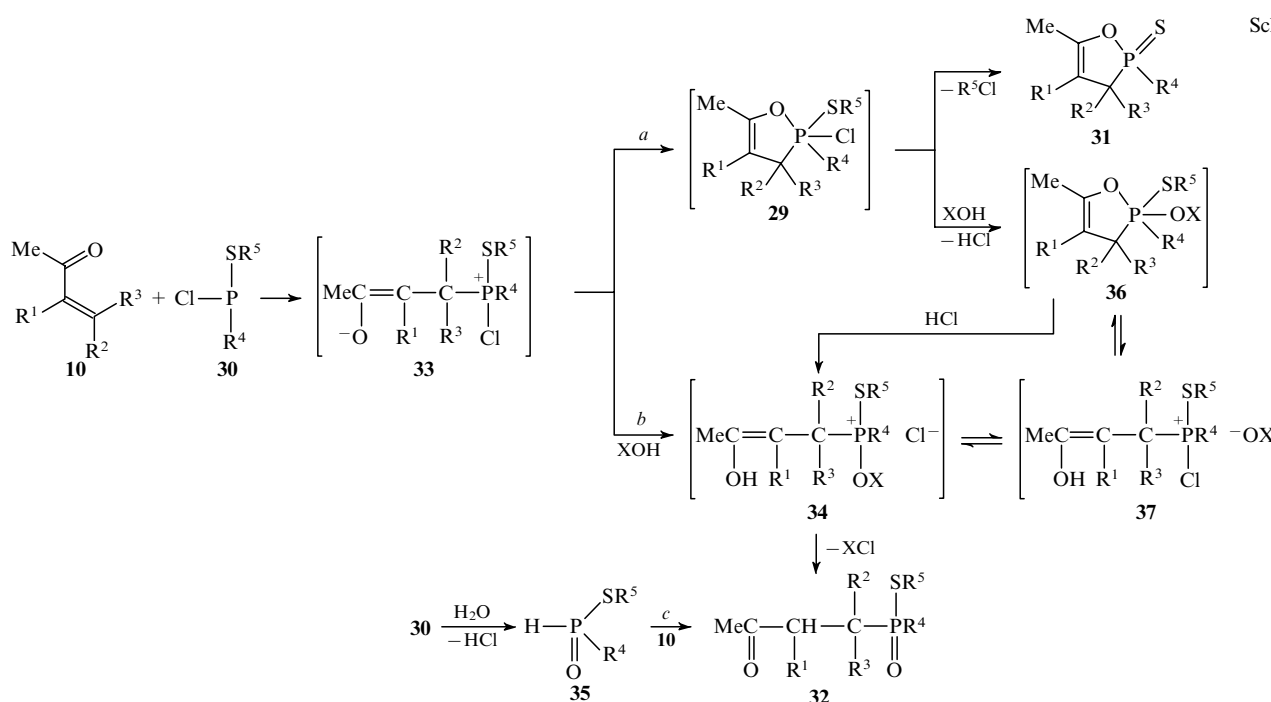
Heating of diethylchlorophosphine and mesityl oxide in a sealed tube in the absence of a solvent resulted in a crystalline adduct **38**, which was converted into phosphine oxide **39** upon treatment with alcohols following the scheme shown below:⁴⁷



$R = \text{Me, Bu}.$

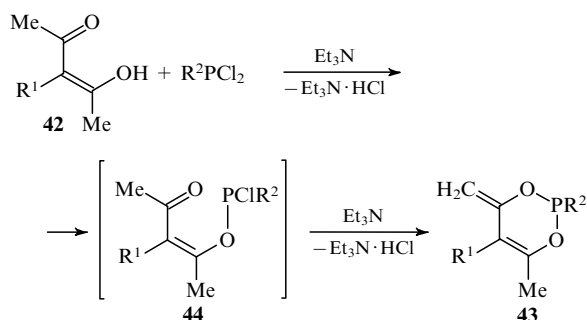
Apparently, the intermediates **3**, **40** and **41** are the analogues of intermediates **29**, **36** and **34**, respectively, while the product **39** is an analogue of the products **32**. It is quite possible that both products **39** and **32** are formed *via* intermediates **33**. Thus, a conclusion can be drawn that the reactions of P(III) acid monochlorides with unsaturated ketones in the presence of proton-donor reagents follow a common mechanism irrespective of the reaction conditions.

A peculiar type of reaction is that of HP with β -diketones in the presence of organic base. It is believed that β -diketones **42** enter into reaction in the enol form, *i.e.*, that they can be considered as a particular case of α,β -unsaturated ketones **10** ($R^2 = \text{Me}, R^3 = \text{OH}$). Reactions of P(III) dichlorides with β -diketones give 4-methylene-4*H*-1,3,2-dioxaphosphorinines **43** with a semicyclic homodiene system of bonds.^{48–51}



Scheme 1

$R^1, R^2, R^3 = \text{H, Me}; R^1 = R^2 = \text{H}, R^3 = \text{Ph}; R^4 = \text{Et, Ph}; R^5 = \text{Et, Pr}^n, \text{Pr}^i, \text{Bu}^n, \text{Bu}^i; \text{X} = \text{H, Ac}.$

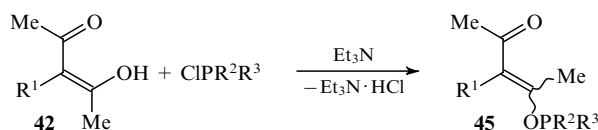


$\text{R}^1 = \text{H, Et, Cl, Ac; R}^2 = \text{Et, Ph, MeO, EtO, Pr}^n\text{O, Pr}^i\text{O, Me}_2\text{N, Et}_2\text{N, EtS.}$

The reaction proceeds *via* intermediate heterodienes, *viz.*, α,β -unsaturated ketones **44**, which are formed upon O-phosphorylation of the hydroxyl group of the ketones **42**, which leaves the diene system intact. Subsequent intramolecular O-phosphorylation leads to the closure of the six-membered ring and the formation of dioxaphosphorinines **43** containing an exocyclic methylene group.^{49–51}

If P(III) monochlorides are used instead of P(III) dichlorides in the reaction with ketones **42**, in most cases the process is completed by the formation of acyclic products **45**, *viz.*, O-phosphorylated derivatives of the ketones **42**, which are analogous to the ketones **44**.^{51–55}

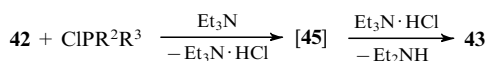
Thus, unlike all reactions considered above, this reaction occurs without involvement of the system of conjugated bonds of the heterodiene at all.



$\text{R}^1 = \text{H, Ac, Cl; R}^2 = \text{EtO, Pr}^n\text{O, Me}_2\text{N, Et}_2\text{N; R}^3 = \text{Me, MeO, EtO, Pr}^i\text{O, Bu}^i\text{O, Ph, Et}_2\text{N; R}^2\text{--R}^3 = \text{O}(\text{CH}_2)_2\text{O, OCH}_2\text{CH}(\text{Me})\text{O, o-O}_2\text{C}_6\text{H}_4.$

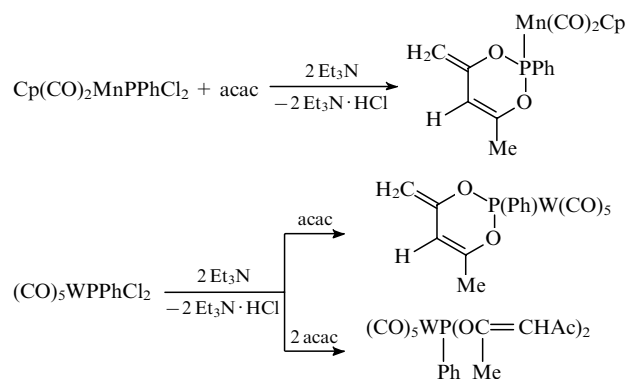
In the case of acetylacetone, it was established that the reaction product **45** is a mixture of *Z*- and *E*-isomers with a considerable predominance of the *E*-isomer.^{51, 54}

If P(III) monochlorides containing a dialkylamino group are introduced into the reaction with acetylacetone (**42**, $\text{R}^1 = \text{H}$), the linear heterodienes **45** formed initially undergo cyclisation into dioxaphosphorinines **43** with the elimination of dialkylamine. Dioxaphosphorinines **43** are isolated as final products after distillation. The reaction occurs successfully in the presence of acidic admixtures, which behave as catalysts and favour the conversion of the dialkylamino group into a good leaving group. Cyclisation occurs with particular ease if the intermediate linear heterodienes **45** contain two dialkylamino groups at the phosphorus atom. An interesting peculiarity was observed in those cases where it was possible to isolate the intermediates **45** or to obtain them by independent synthesis, *viz.*, the yields of the cyclisation products **43** were higher than the portion of *Z*-isomer in the intermediates **45**. This indicates that *Z,E*-isomerisation of heterodienes **45** occurs under the cyclisation conditions.^{51, 54}

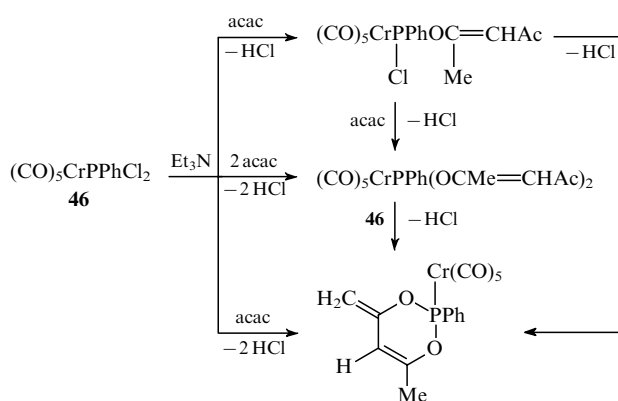


$\text{R}^1 = \text{H; R}^2 = \text{EtO, Pr}^n\text{O, Pr}^i\text{O, Et}_2\text{N; R}^3 = \text{Me}_2\text{N, Et}_2\text{N.}$

Metal complexes of phenyl(dichloro)phosphine react with acetylacetone in the presence of triethylamine analogously to uncoordinated dichlorophosphines, leaving the metal-containing groups intact.^{56, 57}

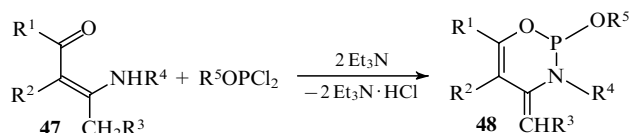


This type of reactions was studied in more detail taking the reaction of pentacarbonylchromium complex **46** with acetylacetone as an example.⁵⁷



Finally, it should be noted that ethyl(dichloro)phosphine reacts in acetic acid with acetylacetone in its diketone form rather than in its enol form.⁵⁸

Reactions of enamino ketones **47** (nitrogen analogues of the diketones **42**) with alkyl phosphorodichloridites yield azaanalogues of dioxaphosphorinines **43**, *viz.*, 4-alkylidene-4*H*-1,3,2-oxazaphosphorinines **48**.^{51, 59}



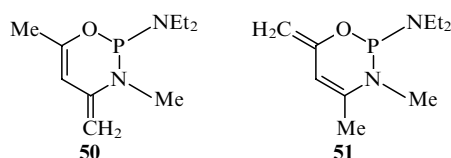
$\text{R}^1 = \text{H, Me; R}^2 = \text{R}^3 = \text{H; R}^4 = \text{Me, Ph; R}^1\text{--R}^2 = (\text{CH}_2)_3;$
 $\text{R}^2\text{--R}^3 = (\text{CH}_2)_2; \text{R}^5 = \text{Me, Et, Pr, Bu.}$

The reaction of enamino ketones **47** with dialkyl phosphorochloridites halts in the stage of N-phosphorylation of the amino group and the formation of acyclic dialkyl phosphoramidites **49**.^{51, 60}

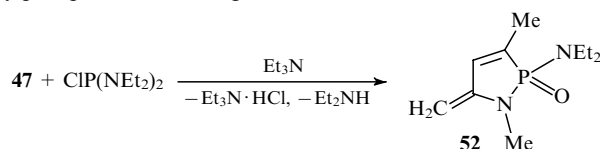


$\text{R}^1 = \text{H, Me; R}^2 = \text{R}^3 = \text{H; R}^4 = \text{Me; R}^5 = \text{Et, Pr.}$

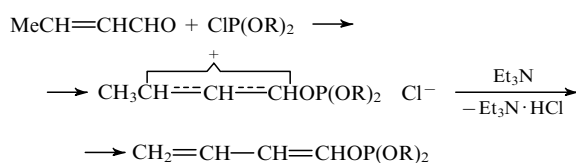
However, as in the case of diketones **42**, the reaction of enamino ketone **47** ($\text{R}^1 = \text{R}^4 = \text{Me; R}^2 = \text{R}^3 = \text{H}$) with bis(diethyl)phosphorodiamidochloridite occurs in a more complex way. Observation of weak signals along with other signals in the ³¹P NMR spectrum indicates that the reaction mixture contains 4-methylene-4*H*-1,3,2-oxazaphosphorinene **50** and/or isomeric 6-methylenephosphorinene **51**.



However, only 5-methylene-2-oxo-5H-1,2-azaphosphole **52** was isolated after distillation^{51, 59} due to the vinyl phosphite–vinylphosphonate rearrangement.^{50, 51, 53}

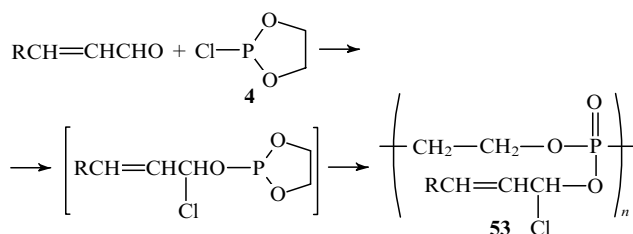


Reactions of phosphorochloridites and crotonaldehyde in the presence of triethylamine occur with proton abstraction from the methyl group at the double bond and the formation of butadienyl phosphites.⁶¹ We believe that the initial attack of phosphorochloridite on the oxygen atom of the carbonyl group is followed by proton abstraction from the methyl group.



R = Et, Ph; (OR)₂ = O(CH₂)₂O.

2-Chloro-1,3,2-dioxaphospholane (**4**) reacts with α,β -unsaturated aldehydes only on the carbonyl group to form phosphorus-containing oligomers **53** with retention of the C=C bond.³⁹



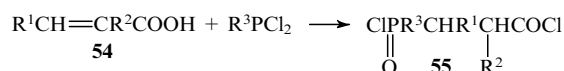
R = H, Me.

The distinction between the reactions of functionalised ketones **42** and **47** with HP and those of aldehydes **20** with phosphoromonochloridites from the reactions of other heterodienes with HP is that these α,β -unsaturated carbonyl compounds react analogously to saturated carbonyl compounds,⁶² i.e., they enter into O-phosphorylation reactions rather than into the [4 + 1]-cycloaddition reactions. In turn, HP act simply as the corresponding acid chlorides rather than as P(III) derivatives, the coordination number of the phosphorus atom in which is increased immediately in the reaction with (hetero)dienes (as in the case of [4 + 1]-cycloaddition reaction). It should be noted that in the formation of oligomers **53** the coordination number of the phosphorus atom increases to four only upon subsequent dioxaphospholane ring opening.

The system of the C=C–C=O bonds can be a fragment of a more extended conjugated cyclic system, e.g., *p*-benzoquinone and its anthraquinone type analogues. A few reactions of these compounds with HP have been documented; however, since they occur with involvement of the entire quinone system, we do not discuss them here and restrict ourselves to referring to the corresponding reviews.^{63, 64}

Numerous studies have been dedicated to reactions of HP with α,β -unsaturated acids and their derivatives. Several early studies have been reviewed.³

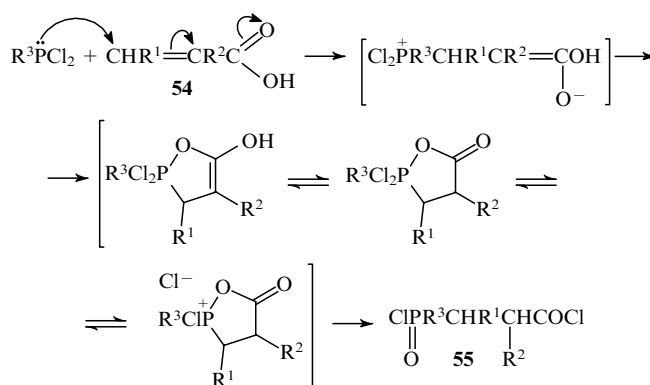
Reactions of HP with acids **54** can follow several pathways. Dihalides most often add to the acids **54** to form β -phosphinocarboxylic acid dichlorides **55**.^{65–77}



R¹, R² = H, Me; R³ = Me, Et, Ph, *p*-MeC₆H₄, 2-thienyl, EtO, Me₂(CCl₃)CO, CH₂Cl.

Two different mechanisms of this reaction have been proposed. According to the first of them, HP react with unsaturated acids **54** following the [4 + 1]-cycloaddition pathway, which most often is considered as stepwise, to give linear phosphoranes, which undergo the intramolecular Arbuzov rearrangement resulting in the final products **55** (Scheme 2).^{65, 66, 68, 71, 73, 76}

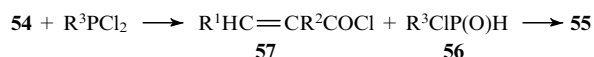
Scheme 2



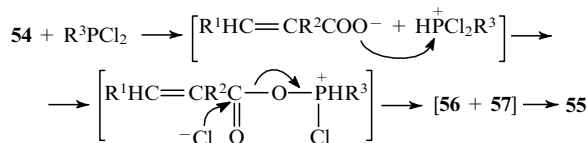
Here the P(III) atom acts as a nucleophile, since the higher the nucleophilicity of the R³ substituent the more readily the reaction proceeds.⁷⁶ However, this is also consistent with an alternative scheme involving no [4 + 1]-cycloaddition.

According to the alternative scheme,^{73, 75–79} (Scheme 3) the chlorine atom in the HP molecule and the hydroxyl group in the molecule of acid **54** exchange in the initial step. Then the hydrophosphoryl compound **56** that formed is added to the unsaturated acid chloride **57** according to the Pudovik reaction.^{80, 81}

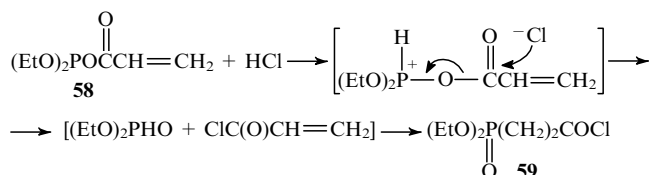
Scheme 3



It is believed⁸² that this scheme involves a preliminary stage of P-protonation of HP by the unsaturated acid **54**.



The presence of the hydrophosphoryl compound **56** and unsaturated acid chloride **57** in the reaction mixture is detected by NMR spectroscopy; sometimes it is possible to isolate these compounds. Moreover, compounds **56** and **57** do add to each other to give the final product **55**, which has been proved in a model reaction.^{77, 82} Scheme 3 is also consistent with increase in the reaction rate with the increase in the electron-donor ability of the substituents at the phosphorus atom. Finally, which is also proved by kinetic studies,⁷⁸ hydrogen chloride, which is always present in the reaction mixture, plays an important role in these reactions. In this connection it is noteworthy that diethyl acryloyl phosphite (**58**) protonated under the action of HCl rearranges into β -diethoxyphosphorylpropionyl chloride (**59**) in good yield. It is most likely that in this case the reaction follows the same sequence of stages as that discussed for the preceding scheme.⁸²



Thus, it can be considered as proved that P(III) acid dichlorides react with unsaturated acids **54** according to Scheme 3. However, this does not imply that the [4 + 1]-cycloaddition scheme is wrong and makes no contribution to the reaction under consideration.

The rate of the reaction of the α,β -unsaturated acids **54** with HP decreases if acids **54** contain α - and/or β -substituents.^{71, 76, 79} Moreover, only acid chlorides **57** can be isolated as the reaction products of ethyl(dichloro)phosphine with several β -substituted α,β -unsaturated acids.^{76, 83, 84}

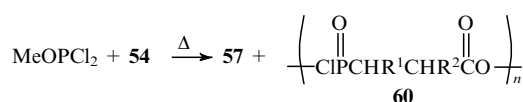


$\text{R}^1 = \text{Ph}, \text{HOOC}, \text{trans-Cl}, 2\text{-furyl}; \text{R}^2 = \text{H}.$

This fact is consistent with both reaction schemes proposed. According to Scheme 2, the phosphorus atom attack on the β -carbon atom of the acid **54** is the key reaction step. β -Substituents in the acid molecule produce steric hindrances, which only results in the formation of acid chlorides **57** from the carboxylic acid **54**. In the framework of Scheme 3, the attack on the carboxylic group in all cases is the initial and necessary stage. Obviously, if acid chlorides **57** contain substituents indicated in the scheme, the addition of ethyl(dichloro)phosphine to compounds **57** occurs very slowly due to both spatial shielding of the β -carbon atom and delocalisation of the electron density on the β -substituent and only these compounds can be isolated from the reaction mixtures.⁸²

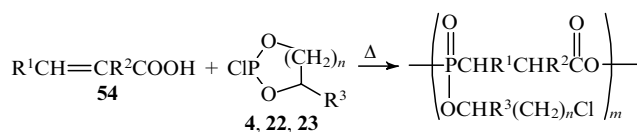
The reaction of dibutyl phosphorochloridite with acrylic acid at a reduced pressure gave only acryloyl chloride.⁷⁷

The acids **54** react with methyl phosphorodichloridite to give unsaturated carboxylic acid chlorides **57** and oligomers **60**.³⁴



$\text{R}^1, \text{R}^2 = \text{H}, \text{Me}.$

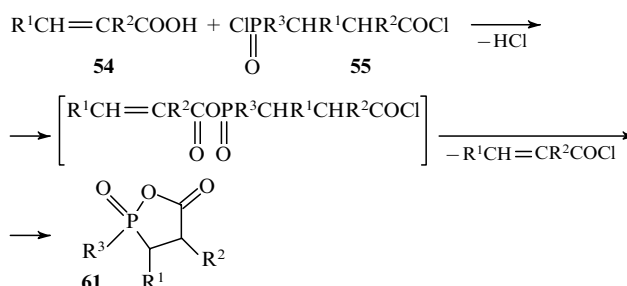
Only oligomeric products were isolated in the reactions of acids **54** with compounds **4**, **22** and **23**.^{39, 85}



$\text{R}^1, \text{R}^2, \text{R}^3 = \text{H}, \text{Me}; n = 1, 2.$

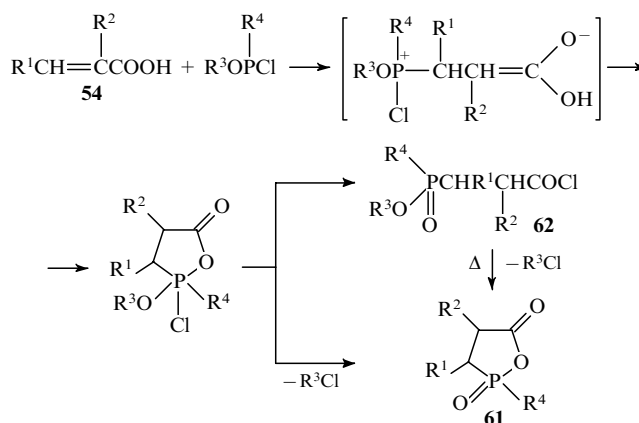
It was assumed^{34, 39, 85} that the reactions of the acids **54** and other (hetero)dienes with HP occur according to the [4 + 1]-cycloaddition mechanism and are followed by the Arbuzov rearrangement of the adduct containing a pentacoordinate phosphorus atom with the formation of oligomers. However, it was shown later that no adduct containing a P(V) atom is formed in the reaction of ethyl phosphorodichloridite with acrylic acid without heating the reaction mixture at very high temperatures. Therefore, the formation of oligomeric products in the reactions of HP with α,β -unsaturated acids was explained by thermal conversions of acid dichlorides **55** that were formed.⁷⁷ It should be noted that the formation of oligomers together with distillable addition products^{65, 68, 79} was also considered as a result of thermolysis of primary reaction products upon distillation.

2,5-Dioxo-1,2-oxaphospholanes **61** are occasionally isolated along with the products **55** in the reactions of P(III) acid dichlorides with acids **54**.^{86–89} These originate from mixed anhydrides formed as byproducts from acid dichlorides **55** and acids **54** and are produced on heating during distillation.^{71, 86}



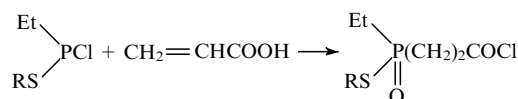
$\text{R}^1, \text{R}^2 = \text{H}, \text{Me}; \text{R}^3 = \text{ClCH}_2, 2\text{-thienyl}, 5\text{-chlorothieryl-2}, \text{Et}, p\text{-MeC}_6\text{H}_4.$

Oxaphospholanes **61** were also obtained in the reactions of phosphorochloridites and phosphonochloridites with the acids **54**. Their formation (as a result of elimination of alkyl chloride from intermediate addition products) competes with the formation of acyclic compounds **62** analogous to acid dichlorides **55**.^{75, 79, 82, 90–92} Either or both linear acid chlorides **62** and oxaphospholanes **61** were isolated under different conditions. Since cyclisation of acid chlorides **62** in the course of distillation can also result in the formation of the phospholanes **61**, it is unclear whether the latter are formed as a result of either or both direct reaction of HP with the acids **54** and thermolysis of the products **62**.



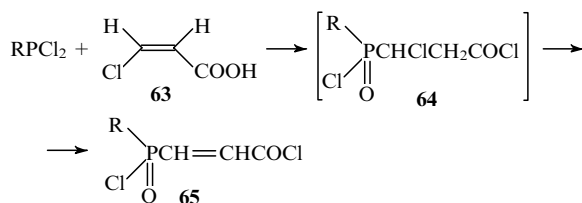
$\text{R}^1 = \text{H}; \text{R}^2 = \text{H}, \text{Me}; \text{R}^3 = \text{Et}, \text{Me}_2(\text{CCl}_3)\text{C}, (\text{ClCH}_2)_2\text{CH}, \text{ClCH}_2\text{CH}_2,$
 $\text{Cyclopentyl-CCl}_3; \text{R}^4 = \text{Et}, \text{Ph}, \text{MeO}, \text{PhO}, \text{Me}_2(\text{CCl}_3)\text{CO}, \text{MeEt}(\text{CCl}_3)\text{CO}.$

Only linear products analogous to compounds **62** are formed in the reactions of alkyl phosphorochloridites with acrylic acid.⁹³ This is associated with the lesser tendency of the $\text{AlkS}-\text{P}$ group to undergo dealkylation as compared to the $\text{AlkO}-\text{P}$ group (see monograph⁹⁴).



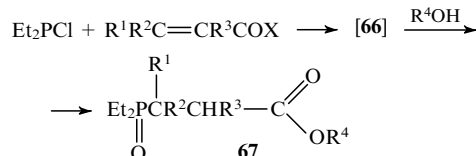
$\text{R} = \text{Et}, \text{Pr}^n, \text{Pr}^i, \text{Bu}^n, \text{Bu}^i.$

Reaction of dichlorophosphines with *cis*- β -chloroacrylic acid (**63**) occurs with elimination of HCl from intermediate compounds **64** to give unsaturated acid dichlorides **65**.⁷⁶



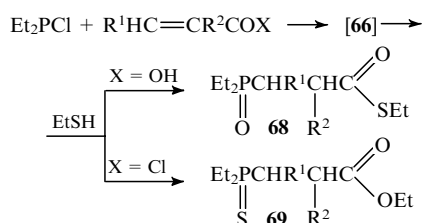
R = Me, Et, Ph.

The products of reactions of dialkyl(chloro)phosphines with α,β -unsaturated acids and their derivatives were not isolated and characterised after treatment with alcohols. For instance, diethyl(chloro)phosphine reacts with α,β -unsaturated acids or their chlorides to form crystalline adducts **66**, the structure of which is not established. Treatment of these adducts with alcohols gave phosphine oxides **67**.^{47, 73, 76, 95–97}



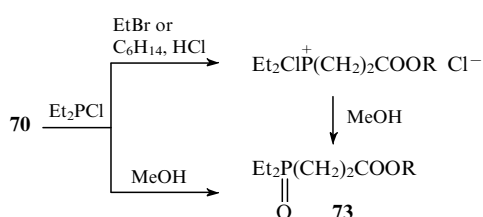
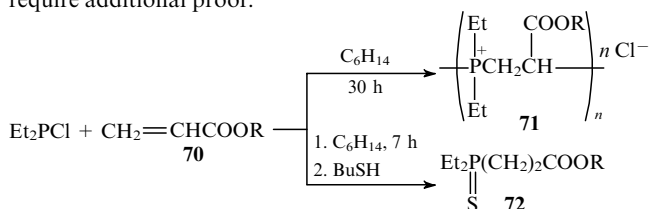
R¹, R², R³ = H, Me; R⁴ = Me, Et, Pr, Bu, C₅H₁₁; X = OH, Cl.

Treatment of the adducts **66** formed from acids (X = OH) and acid chlorides (X = Cl) with ethanethiol instead of alcohols gives phosphine oxides **68** containing a thioester group and phosphine sulfides **69**, respectively.⁹⁶



R¹, R² = H, Me; X = OH, Cl.

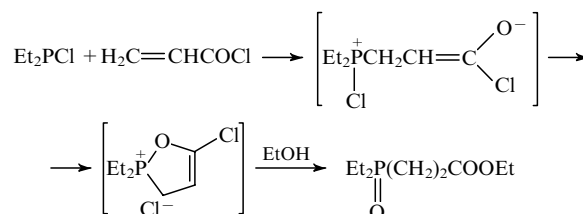
Reactions of alkyl acrylates **70** with diethyl(chloro)phosphine result in different products depending on the reaction conditions. For instance, polymers or oligomers **71** containing a quaternary phosphonium unit in the main chain are formed quantitatively in a hexane solution after 30 h. However, monomeric phosphine sulfides **72** can be isolated in high yields from the reaction mixtures after 7 h following treatment with butanethiol. The adducts formed in the reaction conducted in ethyl bromide (or in hexane, in the presence of HCl) and then treated with methanol decompose to give phosphine oxides **73**.⁹⁸ These contradictory results require additional proof.



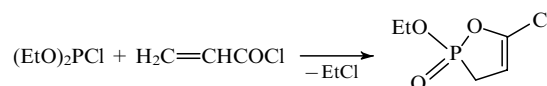
R = Me, Et, Bu.

It is believed that the mechanisms of reactions of unsaturated acids and their derivatives with diethyl(chloro)phosphine are the same or similar to those of their reactions with P(III) acid dichlorides.^{47, 73, 76, 95–97} However, it is likely that higher nucleophilicity of the phosphorus atom in diethyl(chloro)phosphine than in P(III) acid dichlorides favours [1 + 4]-cycloaddition. This assumption is confirmed by the fact that methyl acrylate readily reacts with diethyl(chloro)phosphine⁹⁸ where the formation of an intermediate hydrophosphoryl compound is impossible.

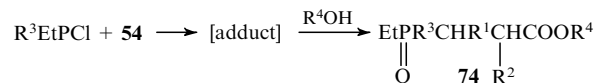
A similar mechanism was proposed⁹⁷ for the reaction of diethyl(chloro)phosphine with acryloyl chloride.



It is confirmed by preparative isolation of 5-chloro-2-ethoxy-2-oxo-3H-1,2-oxaphosphole from the reaction of diethylphosphorochloridite with acryloyl chloride.⁹⁷

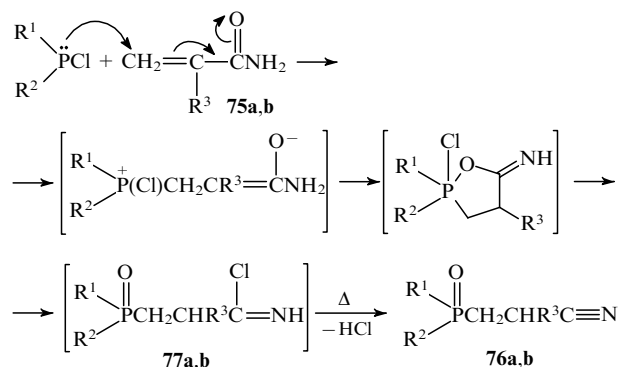


Other monochlorophosphines react with the acids **54** analogously to diethyl(chloro)phosphine. Treatment of initially formed adducts of unknown structure with alcohols results in their decomposition and the formation of phosphine oxides **74**.^{99, 100}



R¹ = H, Ph; R² = H, Me; R³ = (CH₂)₂CN, CH₂CH(Me)CN, CH₂CH=CH₂, 2-thienyl; R⁴ = Me, Et.

Acrylamide and methacrylamide (compounds **75a** and **75b**, respectively) react with various HP analogously to the corresponding acids. Nitriles **76a,b** resulting from dehydrochlorination of imidoil chlorides **77a,b** are the major reaction products.^{76, 99, 101–110}

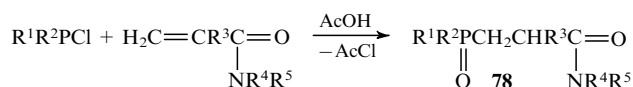


R¹, R² = Me, Et, Ph, Buⁱ, (CH₂)₂CN, CH₂CH(Me)CN, CH₂CH=CH₂,

OC(CCl₃)Me₂, OBU, OCH(CH₂Cl)₂, *p*-MeC₆H₄, CH₂Cl, Cl, 

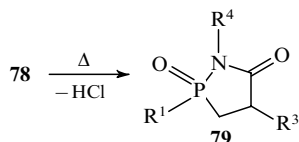
R³ = H (**a**), Me (**b**).

In the presence of acetic acid, HP react with primary and tertiary acrylamides to form compounds **78** with the amide group remaining intact.^{99, 100, 111, 112}



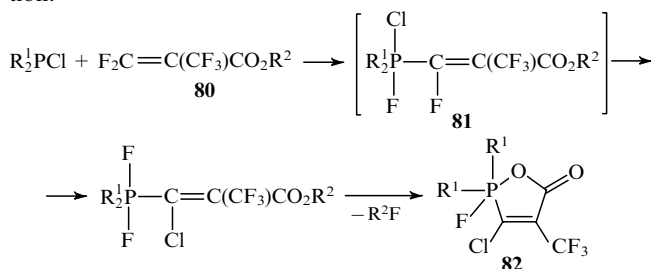
$R^1 = \text{Me, Et, Ph, } p\text{-MeC}_6\text{H}_4$; $R^2 = \text{Cl, Et, 2-thienyl, EtOOC(CH}_2)_2$, $\text{Me}_2(\text{CCl}_3)\text{CO}$; $R^3 = \text{H, Me}$; $R^4, R^5 = \text{H, Et, Pr}^i$.

In some instances, distillation of products **78** is accompanied by elimination of hydrogen chloride (probably, due to thermolysis) and the formation of 2,5-dioxo-1,2-azaphospholanes **79**.¹¹²



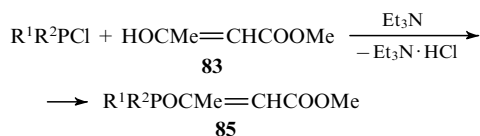
$R^1 = \text{Et, Ph}$; $R^2 = \text{Cl}$; $R^3 = \text{H, Me}$; $R^4 = \text{H, Bu, CH}_2=\text{CHCH}_2$; $R^5 = \text{H}$.

Halophosphines react with several other functional derivatives of acids in a somewhat different pathway. Reactions of dialkyl(chloro)phosphines with alkyl perfluoromethacrylates **80** occur with a characteristic replacement of a fluorine atom at the C=C bond to form an intermediate **81**. Then, the chlorine atom and a fluorine atom in compound **81** are exchanged. The reaction results in the formation of phosphines, which usually undergo cyclisation into 5-oxo-5*H*-1,2-oxaphospholes **82** in the isolation.¹¹³

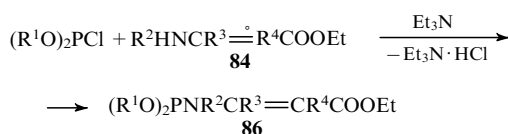


$R^1 = \text{Et, Me}$; $R^2 = \text{Me}$; $R^1 = \text{Pr}^i$, $R^2 = \text{Et}$.

β -Hydroxy derivatives **83**⁵² and β -amino derivatives^{51,60,114} of esters of α,β -unsaturated carboxylic acids **84** (enol tautomers of acetoacetic esters and β -aminocrotonates, respectively) react with P(III) monochlorides in the presence of triethylamine to undergo O- or N-phosphorylation without affecting the double bonds. The reaction occurs due to the presence of an acidic proton of the hydroxyl or amino group in the heterodiene and results in unsaturated phosphites **85** and **86**, respectively.

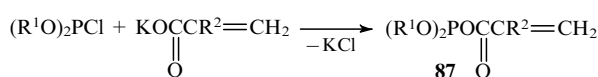


$R^1, R^2 = \text{EtO, Et}_2\text{N}$.



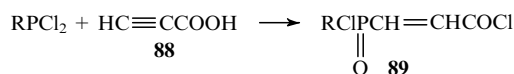
$R^1 = \text{Et, Pr}$; $R^2, R^3 = \text{H, Me}$; $R^4 = \text{H, CN}$.

Acrylates and methacrylates react with dialkyl phosphorochloridites in a similar way, *i.e.*, without affecting the heterodiene system. The reactions result in mixed anhydrides **87**, which are the products of O-phosphorylation.¹¹⁵



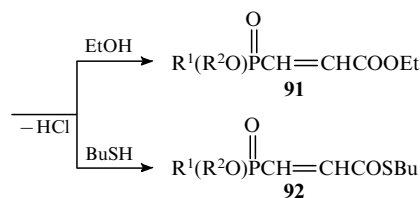
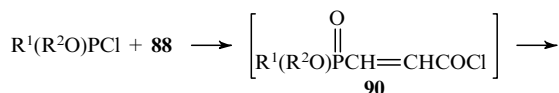
$R^1 = \text{Et, Pr, Bu}$; $R^2 = \text{H, Me}$.

α,β -Acetylenic acids also react with HP analogously to α,β -unsaturated acids. For instance, propiolic acid (**88**)^{70,76,116–118} reacts with dichlorophosphines to form unsaturated acid dichlorides **89** similar to the acid dichlorides **55**.

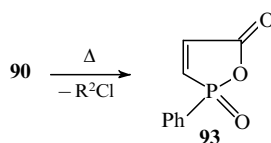


$R = \text{Et, ClCH}_2, \text{Ph}$.

When alkylphosphonochloridites were used in this reaction instead of dichlorophosphines, the products **90** were not isolated but rather were directly converted into diesters **91** by treatment with ethanol or into thioesters **92** by treatment with butanethiol. An attempt at distilling compound **90** [$R^1 = \text{Ph}$, $R^2 = \text{Me}_2(\text{CCl}_3)\text{C}$] resulted in isolation of a product of its cyclisation, *viz.*, 2,5-dioxo-5*H*-1,2-oxaphosphole **93**, which is an unsaturated analogue of phospholane **61**.¹¹⁹

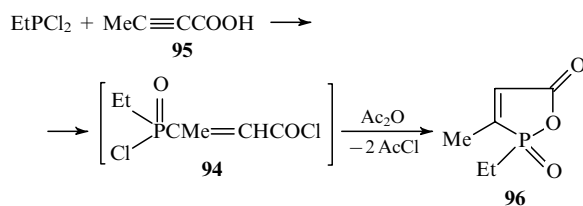


$R^1 = \text{Et, Ph, } p\text{-MeC}_6\text{H}_4$; $R^2 = \text{Me}_2(\text{CCl}_3)\text{C}$,  CCl_3 .



$R^1 = \text{Ph}$, $R^2 = \text{Me}_2(\text{CCl}_3)\text{C}$.

Treatment of an intermediate product **94**, obtained in the reaction of tetrolic acid (**95**) with ethyl(dichloro)phosphine, with acetic anhydride resulted in the 5*H*-1,2-oxaphosphole **96**.¹²⁰



III. Reactions with azadienes

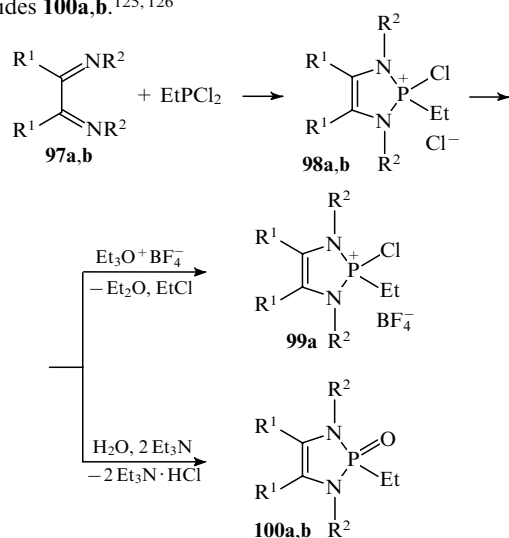
Investigation of reactions of HP with dienes containing one or several nitrogen atoms in the conjugation chain was begun recently. Most studies in this field were carried out in the late 1980's and the early 1990's. Currently, it is azadienes (among different types of heterodienes that react with HP) that attract the greatest attention of researchers. However, whereas the reactions of azadienes with dienophiles containing no phosphorus atom have long been studied and are well known (see, *e.g.*, a review¹²¹), almost no overview information concerning their reactions with phosphorus-containing dienophiles is available.

1. Reactions with α -diimines

Characteristic of α -diimines capable of adopting *s-cis*-conformation¹²² are [4 + 1]-cycloaddition reactions.^{121,123}

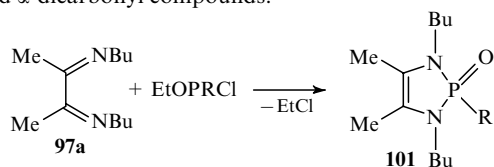
Diimines **97a,b** react with ethyl(dichloro)phosphine to form cyclic diaminophosphonium salts **98a,b**. It is convenient to isolate

them as the corresponding tetrafluoroborates **99a**¹²⁴ or phosphine oxides **100a,b**.^{125, 126}



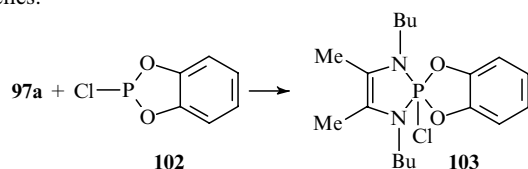
$\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Bu}$ (**a**); $\text{R}^1 - \text{R}^1 = (\text{CH}_2)_4$ (**b**).

Reactions of HP with *N,N'*-dibutylbiacetyldiimine **97a** occur to give 1,3-dihydro-1,3,2-diazaphospholes **101**.¹²⁷ The reaction occurs with dealkylation, as in the case of dienic hydrocarbons and α -dicarbonyl compounds.

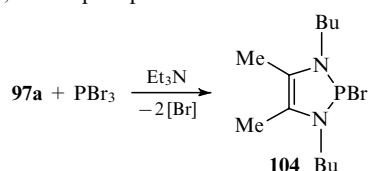


$\text{R} = \text{Cl}$, EtO , Et_2N .

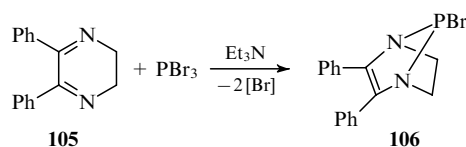
Reaction of 2-chlorobenzo-1,3,2-dioxaphosphole **102** with the diimine **97a** resulted in the phosphorane **103**.¹²⁸ An analogous product was obtained in the reactions of compound **102** with 1,3-dienes.



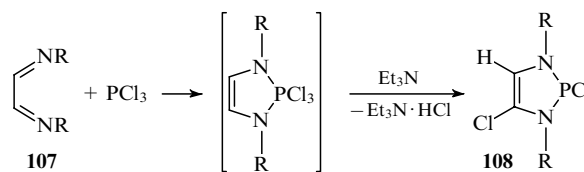
The reaction of the diimine **97a** with phosphorus trichloride results in resinification only.¹²⁸ However, its reaction with phosphorus tribromide in the presence of an organic base follows the [4+1]-cycloaddition pathway, and the reaction product is a tricoordinate phosphorus derivative, *viz.*, 2-bromo-1,3-dihydro-1,3,2-diazaphosphole **104**.¹²⁸



2,3-Diphenyl-5,6-dihydropyrazine (**105**) reacts with PBr_3 in an analogous manner to give a bridged product **106**.¹²⁹



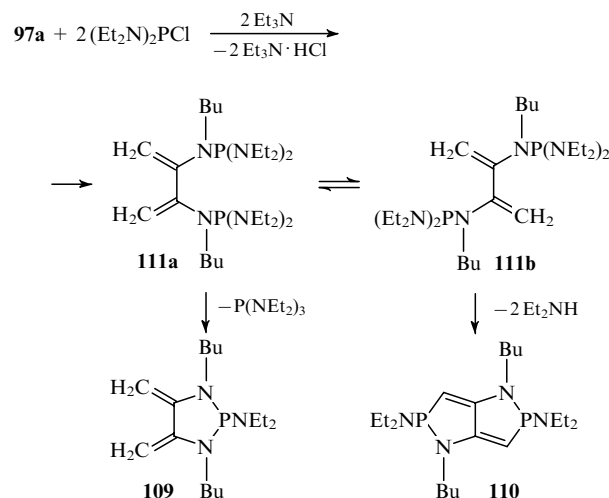
Reactions of glyoxal diimines **107** with PCl_3 in the presence of a base also follow the [4+1]-cycloaddition pathway to form tricoordinate phosphorus derivatives, *viz.*, 2,4-dichloro-1,3-dihydro-1,3,2-diazaphospholes **108** as the reactions products. Their formation can be rationalised by elimination of HCl from an intermediate cyclic adduct.^{128, 130, 131}



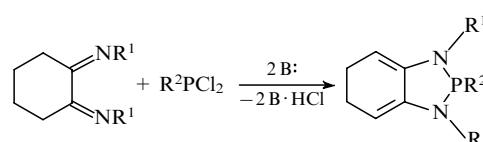
$\text{R} = \text{cyclo-C}_6\text{H}_{11}$, Bu^t .

Diimine **97a** reacts with tetraethylphosphorodiamidochloride in the presence of triethylamine¹³² to give a mixture of two 1,3-dienes, *viz.*, 1,3,2-diazaphospholane **109** with an exocyclic system of conjugated double bonds and bicyclic compound **110**.

It was assumed¹³² that N-phosphorylation of both imino groups followed by dehydrochlorination results in an intermediate diene **111** as a mixture of *s-cis*- (**111a**) and *s-trans*-conformers (**111b**) (analogously to the formation of phosphorylated enamines from imines of saturated aldehydes^{128, 133}). Then, the reactions of *cis*- and *trans*-forms of compound **111** follow different pathways. Elimination of tris(diethylamino)phosphine from the *s-cis*-form **111a** results in monocyclic diazaphospholane **109**. *s-trans*-Isomer **111b** is converted into diazadiphosphabicyclooctadiene **110** as a result of elimination of two molecules of diethylamine. The bicyclic compound **110** was isolated in an individual form, while the formation of phospholane **109** was proved by spectroscopic methods.¹³²

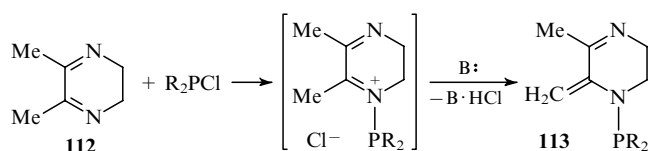


Reactions of PCl_3 and phosphorodichloridites with diimines containing an exocyclic system of double bonds in the presence of a base result in bicyclic 1,3,2-diazaphospholane derivatives containing a cyclohexadiene fragment. These reaction products are bicyclic analogues of the phospholanes **109**.¹²⁶



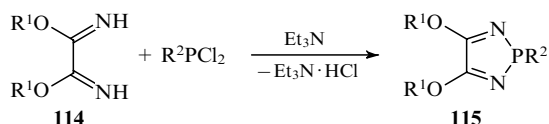
$\text{R}^2 = \text{Cl}$, AlkO , Alk_2N .

Reaction of 2,3-dimethyl-5,6-dihydropyrazine (**112**, a cyclic analogue of diimine **97**) with dialkyl(chloro)phosphines (alkyls were not specified) in the presence of a base occurs with the formation of monophosphorylated tetrahydropyrazine **113** containing one exocyclic methylene group,¹²⁹ which means that the reaction proceeded only on one $\text{C}=\text{N}$ bond.



R = Alk.

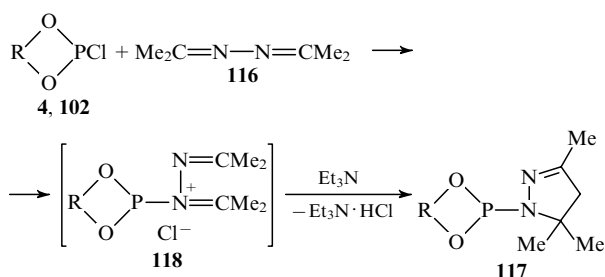
Reactions of dialkylloxalimides **114** with dichlorophosphines and phosphorodichloridites occur with elimination of two mobile protons to form derivatives of 1,3,2-diazaphospholes **115**,¹³⁴ i.e., compounds **114** undergo cyclisation without participation of the heterodiene system as such.



R¹ = Me, Et; R² = Bu, Ph, *p*-MeC₆H₄, *p*-ClC₆H₄, PhO, *p*-MeC₆H₄O, *p*-ClC₆H₄O.

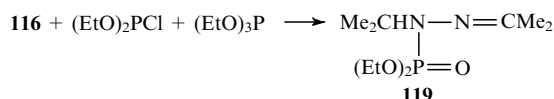
2. Reactions with azines

It was argued^{39, 135} that the reactions of cyclic phosphorochloridites with azines and with other conjugated systems proceed as [4 + 1]-cycloadditions; the 1,3,2-dioxaphospholane that forms undergoes ring opening according to the second stage of the Arbuzov reaction to give 3,5-dihydro-1,2,4-diazaphospholes. However, it was established later that dioxaphospholanes **4** and benzodioxaphospholes **102** react with acetoneazine (**116**) in the presence of triethylamine to form 3,5,5-trimethyl-4,5-dihydropyrazolophosphites **117**. Initially, electrophilic attack of the phosphorus atom on the nitrogen atom of ketazine **116** occurs, as in reactions of HP with imines.^{128, 133} The immonium salt **118** that forms undergoes the pyrazoline condensation to give the final product **117**.¹³⁶

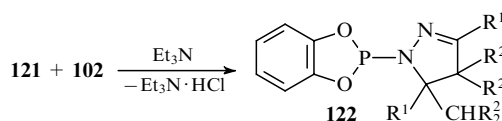
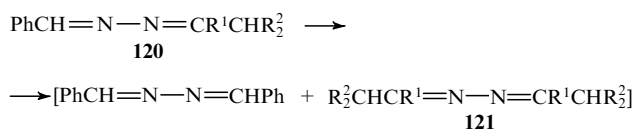


R = (CH₂)₂ (**4**), *o*-C₆H₄ (**102**).

Reaction of diethyl phosphorochloridite with acetoneazine **116** in the presence of triethyl phosphite only resulted in compound **119**, the product of addition of diethyl phosphite to one of the C=N bonds. The formation of pyrazolinophosphite **117** was detected only by spectroscopic methods.¹³⁷



Reactions of asymmetrical azines **120** with the phosphite **102** occur with symmetrisation of the azine in the initial step.¹³⁸ This process is accelerated by diethyl phosphorochloridite (a Lewis acid) present in the reaction mixture. The symmetrical azine **121** that forms then reacts with phosphite **102** analogously to acetoneazine **116** to form pyrazolinophosphites **122**.¹³⁷

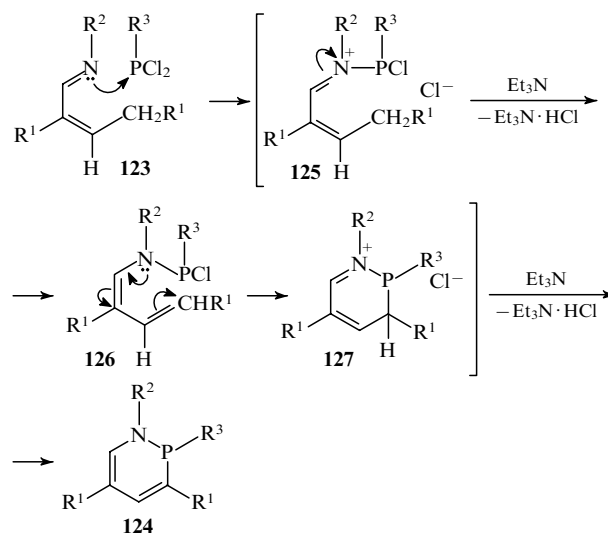


R¹, R² = H, Me.

3. Reactions with α-enimines

It was postulated¹³⁵ that α-enimines, as well as other 1,3-dienes and heterodienes, react with 1,3,2-dioxaphospholanes according to the [4 + 1]-cycloaddition pathway. However, the absence of any specific information on the products of these reactions makes one treat such an argument with precaution.

Reactions of enimes **123** with phosphorus trichloride or ethyl(dichloro)phosphine in the presence of an organic base^{139–141} result in 1,2-dihydro-1,2-azaphosphorinines **124**.

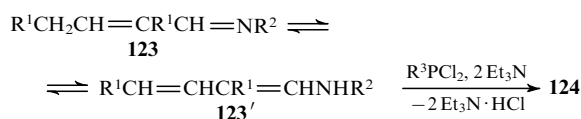


R¹ = Et, R² = Buⁿ, R³ = Cl, Et; R¹ = H, R² = Bu^t, R³ = Cl.

The reaction begins with electrophilic attack of the phosphorus trichloride or ethyl(dichloro)phosphine on the lone electron pair of the nitrogen atom of enime **123**, which results in an immonium salt **125** containing a P–N bond and a positive charge delocalised over the system of conjugated bonds. Then the first triethylamine molecule eliminates an acidic proton from the δ-carbon atom of the salt **125** to give an intermediate adduct **126**. This reaction is analogous to that leading to phosphorylated enamines from imines of saturated aldehydes and is similar to reactions resulting in the formation of heterodienes **111** and **118**.^{128, 133} Then, the closure of the six-membered ring containing the P–C bond occurs to form the intermediate **127** as a result of the intramolecular interaction of the phosphorus atom with the δ-carbon atom on which partial negative charge is localised due to conjugation with the lone electron pair of the nitrogen atom. The second molecule of the base eliminates hydrogen chloride from the intermediate **127**, which results in 1,2-dihydro-1,2-azaphosphorinine **124** as the final product.

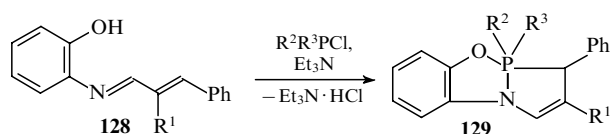
It was assumed¹⁴¹ that in this case the [4 + 1]-cycloaddition reaction cannot compete with the attack on the nitrogen atom due to kinetic control because of asymmetry of the enime molecule. In addition, the nitrogen atom in α-enimines is more nucleophilic than that in α-diimines, since two electronegative azomethine groups in the latter interact with each other to weaken the nucleophilicity of the nitrogen atom in each of them.

Butadienylamine **123'**, the possible existence of which has been discussed,¹²¹ is the minor tautomer of the enimine **123** and can also contribute to the formation of azaphosphorinine **124**.



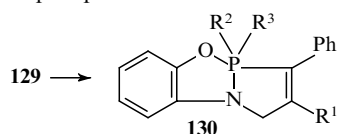
The similarity of behaviour of the enimes **123** and their oxygen analogue, crotonaldehyde, in reactions with HP in the presence of an organic base is obvious. These asymmetrical heterodienes can be represented by a general formula $\text{RCH}_2\text{CH}=\text{CRCH}=\text{Y}$ ($\text{Y} = \text{O}, \text{NAlk}$). In contrast to their symmetrical analogues, α -diimines and α -diketones, the above-mentioned heterodienes undergo phosphorylation at the nucleophilic centre Y rather than enter into [4 + 1]-cycloaddition reactions leading to the increase in the coordination number of the phosphorus atom.

However, reactions of functionalised enimes, *e.g.*, cinnamaldehyde *o*-hydroxyanils **128**, with P(III) chlorides proceed by [4 + 1]-cycloaddition, which precedes O-phosphorylation of the hydroxyl group or follows it. This reaction results in fused five-membered heterocyclic compounds **129** containing the pentacoordinate phosphorus atom.¹⁴²



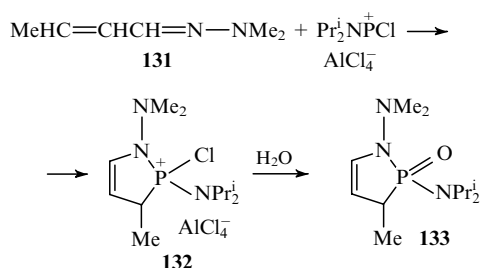
$\text{R}^1 = \text{Me}$; $\text{R}^2-\text{R}^3 = \text{MeN}(\text{CH}_2)_2\text{NMe}$; $\text{R}^1 = \text{H}, \text{Me}$; $\text{R}^2 = \text{R}^3 = \text{Me}$, Ph, OMe ; $\text{R}^2-\text{R}^3 = \text{O}(\text{CH}_2)_2\text{O}, o\text{-C}_6\text{H}_4\text{O}_2$.

As in the case of reactions of dienes with HP,⁴⁻⁷ tricyclophosphoranes **129** can have structural isomers as a result of the double bond migration in azaphosphole (prototropism), and geometric isomers due to pseudorotation.¹⁴³ For instance, if amino groups are bonded to the phosphorus atom, the primary reaction product **129** undergoes partial [for $\text{R}^2-\text{R}^3 = \text{MeN}(\text{CH}_2)_2\text{NMe}$] or complete (for $\text{R}^2 = \text{R}^3 = \text{NMe}_2$) rearrangement into a thermodynamically more stable isomer **130**. The latter is isolated as the final reaction product of compounds **128** with bis(dimethylamino)-chlorophosphine.

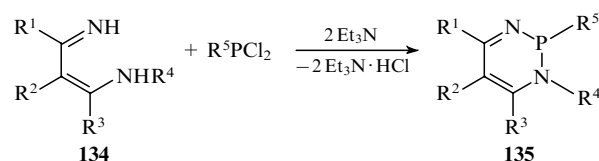


$\text{R}^1 = \text{Me}$; $\text{R}^2-\text{R}^3 = \text{MeN}(\text{CH}_2)_2\text{NMe}$, $\text{R}^2 = \text{R}^3 = \text{NMe}_2$.

Reaction of diisopropylamino(chloro)phosphonium tetrachloroaluminate with crotonaldehyde dimethylhydrazone (**131**)¹⁴⁴ proceeds as a classical [4 + 1]-cycloaddition and is analogous to reactions with 1,3-dienes²⁸⁻³⁰ and α -dicarbonyl compounds;²⁷ this results in cyclic phosphonium salt **132**, which is hydrolysed to give 2-oxo-1,2-dihydro-3*H*-1,2-azaphosphole **133**.



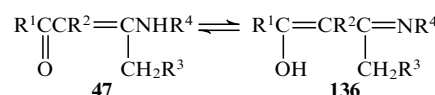
Aminoenimes **134** react with P(III) chlorides in the presence of triethylamine. Their cyclisation occurring with elimination of two HCl molecules results in 1,2-dihydro-1,3,2-diazaphosphorinines **135**,¹⁴⁵ like the reaction of dialkylloxalimides with dichlorophosphines leading to derivatives of 1,3,2-diazaphospholes (see Section III.3).



$\text{R}^1 = \text{H}, \text{Me}$; $\text{R}^2, \text{R}^4 = \text{Ph}, p\text{-MeC}_6\text{H}_4, \text{cyclo-C}_6\text{H}_{11}$; $\text{R}^3 = \text{H}, \text{Ph}$; $\text{R}^5 = \text{Ph}, \text{Cl}$.

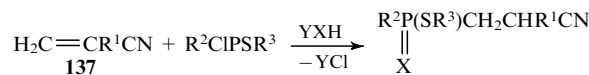
This is an example of synthetic procedures used for the preparation of nitrogen heterocycles based on azadienes, which has been discussed in detail.¹⁴⁶⁻¹⁴⁸

Reactions of HP with enamino ketones **47**, which are nitrogen analogues of β -diketones, were considered in Section II.2.a; however, these can also be discussed in this Section. Indeed, compounds **47** can also exist in the imine form **136**.¹⁴⁹



Tautomers **47** and **136** can react with HP concurrently to give the same final products.

Finally, reactions of HP with heteroenyne $\text{C}=\text{C}-\text{C}\equiv\text{N}$ systems are formally similar to the reactions of HP with enimine $\text{C}=\text{C}-\text{C}=\text{N}$ systems considered in this Section. Acrylo- and methacrylonitriles **137** react with alkylphosphonochloridothioites in the presence of proton donors according to the scheme:⁴⁶

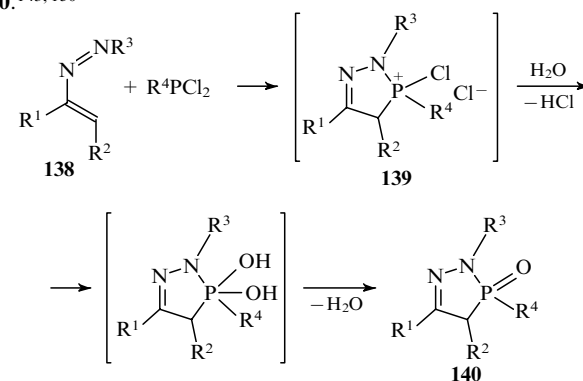


$\text{R}^1 = \text{H}, \text{Me}$; $\text{R}^2 = \text{Et}, \text{Ph}$; $\text{R}^3 = \text{Et}, \text{Pr}, \text{Bu}$; $\text{X} = \text{O}, \text{S}$; $\text{Y} = \text{H}, \text{Ac}$.

These reactions are analogous to those of compounds **30** with α, β -unsaturated ketones in the presence of proton donors and follow the same mechanism (see Section II.2.a).

4. Reactions with azoalkenes

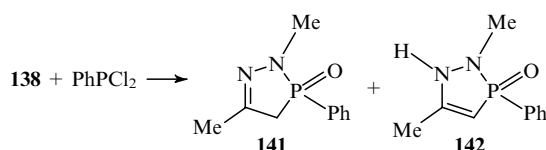
Dichlorophosphines react with azoalkenes **138** to give [1 + 4]-cycloaddition products, *viz.*, cyclic phosphonium salts **139**. Hydrolysis of compounds **139** results in a mixture of stereoisomers, *viz.*, 3-oxo-2,3-dihydro-4*H*-1,2,3-diazaphospholes **140**.^{143, 150}



$\text{R}^1 = \text{Me}, \text{Ph}, \text{Bn}$; $\text{R}^2 = \text{H}, \text{Me}, \text{Ph}$; $\text{R}^3 = \text{Me}, \text{Ph}$; $\text{R}^4 = \text{Me}, \text{Ph}, \text{Bu}^t, \text{Bn}, o\text{-ClC}_6\text{H}_4, p\text{-MeC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4$.

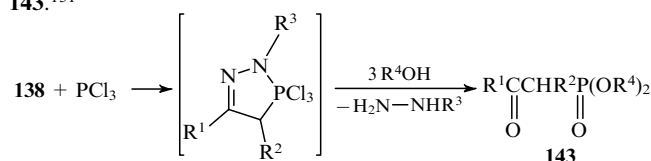
Reaction of the azoalkene **138** ($\text{R}^1 = \text{R}^3 = \text{Me}, \text{R}^2 = \text{H}$) with PhPCl_2 results in a mixture of products with different position of

the double bond, *viz.*, 2,3-dihydro-4*H*- and 1*H*-1,2,3-diazaphospholes (**141** and **142**), as is observed for isomerisation of phosphoranes **129** into phosphoranes **130**.



An analogous double bond migration in the ring is also often observed for phospholes formed in reactions of HP with dienic hydrocarbons.^{5,6}

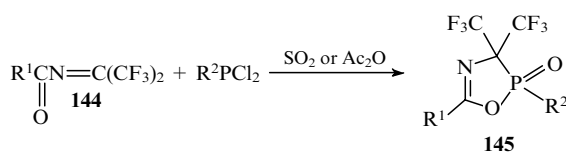
The azoalkenes **138** react with PCl_3 to give diazaphosphole intermediates; treatment of the latter with alcohols causes elimination of a hydrazine fragment to form β -oxo phosphonates **143**.¹⁵¹



$\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Me, Ph; R}^4 = \text{Me, Et, Ph; R}^1\text{--R}^2 = (\text{CH}_2)_4$;
 $\text{R}^3 = \text{R}^4 = \text{Me}$.

IV. Reactions with oxazadienes

Reactions of HP with 1,3-oxaza-1,3-dienes (*N*-acylketimines) **144** follow the [4+1]-cycloaddition pathway to give 5-oxo-4,5-dihydro-1,3,5-oxazaphospholes **145**.¹⁵²

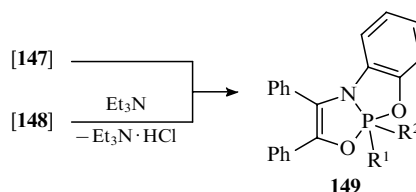
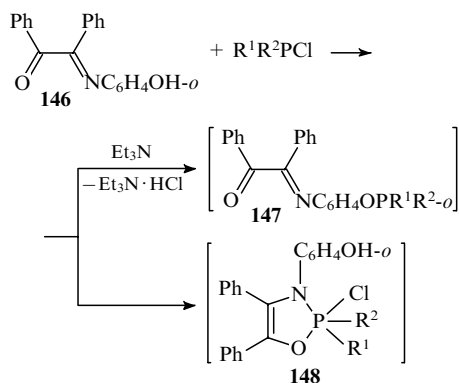


$\text{R}^1 = \text{CF}_3, \text{OEt; R}^2 = \text{Me, OEt}$.

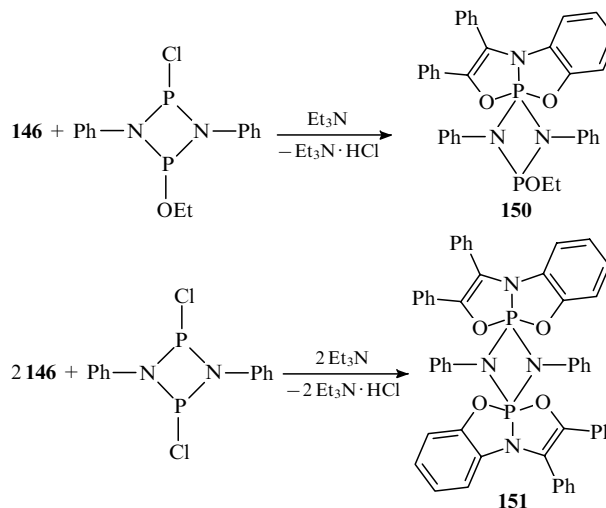
The reaction proceeds only in the presence of acetic anhydride or sulfur dioxide. Trialkyl phosphites¹⁵³ react according to the same scheme without these additives.

Halophosphines can be added to 1,4-oxaza-1,3-dienes (monimines of α -diketones) as has been exemplified in benzyl *o*-hydroxyanil (**146**).^{154,155} The latter reacts with different HP with the formation of intermediate compounds **147** and **148**, which are then transformed into polycyclic phosphoranes **149** or diphosphethanes **150** and **151**.

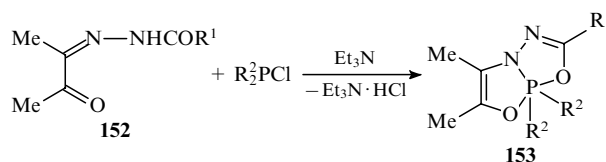
The key stage of this reaction is [4+1]-cycloaddition, which precedes phosphorylation of the hydroxyl group and/or follows it.



$\text{R}^1, \text{R}^2 = \text{Me, Ph, OMe, OPh, OCH}_2\text{Ph, NMe}_2$; $\text{R}^1\text{--R}^2 = \text{O}(\text{CH}_2)_2\text{O, O}(\text{CH}_2)_3\text{O, S}(\text{CH}_2)_3\text{S, } o\text{-C}_6\text{H}_4\text{O}_2, \text{MeN}(\text{CH}_2)_2\text{NMe}$.



Biacetyl acylmonohydrazones **152** react analogously. As in the case of oxazadiene **146**, the final bicyclic dioxadiazaphosphoranes **153** result from [4+1]-cycloaddition and O-phosphorylation.¹⁵⁴



$\text{R}^1 = \text{Me, Ph, Bn; R}^2 = \text{Me, Ph}$.

V. Conclusion

Though certain judgements on the mechanisms of the reactions considered in this review cannot be called indisputable, summing up the above information makes it possible to state that, despite the variety of types of HP, heterodienes, and the products that formed, the initial steps of these reactions belong to three types:

- (1) 1,4-addition reaction, in particular, [4+1]-cycloaddition reaction (concerted or stepwise);
- (2) reaction involving one of the multiple bonds of a heterodiene; and
- (3) reaction without participation of multiple bonds.

Differences in the structure of the final products formed in each of these three types of reactions are determined by further transformations of the primary reaction products.

Most often the reactions under consideration follow the [4+1]-cycloaddition pathway to give usually cycloadducts containing the pentacoordinate phosphorus atom. In some instances, it is possible to isolate them or to detect them by spectroscopic methods. However, [4+1]-cycloaddition reactions of HP with α -diketones, their diimines and mono-*o*-hydroxyanils, α,β -unsaturated ketones, azoalkenes and 1,2-oxazadienes result in various five-membered phosphole-type heterocycles containing P(III), P(IV) or P(V) atoms as the final products. α,β -Unsaturated carboxylic acids and their derivatives also react with HP according

to this scheme (not always) to give acyclic compounds. In some instances, linear products are also formed from unsaturated carbonyl compounds.

If only one of two double bonds of the heterodiene system is involved in the reaction with HP in the initial stage, the second double bond can be either involved in further transformations or left intact. This occurs in the reactions of HP with different types of heterodienes in the presence of organic bases, *e.g.*, in the reactions with crotonaldehyde and enamines, which are nitrogen analogues of α,β -unsaturated aldehydes. Unlike their symmetrical analogues (α -diketones, α -diimines), enamines do not enter into [4 + 1]-cycloaddition reactions, which result in an increase in the coordination number of the phosphorus atom, since HP react with their nucleophilic centre (the oxygen or nitrogen atom) thus phosphorylating it. Reactions of several cyclic α -diimines (dihydropyrazines) and azines proceed analogously involving one C=N bond. The same occurs in the reaction of tetraethylphosphorodiamidochloridite with acyclic α -diimine: each of the C=N bonds reacts independently. Usually, the alkyl group adjacent to the double bond is inert and left intact in the first reaction stage; the involvement of such a group in the reaction is one of the peculiarities of the reactions of HP with heterodienes in the presence of an organic base. Under the action of a base, proton abstraction from these groups occurs, which results in the formation of a new double bond and/or in the closure of phosphorus-containing rings. Reactions involving one of the double bonds can also occur in the absence of a base and, correspondingly, without dehydrohalogenation. For instance, unsaturated aldehydes react with 2-chloro-1,3,2-dioxaphospholane at the C=O bond, which results in the formation of phosphorus-containing oligomers. Perfluoromethacrylates react with dichlorophosphines only at the C=C bond leaving the ester group intact. It is possible to consider the reactions of α,β -unsaturated acids with HP as those occurring at the C=C bond if they proceed *via* exchange of the chlorine atom by the hydroxyl of the carboxy group followed by reaction between hydrophosphoryl compound and unsaturated acid chloride that formed according to the Pudovik reaction. Alkylphosphonochloridothioites react analogously with α,β -unsaturated ketones in the presence of proton donors.

Finally, reactions of several heterodienes (capable of eliminating one or two protons in the presence of an organic base) and salts of α,β -unsaturated carboxylic acids with HP proceed without participation of conjugated bonds at all. These reactions result in the formation of phosphorylation products. In these cases, HP behave as ordinary acid halides. If the phosphorus atom carries appropriate substituents, the phosphorylated heterodiene that formed can enter into further intramolecular reactions. These involve the diene system and result in its cyclisation. Acyclic P(III) derivatives initially obtained from HP and enol tautomers of β -diketones or their nitrogen analogues react in such a manner.

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Magnetic force microscopy

I V Yaminsky, A M Tishin

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Abstract. Principles of the operation of the magnetic force microscope are considered. The main areas of application of magnetic force microscopy are characterised. The prospects are shown of using this method for solving problems of materials science, including the most topical problem, *viz.*, the creation of magnetic recording media with ultrahigh recording density. Unique potentials for investigation of nanostructures using a combination of magnetic force microscopy with electron spin resonance and nuclear magnetic resonance are pointed out. Primary attention is focused on the description of experimental techniques. The bibliography includes 27 references.

I. Introduction

The interest in magnetic force microscopy is due to its unique potential, which makes it possible to solve the problems of both basic and applied investigation, *e.g.*, the development of modern nanotechnologies. In chemistry, magnetic force microscopy is indispensable in the studies of the morphology, structure and properties of nanocomposites with magnetic inclusions. Magnetic force microscopy is of particular significance in the studies of magnetic properties of nanostructures, in particular, in the search for size and quantum effects. Magnetic force microscopy combines a modern technique of magnetic measurements with the unique potentials of probe microscopy.

The first probe microscopes, *viz.*, scanning tunnelling microscope, made it possible to investigate conducting surfaces and to perform their targeted modification on an atomic and molecular level.¹ This type of microscope has become an ancestor of a family of probe microscopes, among which the atomic force microscope² and its modifications³ are most often used.

In a scanning probe microscope there is a microprobe (a tip) with the help of which the precision mechanical system scans the surface. Simultaneously, the control unit of the microscope detects specified characteristics of the interaction between the probe and the surface under study. This can be the tunnelling

current between the metal tip and the surface of a conductor in the case of the tunnelling microscope and the force of the interaction between the sharpened tip made of a hard material and the surface of the sample for an atomic force microscope. The atomic force microscope is in essence a sensitive profilometer, *i.e.*, an instrument for measuring the roughness and topography of the surface, and in a sense it can be considered as a 'distant relative' of a phonograph with a diamond tip.

Tunnelling and atomic force microscopes have a spatial resolution better than 1 Å, *i.e.*, these make it possible to observe individual atoms and molecules on the surface of various materials. The images of different surfaces obtained using scanning tunnelling and atomic force microscopes⁴ are shown in Figs 1 and 2 as examples.

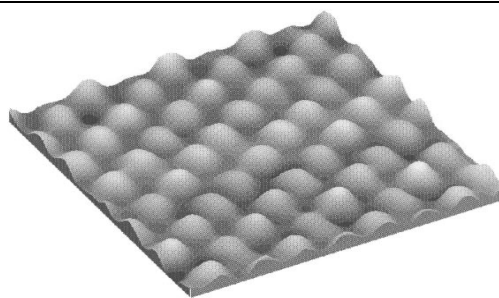


Figure 1. The surface of pyrolytic graphite.

The size of the area scanned is $2 \times 2 \text{ nm}^2$; a 'Scan-8' scanning tunnelling microscope developed by the 'Advanced Technologies Centre' (Moscow, Russian Federation) was used.

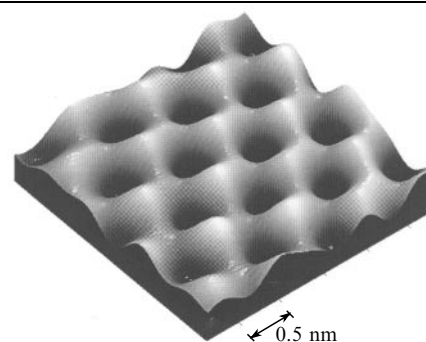


Figure 2. The surface of mica.

An NanoScope atomic force microscope (Digital Instruments, USA) was used.

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Martin and Wickramasinghe⁵ have improved the atomic force microscope in order to investigate magnetic properties of the surface with submicron spatial resolution. It was proposed to use a microneedle made of ferromagnetic material as a probing tip for measuring the magnetic force experienced by this micro-magnet in the vicinity of the surface of a magnetic specimen. This modification of the atomic force microscope is called the magnetic force microscope. Further stages in the development of magnetic force microscopy have been repeatedly documented (see, e.g., Grütter *et al.*⁶).

Let us consider specific features of the operation of the atomic force and magnetic force microscopes in detail. The highest (atomic or molecular) spatial resolution is achieved if the atomic force microscope operates in the contact mode where the tip contacts the surface of the specimen under study. The resolution achieved in different 'tapping' modes is, as a rule, somewhat worse than in the preceding case. However, stable atomic resolution can also be achieved in the 'tapping' mode, *viz.*, in ultrahigh vacuum.⁷ In the 'tapping' mode, a springy microconsole (a cantilever) on which the tip is mounted oscillates at a resonant frequency in the vicinity of the surface of the specimen. A cantilever is a mechanical resonator similar to a miniature tuning-fork. As the cantilever approaches the surface, the force action of the surface can cause additional damping of the oscillations of the cantilever. Under conventional laboratory conditions, the viscosity of air and the presence of adsorbed water film on the surface negatively affect the accuracy of measurements. Measurements *in vacuo* are free of these perturbing factors, which makes it possible to maintain the force of the interaction between the probe and the sample at a minimum level and thus to improve the spatial resolution up to the atomic level.⁸

In the contact-free mode, the forces acting on the tip of the atomic force microscope are due to the van der Waals interaction.

In the magnetic force microscope, the tip experiences an additional action of magnetic forces. As the tip is raised above the surface to a height of 10 to 50 nm, the universal van der Waals attraction almost completely vanishes and the tip is mainly affected by magnetic forces. In this case, it is the magnetic interaction that causes the deviation of the tip from rectilinear motion (Fig. 3). Because of its small size, the tip of the magnetic force microscope can be approximated by a magnetic dipole. The force F acting on the tip is determined by the following relationship

$$F = m_0 \text{grad} H, \quad (1)$$

where m_0 is the magnetic moment of the tip and H is the magnetic field strength.

A magnetic microinclusion in the specimen will produce a magnetic field, the strength of which at a distance R is

$$H(R) = \frac{3r(\mathbf{r}m) - m}{R^3}, \quad (2)$$

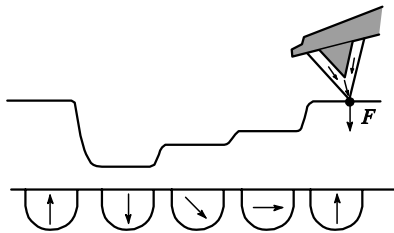


Figure 3. A diagram illustrating the action of a magnetic force on the microtip of the magnetic force microscope. The orientation of magnetic domains on the surface of the sample is shown by arrows in the bottom part.

where $\mathbf{r}$ is the unit radius-vector along the specified direction and m is the magnetic moment of the microinclusion.

Taking into account Eqns (1) and (2), the force of the interaction between the microscope tip and the magnetic microinclusion is

$$F = \text{grad} \left[\frac{3(\mathbf{r}m)^2 - mm_0}{R^3} \right]. \quad (3)$$

Relation (3) can be used for approximate calculations. Let us assume that both dipole moments have the same vertical orientation along the direction of the z axis. Then the force of the interaction between them is

$$F_z = -\frac{6m_0m}{z^4},$$

and the force field gradient is

$$\frac{dF_z}{dz} = \frac{24m_0m}{z^5}.$$

For instance, for two iron microparticles with diameters 10 nm ($m_0 = m \simeq 9 \times 10^{-29}$ A m²) located at a distance of 10 nm, the magnetic force of the interaction is $\sim 4.9 \times 10^{-11}$ N and the force gradient is $\sim 1.9 \times 10^{-2}$ N m⁻¹. It is this order of magnitude of the values that are detected by the magnetic force microscope.

Comparative analysis of different methods used to study magnetic properties of the surface shows that magnetic force microscopy is highly sensitive to the magnetic flux (at a level of 10^{-4} T) and makes it possible to achieve a unique spatial resolution as compared to that obtained by other methods of magnetic measurements.⁹ The sensitivity of the magnetic force microscope to the magnetic flux is only slightly lower than that of the SQUID-based scanning microscope.¹⁰

II. The principle of operation of magnetic force microscope

A block diagram of the mechanical part of a magnetic force microscope is shown in Fig. 4a. The specimen is mounted on a piezoscanner, which provides spatial movement of the specimen along the three coordinate axes. Usually, the piezoscanner is a thin-walled tube made of piezoceramics coated with a system of metal electrodes. The electric voltage applied to the electrodes changes the geometric size of the tube because of the inverse piezoelectric effect. The piezoscanner is characterised by a high

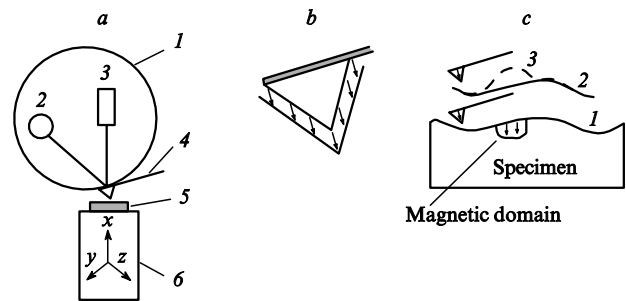


Figure 4. A block diagram of the mechanical system of a magnetic force microscope (a), the cantilever tip coated with a ferromagnetic material (b) and the trajectory of the motion of the microtip (c); (a): (1) small displacement; (2) photodetector; (3) laser; (4) cantilever; (5) specimen; and (6) piezoscanner; (c): (1) trajectory in the course of recording the surface profile; (2) trajectory in the course of recording the magnetic profile; and (3) deviations from the selected trajectory caused by the interaction between the microtip and a magnetic domain in the specimen.

mechanical rigidity and, hence, it is insensitive to seismic and acoustic interferences, simple to control and has a long lifetime. It is these advantages that have determined wide use of this design of the piezoscanner in actual microscopes. Errors of movements, which are due to, *e.g.*, nonlinearity of the properties of the material of the piezoscanners are the drawbacks of this type of piezoscanner. However, the errors of the movement of the object under study can be reduced by software control, *viz.*, by applying a controlling voltage to the electrodes of the piezoscanner in accordance with special correcting algorithms. In metrological systems, additional capacitive or optical transducers are used; they provide the linear movement of the specimen in the range from 1 to 250 μm in the plane of the specimen (along the x and y coordinates) and from 1 to 15 μm normal to this plane (along the z coordinate) for different piezoscanners.

In a magnetic force microscope, the cantilever is above the specimen. The magnetic force F acting on the tip causes a bending of the cantilever and a vertical movement of the tip (Fig. 4*b*). According to Hooke's law, this movement is determined by the mechanical rigidity of the cantilever (by the spring constant) lying typically in the range from 0.1 to 10 N m^{-1} .

Bending of the cantilever is detected using a small displacement transducer. Among different transducers (capacitive, inductive, tunnelling, *etc.*), optical sensors have found the widest practical use. They detect angular deflection of the light beam reflected from the surface of the cantilever. A laser beam is focused on the reflecting surface of the free (unfastened) end of the cantilever and the changed position of the reflected beam, indicating a bending of the cantilever, is determined by a split photodiode.

When scanning the specimens under actual experimental conditions (the relative displacement of the probe and the surface under study), the probe successively scans each surface area and the electronics detects the total force of the interaction in the probe-sample system. The results of measurements, displayed after processing of the data, are three-dimensional (3D) images of the surface. If the bending of the cantilever is maintained constant during the scanning process, the images obtained correspond to the surfaces of constant force. This mode is called a 'constant force' mode. In the 'deflection mode' the cantilever moves in the horizontal plane above the specimen and the bending of the cantilever is detected, which is proportional to the force acting on the tip.

When scanning a rough surface, the contribution from the topography should be separated from that of the magnetic forces. To this end, the tip scans the same surface area twice. For the first pass, it moves contacting the surface of the specimen and the trajectory of the movement of the tip, which corresponds to the profile of the surface under study, is stored in a computer. The magnetic properties of the specimen (neglecting the surface deformations, which are small, as a rule) have no effect on the observed trajectory. For the second pass, the microconsole moves along the known trajectory above the same surface area without contacting the specimen. In this case, the tip is affected by long-range forces rather than by contact forces, as in the first case. The deviation of the tip from the specified trajectory depends on the magnetic properties of the specimen (Fig. 4*c*). In actual experiments, to achieve the maximum sensitivity, oscillations are induced of the cantilever at a natural resonant frequency and the tip also scans the specimen twice, *viz.*, first in the 'tapping' mode and then in the free oscillations mode at some distance from the surface. Recording the amplitude, phase or frequency of the oscillations provides more precise information on the magnetic inclusions (domains, clusters) in the specimen under study.

III. Areas of application of magnetic force microscopy

Magnetic force microscopy is used in the creation of materials for magnetic recording media [magnetic tapes, hard ('Winchester')

disks, magneto-optical disks,^{11, 12 *etc.* 13}], in the optimisation of the recording modes of magnetic heads,¹⁴ in the studies of the structure and properties of nanoparticles, alloys,¹⁵ nanocomposites and thin films,¹⁶ in the development of the methods for magnetic recording with ultrahigh density,¹⁷ in the studies of superconductors as well as in biological and geophysical studies. This makes it possible to observe single magnetic domains whose sizes vary from several nanometres to several tens of nanometres.

For instance, the formation of Ni particles on a quartz glass (silicon dioxide) resulting from autocatalysis of an 'island' Ni film upon annealing (at 800 °C) in an atmosphere of hydrogen was studied.¹⁸ Using magnetic force microscopy, it was shown that particles with sizes from 40 to 100 nm are single domain particles (Fig. 5), which agrees well with theoretical estimates.

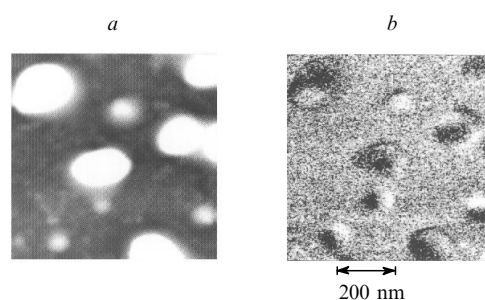


Figure 5. A microtopographical (*a*) and the corresponding magnetic (*b*) image of Ni particles.

Magnetic force microscopy has found an important application in the development of novel methods for magnetic recording with ultrahigh density: the leading manufacturers of magnetic recording media make wide use of commercial magnetic force microscopes in the steps of design and quality control of finished products.

In Fig. 6, a topographical profile of a fragment of a surface of a magneto-optical disk (the dark lines seen are rectilinear micro-recesses, Fig. 6*a*) and a magnetic image of the microstructure of magnetised domains on the surface are shown. Elongated islands of dimensions $2 \times 1 \mu\text{m}^2$ corresponding to recording of one data bit (Fig. 6*b*) are fairly clearly seen. The domain structure of the magnetic film in the area of recesses (light longitudinal strips) is also visible. Magnetic force microscopy makes it possible to distinguish single grains of size 50 nm. The magnetic structure of the surface is intensively studied in research laboratories of the leading manufacturers of recording media in order to minimise the surface area corresponding to one data bit and to solve the problems of noise immunity, noise reduction during the recording and reproduction of the data. The results of these investigations are used in the development of novel principles and devices for magnetic and magneto-optical recording. We note that it is the use

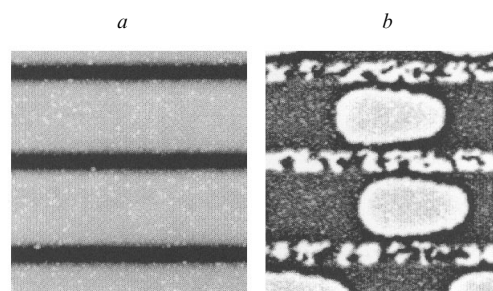


Figure 6. The surface of a disk of size $5 \times 5 \mu\text{m}^2$ consisting of microtracks separated by longitudinal recesses (*a*) and the magnetic structure of the same surface (*b*).

of modern methods of investigation such as magnetic force microscopy that made it possible to provide a virtually exponential increase in the magnetic recording density on magnetic and magneto-optical disks in recent years. Currently, the storage capacity of hard disks can be as high as 20 Gbytes and even more.

In Fig. 7, a magnetic 'image' is shown of lithographically patterned Co metal particles.¹⁹ The procedure of patterning of metal 'islands' is used in the technology of production of magnetic media with digital type of data recording. Using a magnetic force microscope, it is possible to 'see' the domain structure of individual clusters (Fig. 7a). Smaller magnetic clusters (Fig. 7b) look like single magnetic dipoles.

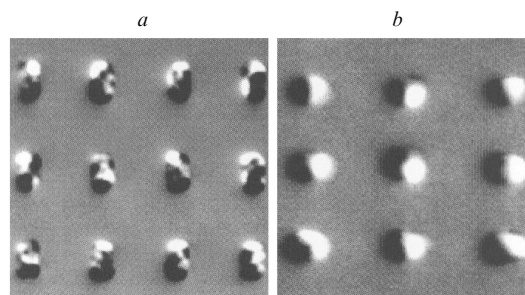


Figure 7. Image of metallic Co 'islets' obtained using a magnetic force microscope.

The 'islet' area: (a) $200 \times 400 \text{ nm}^2$; (b) $1.7 \times 1.7 \text{ }\mu\text{m}^2$.

The magnetic force microscope can be used not only for the observation (mapping) of the magnetic field, but also for magnetic recording with ultrahigh density. In Fig. 8, the projections correspond to the magnetic domains formed on the surface of a TbFeCo film using the microscope tip. These domains are formed at an instant when a certain threshold value of the strength of the magnetic field produced by an external magnet and the tip is achieved. The threshold magnetic field strength is determined by the coercivity of the magnetic film. The magnetised domains decrease in size and gradually disappear as the net magnetic field decreases successively. In this case the recording density is 10 Gbit cm^{-2} , which is substantially higher than that achieved for hard ('Winchester') disks and magneto-optical disks used in modern computers.

In Figs 9a and 9b, a magnetic image of a hard disk and the result of averaging of the magnetic image in the central surface area of the disk (between the dashed lines in Fig. 9a) over a large number of cross-sections are shown, respectively. Figure 9c represents a signal in the reading magnetic head that had scanned the same surface area of the disk. The curves shown in Figs 9b and

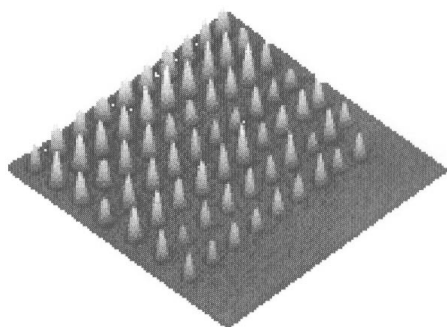


Figure 8. Single magnetic domains (a bit array) formed on the surface of TbFeCo carrier with the aid of the tip of a magnetic force microscope in the presence of external magnetic field. The same tip was used to obtain the magnetic image. The surface area scanned is $12 \times 12 \text{ }\mu\text{m}^2$.

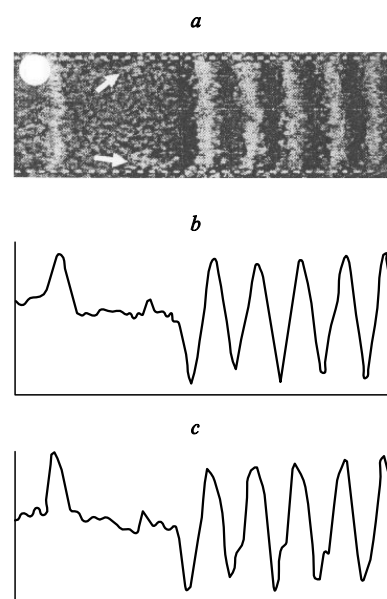


Figure 9. Image of a track of a magnetic disk obtained using a magnetic force microscope (a), averaged cross-section of the magnetic profile in the area between the dashed lines (b) and the signal in the reading magnetic head detected in the same area of the track (c).

9c are identical even in minor details, which indicates that the signals detected by the magnetic force microscope and conventional magnetic head coincide. The magnetic force microscope provides a much higher spatial resolution, which makes it possible to use this instrument in the detailed analysis and optimisation of read–write modes of standard magnetic heads.

The use of magnetic force microscopy in the studies of magnetic properties of biological objects is also promising. Micro-magnets play a significant role not only in artificial systems, but also in nature. For instance, bacteria *Aquaspirillum magnetotacticum* can move along the magnetic field lines. These bacteria contain specific organelles, viz, magnetosomes. The magnetosomes are chains of 10 to 25 permanent magnets, viz., iron oxide crystals of size $\sim 50 \text{ nm}$. Single crystals are clearly seen in nonstained cells using transmission electron microscopy. Magnets inside the cells determine the specified direction of motion of the bacteria in sea-water: to the north in the Northern hemisphere and to the south in the South hemisphere. It has been possible to measure the magnetic moment of a single bacterium *Aquaspirillum magnetotacticum* using a magnetic force microscope.²⁰ The length of the bacterium was $2 \text{ }\mu\text{m}$ and the measured magnetic moment was negligibly small, viz., 10^{-16} A m^2 .

Currently, 'Digital Instruments' and 'Park Scientific Instruments' companies (both from USA) produce magnetic force microscopes for use both in industry and scientific research. In the 'Centre of advanced technologies' (Moscow, Russian Federation), a promising model of scanning probe microscope, 'Femto-Scan' has been developed, which permits measurements of magnetic properties of the surface.

Cantilevers for both magnetic force microscopy and atomic force microscopy are fabricated by microlithography using a silicon technology, which means that one or several cantilevers at a time are formed at the edges of a silicon plate. Then the surface of the tip is coated with a thin layer of a ferromagnetic material. A scheme of the components for the probe of a magnetic force microscope made by Park Scientific Instruments (USA) is shown in Fig. 10.

A problem of calibrating the magnetic force microscope appears in relation to metrological measurements of magnetic forces. This problem has successfully been solved by Kong and

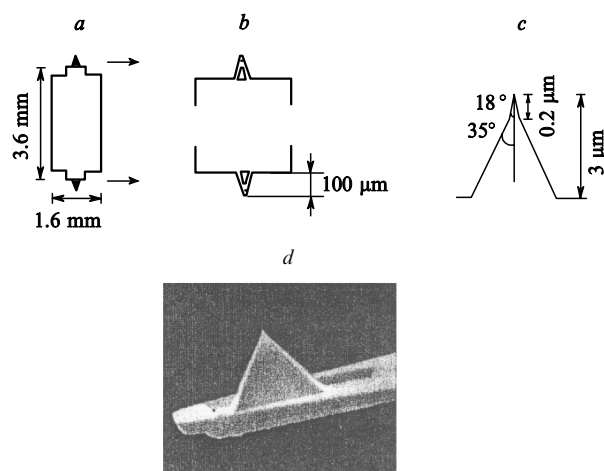


Figure 10. Scheme of manufacture of a cantilever with a tip (*a–c*) and the image of the tip mounted on a microconsole obtained using an electron microscope (*d*); (*a*) silicon plate holder with two cantilevers (*b*); (*c*) tip.

Chou,^{21,22} who have used metal microrings. The calibrating rings with diameters of 1 and 5 μm (Fig. 11) were made using electron-beam lithography (metal strips on a silicon surface). The magnetic tip moved at variable distances above the rings and its magnetic moment was evaluated from the electric current induced in the rings. The axial magnetisation of the silicon tip coated with a 65-nm thick cobalt film measured using this procedure was $3.8 \times 10^{-22} \text{ A m}^2$. Considerable attention is given to the procedure for fabrication of the tips, since it is the tips that largely determine the quality of the magnetic image of the surface.²³

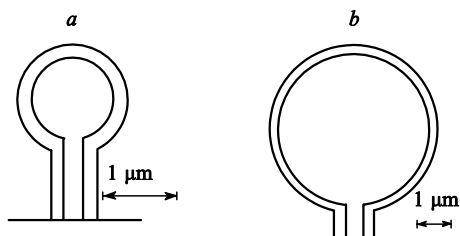


Figure 11. Microrings used for calibration of a magnetic force microscope.

IV. Magnetic-resonance force microscopy

In the year 1991, it was suggested that a magnetic force microscope can be used to obtain three-dimensional images of individual biomolecules.²⁴ To this end, it was proposed to combine the existing methods of nuclear magnetic resonance and magnetic force microscopy. The novel method has been called magnetic-resonance force microscopy.^{25,26} Its major advantages are safety for the object under study (*i.e.*, it is a nondestructive method), a subnanometre spatial resolution and the possibility of studying individual biomolecules.

At present, magnetic-resonance force microscopic experiments are carried out as follows. A specimen under study of negligible mass ($\sim 10^{-11} \text{ kg}$) is mounted on a springy cantilever analogous to that used in atomic force microscopy (Fig. 12). A constant magnetic field in the specimen is produced by a magnet placed near the cantilever. The magnetic force from the side on which the tip is mounted, acting on the surface atoms of the specimen, is proportional to the spin of the unpaired electrons or to the magnetic moment of the nuclei. In an alternating magnetic

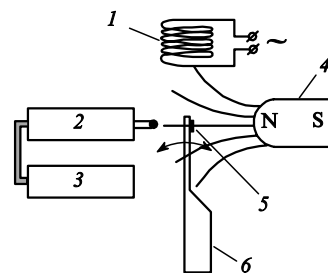


Figure 12. A block diagram of a magnetic-resonance force microscope; (1) magnetic coil; (2) fiber optic interferometer sensor; (3) detection electronics; (4) magnet; (5) specimen; (6) cantilever.

field, a quantum transition occurs between the energy sublevels of the electron or nucleus under the conditions of resonance, which causes a change in the orientation of the magnetic moment of the system. By periodically changing the frequency of the alternating magnetic field produced by an additional coil, one can modulate the magnetisation of the sample. The modulation frequency is chosen to be equal to the resonant frequency of the cantilever. The amplitude of the forced oscillations of the cantilever is measured with a small displacement transducer (*e.g.*, a fiber interferometer). For a chosen geometry of experiment, the conditions of nuclear and electron spin resonances in the system are held in the region of a specimen of subnanometre size.

The method of magnetic-resonance force microscopy has nontrivial possibilities for the structure determination of proteins and viruses. The results of the first successful experiments on the observation of electron paramagnetic resonance are documented.²⁷ Spin resonance in a sample of diphenylpicrylhydrazyl of mass 30 ng was detected. The force acting on the cantilever was 10^{-14} N . According to an assessment made, the observation of resonance from a single molecule requires the enhancement of sensitivity to force at least by 4 orders of magnitude. Recently, the construction of a microcantilever of length 230 μm and thickness of only 60 nm with a micromagnet mounted atop was reported.[†] The magnetic field of the micromagnet interacts with the magnetic moments of the atoms of a specimen. The magnetisation of the specimen is varied periodically (as in the preceding case) to achieve the conditions of electron (paramagnetic) or nuclear magnetic resonance. The force measured was $6 \times 10^{-18} \text{ N}$.

A description of early successful experiments on the observation of electron spin resonance using the magnetic force microscope is given in Ref. 27. The strength of the constant magnetic field is modulated, which changes the magnetisation of the specimen under conditions of spin resonance (Fig. 13). During the modulation period, the system will be at resonance twice and, in the case of sufficient strength of the alternating magnetic field, the absorption of energy reaches its maximum. This leads to the levelling of the populations of magnetic energy sublevels corresponding to the quantum numbers lying in the range from $-m$ to $+m$ and to the decrease in the magnetisation down to zero. To eliminate interference, the signal is detected at a frequency of the second-harmonic component of the modulation signal. The calculated and experimental spectra (Fig. 14) virtually coincide.

In early experiments on the observation of 3D images, a 2- μm particle of diphenylpicrylhydrazyl was mounted on a cantilever in a constant nonuniform magnetic field produced by a conical tip made of NdFeB. The magnetic field gradients were 4.3 and 0.94 $\text{G } \mu\text{m}^{-1}$ normal to the specimen and in the longitudinal direction, respectively. The transverse and longitudinal spatial resolutions were 1.2 and 5.3 μm , respectively. A 3D image of the sample with a resolution of $\sim 3 \mu\text{m}$ was obtained in the observa-

[†] The report was posted in January, 1997 at the URL <http://www.aip.org/physnews>

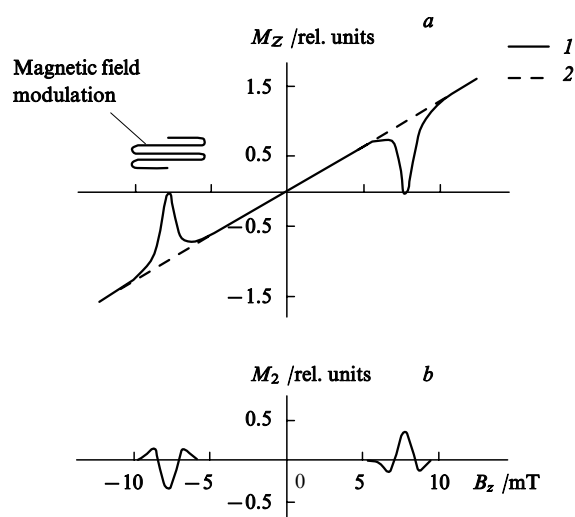


Figure 13. Dependences of the magnetisation of a specimen (a) and the amplitude of the magnetisation signal measured at the frequency of the second-harmonic component (b) as functions of the constant magnetic field strength.

In the presence (1) and in the absence (2) of high-frequency field.

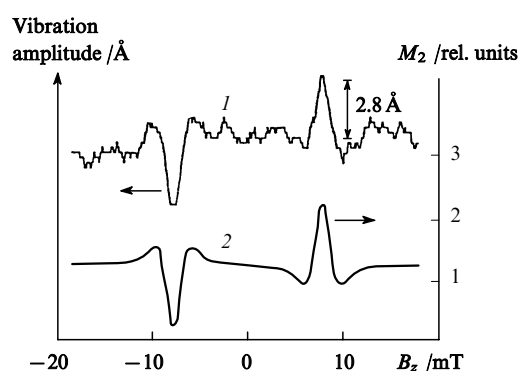


Figure 14. Experimental (1) and calculated (2) electron spin resonance spectra obtained using a magnetic-resonance force microscope.

tion of NMR in ammonium nitrate at a field gradient of $22 \text{ G } \mu\text{m}^{-1}$.

Production of a constant magnetic field with the highest uniformity in the bulk of the entire specimen is the principal condition that should be met in the classical ESR and NMR methods. On the contrary, in the case of magnetic-resonance force microscopy the higher the nonuniformity of the constant magnetic field, the smaller the spatial region in which the resonance condition holds and, hence, the higher the spatial resolution obtained when constructing 3D images.

V. Conclusion

The material presented in this review shows that the investigations in the field of magnetic force microscopy are being intensively developed in the last decade. This method is used in both fundamental science and industry. Of particular interest and fruitfulness are the results of application of the magnetic force microscopy in the creation of magnetic media that make it possible to perform magnetic recording with ultrahigh density.

The latest studies have shown that combination of magnetic force microscopy and traditional methods of electron paramagnetic resonance and nuclear magnetic resonance opens unique potentials for the investigation of nanostructures including biomolecules.

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Time-resolved IR chemiluminescence in gas-phase chemical kinetics

E N Chesnokov, V N Panfilov

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Abstract. The time-resolved IR chemiluminescence method based on the study of the chemiluminescence of vibrationally excited molecules formed in chemical reactions is discussed. The approaches used in the study of elementary reactions and complex processes are systematised. The technique is compared with other methods for the study of gas-phase chemical kinetics. The bibliography includes 76 references.

I. Introduction

In modern gas-phase chemical kinetics, methods that enable the real-time detection of chemically active species in an excited state are used in studies of elementary reactions. These methods include laser-induced fluorescence, intra-cavity laser spectroscopy, laser magnetic resonance, resonance-amplified multiphoton ionisation and the IR chemiluminescence method (IR-CL) based on the study of the luminescence of vibrationally excited molecules formed in reactions.

The energy evolved in an elementary exothermic chemical process manifests itself most commonly as vibrational excitation of the reaction products.¹ The practical application of this kind of reaction for the pumping of chemical lasers is well known.^{2,3}

The works devoted to the IR-CL study of the vibrationally excited products of chemical reactions may be divided in two groups. The first one includes those where a steady-state IR-CL spectrum with rather a high spectral resolution is the quantity determined experimentally. This spectrum contains information on the distribution of the reaction products over the vibrational and rotational states. Many reactions resulting in the formation of vibrationally excited molecules, such as HF,^{4–9} HCl,¹⁰ HBr,¹¹ CO,¹² OH¹³ and H₂O,¹⁴ have been studied by this method. The study of the reactions is complicated by the disturbing effect of fast vibration and rotation relaxation processes. To reduce the

effect of relaxation processes, the experiments are carried out at low pressure using fast gas flow.

In another group of works, the kinetic approach is used. In these experiments, the dependence of the IR-CL intensity on the time elapsed after the pulse initiation of the chemical reaction is determined. The radiation is recorded in rather a wide spectral band. Based on this dependence, it is possible to determine the rate constants for reactions resulting in excited molecules and those of other reactions accompanying this process, as well as to find the rates of vibrational relaxation. From the methodical viewpoint, these works may be considered as a contribution to the development of the method of studying the vibrational relaxation of molecules based on their IR luminescence, which has been extremely fruitful in studies of the relaxation of polyatomic molecules.¹⁵

This review analyses the publications where the kinetic approach has been used. The main attention is given to methodical problems related to the use of kinetic IR-CL for the study of non-chain and chain reactions. A method for the measurement of the rate constants for reactions involving atoms and free radicals is discussed, in which a chain reaction resulting in the formation of vibrationally excited products manifests itself as an original 'probe' which makes it possible to trace the changes in the concentration of reactive species with time.

II. Processes resulting in IR chemiluminescence of vibrationally excited products of chemical reactions

Extensive studies on the processes of the formation of vibrationally excited molecules in exothermic reactions were linked with the research aiming at the development of chemical lasers and the optimisation of their operation. To date, the formation of diatomic vibrationally excited molecules in atom abstraction reactions have been studied rather thoroughly. Table 1 presents some typical exothermic reactions producing vibrationally excited molecules. Based on the analysis of the published data, one can state with a high degree of certainty that, if the energy liberated in the abstraction of an atom exceeds the energy of the quantum of the vibration energy of the molecule formed, this reaction should result in vibrationally excited molecules. The fraction of the vibrational energy is ten percent of the exothermicity of a reaction.

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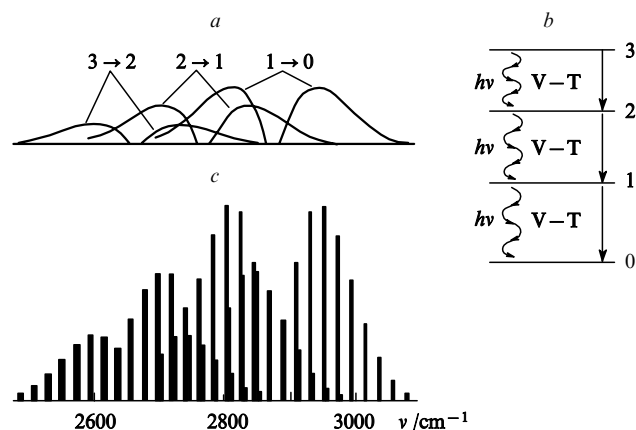
Uspekhi Khimii 68 (3) 194–204 (1999); translated by S S Veselyi

Table 1. Mean vibration energy ($\langle E_{\text{vib}} \rangle$) of excited products and thermal effect ($-\Delta H_0$) of certain exothermic reactions.

Reaction	Excited species	$-\Delta H_0$	$\langle E_{\text{vib}} \rangle$	Ref.
		kcal mol ⁻¹		
$\text{F}^* + \text{H}_2 \rightarrow \text{HF}^* + \text{H}^*$	$\text{HF}(v = 1, 2, 3)$	32	21.0	16
$\text{F}^* + \text{CH}_4 \rightarrow \text{HF}^* + \text{CH}_3^*$	$\text{HF}(v = 1, 2, 3)$	33	19.0	17
$\text{F}^* + \text{C}_6\text{H}_{12} \rightarrow \text{HF}^* + \text{C}_6\text{H}_{11}^*$	$\text{HF}(v = 1, 2, 3)$	41	22.0	18
$\text{H}^* + \text{Cl}_2 \rightarrow \text{HCl}^* + \text{Cl}^*$	$\text{HCl}(v = 1, \dots, 6)$	45	17.6	19
$\text{Cl}^* + \text{H}_2\text{S} \rightarrow \text{HCl}^* + \text{HS}^*$	$\text{HCl}(v = 1)$	12	5.2	20
$\text{Cl}^* + \text{GeH}_4 \rightarrow \text{HCl}^* + \text{GeH}_3^*$	$\text{HCl}(v = 1, 2, 3)$	24	5.6	21
$\text{O}^{*} + \text{CS} \rightarrow \text{CO}^* + \text{S}^{*}$	$\text{CO}(v = 5, \dots, 18)$	85	66.0	22
$\text{Cl}^* + \text{SiH}_4 \rightarrow \text{HCl}^* + \text{SiH}_3^*$	$\text{HCl}(v = 1)$	12	3.4	23
$\text{O}^{*} + \text{HI} \rightarrow \text{OH}^* + \text{I}^*$	$\text{OH}^*(v = 1, 2, 3)$	31	9.7	24
$\text{O}^{*} + \text{GeH}_4 \rightarrow \text{OH}^* + \text{GeH}_3^*$	$\text{OH}^*(v = 1, 2)$	33	12.5	13
$\text{OH}^* + \text{HI} \rightarrow \text{H}_2\text{O}^* + \text{I}^*$	H_2O	48	17.0	14
$\text{O}^{*}({}^1\text{D}) + \text{H}_2\text{CO} \rightarrow \text{CO}_2^* + \text{H}_2$	CO_2	170	33.0	25

The study of the formation of polyatomic vibrationally excited molecules in chemical reactions is only beginning. However, the data available in the literature are consistent with the qualitative concept that in this case, too, a considerable fraction of energy produced in the reaction is transformed into the vibrational energy of the product containing the newly formed chemical bond.

The vibrationally excited molecules resulting from an exothermic reaction can lose energy either through spontaneous emission of IR radiation quanta or by relaxation of the vibrational energy in collisions. These processes are schematically shown in Fig. 1.

**Figure 1.** Scheme of the processes forming an IR chemiluminescence spectrum;

(a) vibrational bands of the corresponding transitions with unresolved rotational structure; (b) scheme of radiation transitive and vibration-translation (V-T) relaxation processes; (c) IR luminescence spectrum of an HCl molecule with well resolved rotational structure.

The characteristic probabilities of spontaneous radiative transitions in unit time (W) for the vibrationally excited molecules are listed in Table 2. The transitions that change the vibration quantum number v by one unit have the highest probability. It is in rare cases that W exceeds 100 s⁻¹ for the vibrations resolved in an IR spectrum.

As a rule, the probability of transitions that change v by two units (overtone luminescence) is one or two orders lower. Accordingly, the intensity of the overtone luminescence turns out to be lower. On the other hand, it has to be noted that overtone transitions play a more significant role in the IR luminescence

Table 2. Energy and probability of spontaneous radiative transitions for vibrationally excited molecules.

Molecule	Transition	E/cm^{-1}	W/s^{-1}	Ref.
HF	$(v = 1) \rightarrow (v = 0)$	3961	189.0	26
	$(v = 2) \rightarrow (v = 1)$	3788	320.0	
HCl	$(v = 1) \rightarrow (v = 0)$	2886	35.0	26
	$(v = 2) \rightarrow (v = 1)$	2782	59.0	
	$(v = 2) \rightarrow (v = 0)$	5668	3.5	
	$(v = 3) \rightarrow (v = 0)$	8347	0.037	
OH	$(v = 1) \rightarrow (v = 0)$	3568	20.0	27
	$(v = 2) \rightarrow (v = 1)$	3398	25.0	
	$(v = 2) \rightarrow (v = 0)$	6966	14.0	
	$(v = 3) \rightarrow (v = 0)$	10 194	0.9	
CO	$(v = 1) \rightarrow (v = 0)$	2170	30.0	28
	$(v = 2) \rightarrow (v = 1)$	2144	59	
CO_2	$(0^001) \rightarrow (0^000)^a$	2349	400.0	29
SiH_4	$(v_3 = 1) \rightarrow (v_3 = 0)^a$	2189	180.0	30

Note. The table presents data for molecules with vibration frequencies $> 2000 \text{ cm}^{-1}$ (the molecules with lower vibration frequencies are not interesting due to the low probability of spontaneous transitions).

^a The linear three-atomic CO_2 molecule has four vibrational degrees of freedom and three different frequencies. The five-atomic SiH_4 molecule has even more frequencies. In both cases, the parameters of only one possible vibrational transition are presented.

spectra than in IR absorption spectroscopy. A reason for this is that the overtone luminescence occurs in the region of shorter wavelengths (with respect to the fundamental luminescence), and hence more sensitive detectors can be used to record it.

Let us consider the energy loss by vibrationally excited molecules in collisional relaxation. The rate constants for the vibration-translation relaxation vary over a very broad range for various colliding partners. For example, the probability of vibrational relaxation of excited HCl molecules equals 10^{-7} in collisions with He atoms, 10^{-4} in collisions with HCl, 10^{-3} in collisions with CH_4 , and 2×10^{-3} in collisions with SiH_2Cl_2 . In a gas mixture prepared for studying a chemiluminescent reaction, vibrational relaxation occurs upon collisions with the molecules of the starting substances. The probabilities of vibrational relaxation upon collisions with polyatomic molecules usually vary from 10^{-2} to 10^{-3} , which corresponds to the time of vibrational relaxation $10^{-4} - 10^{-3} \text{ s}$ at a pressure of 1 Torr.

The above estimates show that the radiative path plays an insignificant role in the energy loss by vibrationally excited molecules. The quantum yield of IR-CL at a pressure of several Torr usually does not exceed 10^{-2} and decreases with an increase in the pressure. Such a dependence determines the upper limit of the pressure range used in experiments on IR-CL; this value is about 30 Torr.

The necessity of using low pressures and the relative simplicity of the luminescing molecules, whose IR spectra display well resolved rotational structure, results in a specific IR-CL spectrum. At low pressures, the width of an individual rotation line is mainly determined by the Doppler effect and does not exceed 10^{-2} cm^{-1} . The distance between the adjacent rotational lines is several units or even several tens of inverse centimetres. Therefore, the IR-CL spectrum is a set of very narrow lines far separated from each other.

If a reaction produces excited molecules in different vibrational states, the bands in their spectra are shifted relative to each other owing to vibrational anharmonicity. The anharmonic shift is usually smaller than the width of a separate band, therefore overlapping of bands occurs. Figure 1 schematically shows the luminescent spectrum of HCl molecules excited in the states $v = 1$,

$\nu = 2$, and $\nu = 3$. There is no actual superposition of the lines in the spectrum, because the width of a separate line is much smaller than the distance between the neighbouring lines. However, high spectral resolution is required to detect the luminescence corresponding to a particular vibrational state in such a spectrum. The spectral resolution in kinetic experiments on the study of IR-CL is small, hence it is helpful to use the so-called 'cold gas filter'. This is a cell filled with the gas whose luminescence is being studied. As the molecules in the gas filter are in the ground vibrational state, the gas filter enables blocking of the radiation of the $1 \rightarrow 0$ transition without affecting the radiation of the other transitions.

III. The sensitivity limit of the IR chemiluminescence method

A typical experimental set-up for the evaluation of the sensitivity of the IR-CL method includes a pulse laser (its radiation initiates the chemical reaction), a system for the preparation and injection of the gas mixture, and a system for the time-resolved recording of IR-CL.^{31–39} The initiation of a reaction most commonly occurs due to the dissociation of molecules under the action of laser radiation in the UV range (excimer lasers, neodymium laser with frequency multiplication, the second harmonic of the ruby laser, the second harmonic of dye lasers). In addition, pulse CO₂ lasers are used, whose IR irradiation causes the dissociation due to multi-photon absorption. The experiments are carried out at pressures from fractions of Torr to several tens of Torr. The repetition frequency of laser pulses is usually several Hertz, less commonly tens of Hertz.

Figure 2 shows the scheme of a typical experimental set-up for recording the luminescence. Luminescence is recorded in a direction perpendicular to the laser beam. Since the signal is usually insufficient for the use of a monochromator, interference filters combined with various absorption filters are used. Often a gas filter is used, which has the form of a gas cell several centimetres long containing an absorbing gas under a pressure of several tens of Torr. Semi-conductor photoresistors or photo diodes cooled to low temperatures are used as IR radiation detectors. Photo-detectors based on InSb are most commonly used for the mid IR region (3–5 μm). These detectors have high sensitivity and are convenient because they do not require cooling below 77 K. The time constant of these detectors is somewhat smaller than 1 μs in the case of photodiodes and several microseconds in the case of photoresistors. A very important requirement for a detector is its large area. This is caused by the fact that an IR-CL source has

considerable geometrical dimensions, hence its radiation cannot be effectively focused on the small area of a detector. In the optimum variant, the size of the detector should match the size of the area in which the reaction occurs (~ 1 cm). Smaller detectors are commonly used.

One can estimate the minimum concentration of vibrationally excited molecules detectable by this method as follows. The noise of a theoretical IR radiation detector is determined by fluctuations of the thermal background radiation reaching this detector. A signal of the excited molecules can be detected if the number of IR luminescence photons (I_{lum}) that have reached the radiation detector during the resolution time of the detecting system (τ_{reg}) exceeds the number of photons from the thermal radiation fluctuation (I_{therm})

$$I_{\text{lum}}\tau_{\text{reg}} > \sqrt{I_{\text{therm}}\tau_{\text{reg}}} \quad (1)$$

For the flux of thermal radiation photons we have

$$I_{\text{therm}} = \frac{2\pi c S \Delta\lambda}{\lambda^4 [\exp(hc/\lambda kT) - 1]} \left(\frac{D}{2l}\right)^2, \quad (2)$$

where c is the speed of light; S is the photodetector area; $\Delta\lambda$ is the wavelength range in which luminescence is recorded; λ is the irradiation wavelength; D and l are geometrical parameters (see Fig. 2b).

The flux of luminescence photons can easily be found if the geometrical dimensions of the experimental set-up are known. Based on the formula (1), the following expression for the minimum detectable concentration of excited molecules was obtained:

$$n_{\text{min}} = 2\sqrt{2\pi} \left(\frac{2l}{D}\right) \frac{\tau_{\text{rad}}}{r\sqrt{S\tau_{\text{reg}}[\exp(hc/\lambda kT) - 1]}} \frac{\sqrt{c\Delta\lambda}}{\lambda^2}, \quad (3)$$

where τ_{rad} is the radiative life time of a vibrationally excited molecule.

For an estimation of n_{min} , let us use the following parameters of a vibrationally excited HCl molecule: $\lambda = 3.6$ μm , $\tau_{\text{rad}} = 3 \times 10^{-2}$ s.²⁶ The typical geometrical parameters are as follows: $S = 10^{-2}$ cm², $r = 0.5$ cm, $2l/D = 5$; the resolution time of the detecting system τ_{reg} is assumed to equal 10^{-6} s, and $\Delta\lambda \approx \lambda$. After substituting these parameters in the formula (3), we obtain $n_{\text{min}} = 10^{11}$ cm⁻³.

Analysis of formula (3) shows that the sensitivity can be increased by using radiation detectors with large area and focusing lenses with large aperture (D/l ratio). The sensitivity can also be increased by narrowing the wavelength range $\Delta\lambda$ of the radiation that reaches the detector to a value equal to the width of the luminescent spectrum with the use of spectral filters. However, the maximum difference in the estimate obtained above due to all of these factors is one order of magnitude. Therefore, the value of $n_{\text{min}} = 10^{11}$ cm⁻³ should be considered as the sensitivity limit of the IR-CL method.

It should be noted that this estimate was obtained under the assumption that the sensitivity is limited by the noise that originates from fluctuations of the thermal radiation reaching the detector. This is true in the standard experiment, in which the gas to be studied is placed in a cell whose walls and the surrounding objects are at room temperature, and hence it is impossible to avoid the effect of thermal irradiation on the detector. The sensitivity is usually increased by accumulation of periodically repeated signals.

A comparison of the IR-CL method with other kinetic methods³² leads to the following conclusions. The sensitivity of IR-CL is inferior to that of laser-induced fluorescence (LIF) and resonance-enhanced multiphoton ionisation (REMPI) and is comparable to the sensitivity of the time-resolved laser magnetic resonance (LMR) and intra-cavity laser spectroscopy (ICLS). The response time of the method is within 10^{-7} to 10^{-6} s. This time is

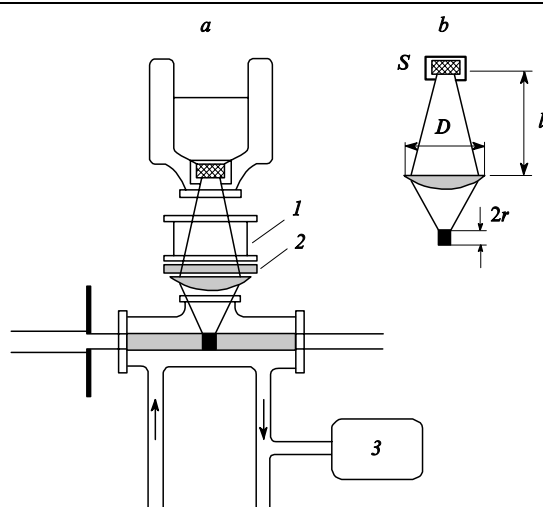


Figure 2. Scheme of set-up for the observation of the IR-CL kinetics (a); part of the set-up with indication of geometrical parameters required for sensitivity estimation (b); (1) interference filter; (2) gas filter; (3) pressure gauge.

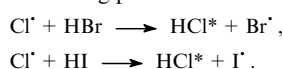
smaller than the response time of time-resolved LMR and somewhat larger than the response time of LIF, ICLS and REMPI. An important characteristic of the methods used in the study of gas-phase reactions is the product of the sensitivity and the response time. This value equals $1/(n_{\min}\tau_{\text{reg}}) \approx 10^{-8} \text{ cm}^3 \text{ s}^{-1}$ for IR-CL, which is much more than the maximum rate constants for bimolecular reactions. Hence, the fastest gas phase reactions can be studied by this method.

The main drawback of the IR luminescence method is its low spectral resolution. It does not exceed $20-50 \text{ cm}^{-1}$ if interference filters are used. The use of a monochromator decreases the sensitivity. The low spectral resolution restricts the scope of the method considered. It can be used when one type of excited molecules is formed in the reaction or the spectra of different excited molecules are separated considerably.

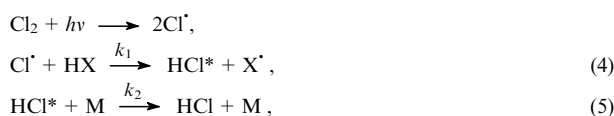
Thus, time-resolved IR-CL is an experimentally simple kinetic method with high sensitivity and fast response. The scope of this method is limited to systems which produce vibrationally excited molecules with simple spectra.

IV. Measurement of rate constants for non-chain reactions

The IR-CL method has been first used for the measurement of the rate constants for chemical reactions by Wodarczyk and Moore.³³ The following processes were studied:



The reactions were initiated by the action of a pulse of radiation of the second harmonic of the ruby laser on a mixture of Cl_2 with a small amount of HBr or HI diluted with a noble gas. The action of a laser pulse on a Cl_2 molecule resulted in its dissociation into two chlorine atoms. The IR luminescence of the excited HCl molecules formed in the reactions was recorded. The $\text{Br}^\bullet$ and $\text{I}^\bullet$ atoms have small reactivities, hence the set of kinetic processes can be represented by the following scheme



where $\text{X}^\bullet = \text{Br}^\bullet, \text{I}^\bullet$; $\text{M} = \text{He}, \text{Cl}_2$.

If a small fraction of Cl_2 molecules dissociates under laser irradiation ($[\text{Cl}^\bullet] \ll [\text{Cl}_2], [\text{HX}]$), the pseudo-first order condition is obeyed for the processes (4) and (5), and the solution of the corresponding kinetic equations can be found easily. It has the form

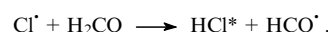
$$[\text{HCl}^\bullet](t) = A[\exp(-k_2[\text{M}]t) - \exp(-k_1[\text{HX}]t)]. \quad (6)$$

The experimentally observed time dependences of the luminescence intensity are well described by the formula (6). Under the experimental conditions used in Ref. 33, the time of vibrational relaxation was much greater than the reaction time. Therefore, the region of increase in the signal intensity was determined by the reaction time, and after passing a maximum, the signal intensity decreased according to vibrational relaxation. Analysis of the region of increase in the signal made it possible to determine the product $k_1[\text{HX}]$ and hence the reaction constant k_1 .

In another study,³⁴ more accurate measurements of rate constants for reactions of chlorine atoms with hydrogen bromide and hydrogen iodide were carried out; in addition, the isotope effect of the reaction rate was studied. The accuracy was increased by more careful determination of the concentration of the reagent, HBr or HI. The rate constants for the reactions at ambient temperature were 7.4×10^{-12} and $1.64 \times 10^{-10} \text{ cm}^3 \text{ s}^{-1}$, and the isotope effects ($k_{\text{H}}/k_{\text{D}}$) were 1.50 and 1.84, respectively. The measured temperature dependences (in the range from 220 to 400 K) of the rate constants for the same reactions were found to be of non-Arrhenius type.³⁵

The reactions of $\text{F}^\bullet$ with HCl, HBr and HI molecules were studied.^{37,38} The fluorine atoms were formed upon dissociation of F_2 molecules under the irradiation by the fourth harmonic of a Nd-laser. The processes considered are strongly exothermic; the HF molecules were excited to $v = 3$ (for the reaction with HCl), $v = 4$ (for the reaction with HBr), and $v = 6$ (for the reaction with HI). This made it possible to detect the excited HF molecules using luminescence at the second overtone frequency. The maximum of the band of the $(3 \rightarrow 0)$ transition in HF is at 879 nm, therefore a photomultiplier was used to detect the radiation. The band corresponding to this transition could easily be separated from the other HF luminescence bands using an interference filter for 880 nm with a band pass of 10 nm. In addition to the rate constants for the reactions of the fluorine atom with HCl, HBr and HI, which are 7.0×10^{-12} , 6.2×10^{-11} and $5.6 \times 10^{-11} \text{ cm}^3 \text{ s}^{-1}$, respectively, the rate constants for vibrational relaxation of HF molecules from the state $v = 3$ in collisions with HCl, CO_2 , N_2O , CO, N_2 and O_2 were measured.

The interpretation of various stages of the IR-CL signal was simple.³³⁻³⁷ As a rule, the region of the signal increase determined the reaction time, and the region of the signal decay determined the time of vibrational relaxation. Such a simple interpretation was possible because the atoms formed in the reaction were less reactive than the starting atoms. Therefore, secondary chemical reactions did not contribute to the observed time dependence of the signal. If species with high reactivity were formed in the reaction, a simple interpretation of the kinetic IR-CL curves was impossible because of secondary reactions. In this case, the role of secondary reactions as a photochemical source of atoms can be diminished by using sufficiently stable molecules which do not react with the newly formed radicals. This approach was used³⁸ for the reaction



The CCl_3F molecule dissociating under the action of radiation of a pulse CO_2 laser served as a source of the chlorine atoms. It was shown that the multiphoton dissociation of CCl_3F did not result in the formation of fluorine atoms. The CCl_3F molecules are sufficiently inert and do not react with the $\text{HCO}^\bullet$ radical. The rate constant for the reaction was $7.4 \times 10^{-11} \text{ cm}^3 \text{ s}^{-1}$.

Multiphoton dissociation of SF_6 was found to be a convenient source of $\text{F}^\bullet$. This is explained by the high probability of SF_6 dissociation under the action of the radiation of CO_2 lasers and relative chemical inertness of SF_6 . The time-resolved IR-CL method was used to study the reaction of fluorine atoms that formed due to multiphoton dissociation of SF_6 , with various molecules. For example, the rate constants of reactions of fluorine with H_2 and D_2 were measured at ambient temperature.³⁹⁻⁴¹ To diminish warming of the gas by the radiation of pulse CO_2 lasers, the measurements were carried out in mixtures strongly diluted with a noble gas.

The numerical simulation of chemical HF- and DF-lasers requires the knowledge of the temperature dependences of the reaction rate constants for fluorine atoms with H_2 and D_2 . The most reliable experimental data for these dependences have been obtained by time-resolved IR-CL.^{42,43} It has been found for the temperature range 190–373 K:⁴³

$$k_{\text{H}_2} = 1 \times 10^{-10} \exp\left(-\frac{860}{RT}\right),$$

$$k_{\text{D}_2} = 9.1 \times 10^{-11} \exp\left(-\frac{1100}{RT}\right).$$

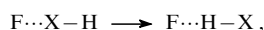
For the temperature range 290–765 K:⁴³

$$k_{\text{H}_2} = 2.1 \times 10^{-10} \exp\left(-\frac{1180}{RT}\right),$$

$$k_{\text{D}_2} = 1.1 \times 10^{-11} \exp\left(-\frac{1200}{RT}\right).$$

In the range of overlapping temperature ranges, the results differ by no more than 30% for the reaction with hydrogen and by much less for the reaction with deuterium. Deviation of the experimental data from the Arrhenius-type dependence over a wide temperature range was reported.

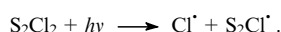
The reactions of the fluorine atom with HCl, HBr, HI, DBr, DCl and DI molecules at room temperature were studied.⁵ The temperature dependences of the rate constants were measured in the range 195–373 K for the first four processes.⁴⁴ It was found that these dependences at temperatures below the room temperature deviate from the Arrhenius-type dependence. The experimental dependence can approximately be described by a sum of two terms, one of which does not depend on temperature and the other has an Arrhenius-type dependence with $E_a = 2-3$ kcal mol⁻¹. The explanation of this temperature dependence is that the reaction occurs by two pathways: first, direct elimination upon the attack by a fluorine atom towards the hydrogen atom in a hydrogen halide molecule, and second, formation of a complex upon the attack of a fluorine atom towards the halogen atom. It is considered that the first pathway does not require an activation energy, whereas the reaction according to the second pathway is supposed to overcome an activation barrier to the reorganisation of the complex



which precedes its decomposition.

A study of the multiphoton dissociation of CF₃Cl by the time-resolved IR-CL method was reported.⁴⁵ Observation of the kinetics of IR-CL of HCl and HF molecules formed in reactions with HBr as a trap for atoms showed that dissociation occurs by two pathways to give F[•] and Cl[•]. When HBr was replaced by H₂, only the formation of excited HF molecules was observed. The rate constants for reactions of fluorine atoms with H₂ and HBr and chlorine atoms with HBr were measured.

The possibility of using the time-resolved IR-CL for the study of a particular reaction is determined to a considerable extent by the existence of a suitable pulse source of atoms. The photolysis of S₂Cl₂ is a convenient photochemical source of the chlorine atoms that makes it possible to avoid or diminish the role of secondary reactions (see Ref. 46).



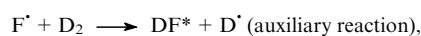
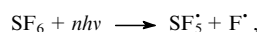
The photolysis of S₂Cl₂ was carried out under irradiation by the second harmonic of a dye laser ($\lambda = 300$ nm)⁴⁶ and the fourth harmonic of a Nd-laser. The rate constants for chlorine reactions with H₂S (see Ref. 44), CH₃SH (see Ref. 47), and SiH₄ (see Ref. 48) were measured with the use of S₂Cl₂ as a source of chlorine atoms. Yet another photochemical source of chlorine atoms is the photolysis of COCl₂ by irradiation with an excimer KrF-laser. This source was used in a study of the reaction of chlorine with SiH₄ and SiH₃[•] (see Ref. 49).

V. Modification of the time-resolved IR chemiluminescence method

In all of the works considered above, the time-resolved IR-CL method was used for the study of reactions of atoms resulting in the formation of vibrationally excited molecules, whose IR luminescence could be recorded. An approach has been suggested which expands the scope of reactions that can be studied by the IR-CL method.⁵⁰ The essence of this approach is that reactive species underwent an auxiliary reaction, in parallel with the 'nonluminous' reaction being studied, which resulted in the formation of vibrationally excited luminescing molecules. By studying the kinetic characteristics of the luminescence signal from the auxiliary reaction, one can obtain information on the rate constant for the 'nonluminous' reaction.

This method was tested⁵¹ for the reaction of fluorine with CH₄. The reaction of fluorine with D₂ was used as the auxiliary reaction. The fluorine atoms were formed by IR multiphoton

dissociation of SF₆. The main processes can be presented by the following scheme:



Let us designate the rate constants for the basic reaction, the auxiliary reaction and vibrational relaxation as k_1 , k_0 and k_2 , respectively. If the concentration of the fluorine atoms is much smaller than that of any of the stable components of the gas mixture, the pseudo-first order condition is obeyed for bimolecular processes, and the following expression is valid for the luminescence intensity of vibrationally excited molecules DF^{*}

$$I_{DF}(t) = \frac{Ck_0[D_2][F]_0}{w' - w'} [\exp(-w't) - \exp(-w't)], \quad (7)$$

where C is a proportionality factor, $[F]_0$ is the initial concentration of the fluorine atoms, w' is the inverse time of the signal growth

$$w' = k_0[D_2] + k_1[CH_4], \quad (7a)$$

and $w'' = k_2[M]$ is the inverse time of the signal decay.

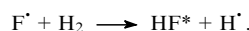
The inverse time of growth of the luminescence signal of DF^{*} molecules depends both on the rate constant for the reaction $F^{\bullet} + D_2$ and on the rate constant for the parallel process $F^{\bullet} + CH_4$. According to equation (7a), the plot of w' versus the CH₄ concentration is a straight line, whose slope determines the required rate constant k_1 , and the intercept with the ordinate axis determines the rate constant k_0 . Thus, the luminescence signal from the products of the 'auxiliary' reaction contains the same kinetic information as that obtained from observation of the luminescence of the reaction of interest.

As the reaction being studied, $F^{\bullet} + CH_4$, also results in the formation of vibrationally excited HF molecules, it was possible to check the equivalence of kinetic information obtained from the auxiliary reaction and by observation of the luminescence of the reaction products.⁵⁰ Experiments were carried out in which the signals of the HF^{*} and DF^{*} luminescence were recorded under identical conditions. It was found that the time of the growth of these signals coincided within the experimental error, as would be expected according to the kinetic scheme considered above.

The same approach was used⁵¹ to study the reaction



The fluorine atoms were obtained by multiphoton dissociation of SF₆. The process



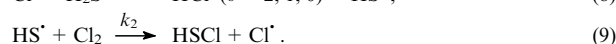
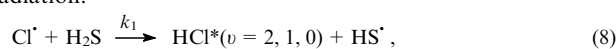
was used as an auxiliary reaction producing vibrationally excited molecules. The dependence of the rate constant for the reaction of fluorine with NO₂ on pressure in the range 1–200 Torr was measured; based on this dependence, the ratio of the isomers FNO₂ and FONO formed in the reaction was determined.

VI. Study of the kinetics of chain reactions by the IR chemiluminescence method

The time-resolved IR-CL method combined with pulse initiation of the reaction by laser irradiation was found to be very convenient for the study of the kinetics of chain reactions. This method made it possible to observe in real time a number of features of chain reactions, for example, the induction period of a reaction with very slow chain growth.⁵² Using the data on the luminescence of the chain reaction products, it became possible to develop new kinetic approaches that enable quantitative information on the rate constants for the elementary reactions to be obtained.

For a non-branched chain reaction (or for a reaction with infrequent branchings) one can distinguish several stages that occur at different times after the pulse initiation of the reaction. The first one is the induction period, during which quasi-steady-state equilibrium between the concentrations of various active centres is established. The duration of the induction period approximately equals the time required for one step of a chain reaction to occur. Then the quasi-steady-state stage ensues. The concentration of active centres in this stage is approximately constant, and the accumulation of chain reaction products occurs. The third stage is the termination of the chain reaction, which occurs when the concentration of the active centres has decreased essentially owing to termination reactions. Let us consider how each of these stages manifests itself in the IR luminescence of the chain reaction products.

The induction period. The induction periods of the chain reactions were studied for the chlorination of H_2S .⁵² The following processes occur in a mixture $\text{Cl}_2 + \text{H}_2\text{S}$ after a pulse of UV irradiation:



In this case, excited molecules are formed in the first stage of the chain reaction. Let us designate the starting concentration of the chlorine atoms formed owing to the photolysis of Cl_2 as $[\text{Cl}^*]_0$. Only a small fraction of the Cl_2 molecules underwent dissociation, hence $[\text{Cl}^*]_0 \ll [\text{Cl}_2]$ and $[\text{Cl}^*]_0 \ll [\text{H}_2\text{S}]$. In the initial stage, it is possible to neglect the chain termination and to neglect the vibrational relaxation of the HCl molecules, therefore the following expression can be written for the concentration of the chlorine atoms:

$$[\text{Cl}^*](t) = [\text{Cl}^*]_0[\theta_2 + \theta_1 \exp(-\varphi t)], \quad (10)$$

where t is time, $\theta_1 = k_1[\text{H}_2\text{S}]/\varphi$, $\theta_2 = k_2[\text{Cl}_2]/\varphi$ and $\varphi = k_1[\text{H}_2\text{S}] + k_2[\text{Cl}_2]$. The following expression is obtained for the concentration of vibrationally excited HCl molecules:

$$[\text{HCl}^*](t) = \alpha k_1 [\text{Cl}^*]_0 [\text{H}_2\text{S}] \left[\theta_2 t + \theta_1 \frac{1 - \exp(-\varphi t)}{\varphi} \right], \quad (11)$$

where α is the probability of the formation of vibrationally excited molecules in reaction (8). During the initial period, the concentration of the chlorine atoms decreases from the starting value $[\text{Cl}^*]_0$ to $\theta_2[\text{Cl}^*]_0$. According to formula (11), the rate of formation of HCl molecules should also decrease during this period.

Thus, in this example the initial period of the chain reaction should manifest itself in the luminescence signal of HCl as a 'kink' segment. During the time corresponding to the initial region, the rate of formation of excited molecules decreases from the initial value to that corresponding to a quasi-steady-state process.

Figure 3a shows a luminescence signal of HCl observed after the irradiation of a $\text{Cl}_2 + \text{H}_2\text{S}$ mixture with a pulse of a UV laser. In the initial region of the signal, the rate of the product formation during the establishment of a quasi-steady-state equilibrium between the active centres decreases. After an equilibrium has established, the increase in the concentration of vibrationally excited HCl molecules continued. The deviation of this increase from the linear dependence is due to the vibrational relaxation of HCl molecules.

If the vibrationally excited molecules are formed in the second stage of the chain process, the induction period of a chain reaction manifests itself in the luminescence signals in a different way. An example of such a process is the reaction of chlorination of hydrogen¹⁹

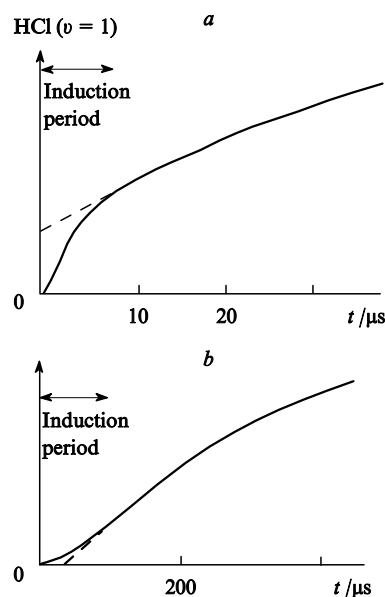


Figure 3. Initial parts of signals of the luminescence of HCl^* molecules formed in chain reactions of H_2S (a) and H_2 (b) chlorination. Partial pressure, Torr: (a) 0.183 (H_2S), 2.20 (Cl_2), 8.48 (Ar); (b) 9.59 (H_2), 0.026 (Cl_2).

In this case, the formula describing the increase in the concentration of vibrationally excited HCl molecules after a laser pulse has the form

$$[\text{HCl}^*](t) = \alpha k_1 [\text{Cl}^*]_0 [\text{H}_2] \left[\theta_1 t - \theta_2 \frac{1 - \exp(-\varphi t)}{\varphi} \right], \quad (14)$$

where $\theta_1 = k_1[\text{H}_2]/\varphi$, $\theta_2 = k_2[\text{Cl}_2]/\varphi$ and $\varphi = k_1[\text{H}_2] + k_2[\text{Cl}_2]$. This formula shows that the rate of formation of the vibrationally excited product increases in the initial region from zero to a certain constant value.

Figure 3b displays an example of an IR-CL signal observed in a $\text{Cl}_2 + \text{H}_2$ mixture (see Ref. 52). It is evident that the rate of formation of excited HCl molecules in the initial region increases (the curve is concave, unlike the curve in Fig. 3a).

The initial region contains complete information on the rate constants for both stages of the chain growth. Using the formulas (11) or (14), it is possible to retrieve this information from the experimental signal. For approximation of the experimental curve, for example by formula (11), only three independent parameters have to be found, i.e., the signal amplitude, the reaction rate constant k_1 and one of the values θ_1 or θ_2 related by $\theta_1 + \theta_2 = 1$. These parameters are sufficient for finding the rate constants. However, this kind of analysis of the shape of the initial region of the luminescence signal has not been carried out.⁵²

Quasi-steady-state chain reaction. After the end of the induction period of the chain reaction, a quasi-steady-state equilibrium is established between the concentrations of the active centres. The concentration of vibrationally excited products increases in this stage at a rate that depends on a combination of the rate constants for the elementary steps of chain growth. It is convenient to consider this using the same reaction of H_2S chlorination as an example. The reaction rate is determined [taking the formula (11) into account] by the derivative

$$w = \frac{d[\text{HCl}^*](t)}{dt} = \alpha \frac{k_1 k_2 [\text{Cl}^*]_0 [\text{H}_2\text{S}] [\text{Cl}_2]}{k_1 [\text{H}_2\text{S}] + k_2 [\text{Cl}_2]}. \quad (15)$$

It is difficult to find w from the luminescence signal, as precise calibration of the absolute sensitivity of the radiation detector is required. Therefore, formula (15) cannot be used to obtain kinetic

information. However, measurement of w even in relative units can give such a kinetic information. Taking into account that the initial concentration of the chlorine atoms $[\text{Cl}^*]_0$ is proportional to the energy of the laser pulse E and the concentration of molecular chlorine, formula (15) can be rewritten as

$$\frac{[\text{Cl}^*]_0[\text{H}_2\text{S}]}{w} = \frac{1}{\alpha k_1} \left(1 + k_1 \frac{[\text{H}_2\text{S}]}{k_2[\text{Cl}_2]} \right). \quad (16)$$

Expression (16) means that the rate of the quasi-steady-state stage of the chain reaction normalised per pulse energy and the product of the concentrations of the starting substances depend only on the ratio of the rates of the stages of the chain growth. It follows from this formula that $E[\text{Cl}_2][\text{H}_2\text{S}]/w$ should depend linearly on the concentration ratio $[\text{H}_2\text{S}]/[\text{Cl}_2]$. Figure 4 demonstrates a plot of this dependence. Analysis of formula (16) shows that the simple graphical method can be used to determine the ratio of rate constants for the elementary steps of chain growth. One has to determine the slope of the straight line and its intercept with the ordinate axis. The ratio of these parameters equals k_1/k_2 .

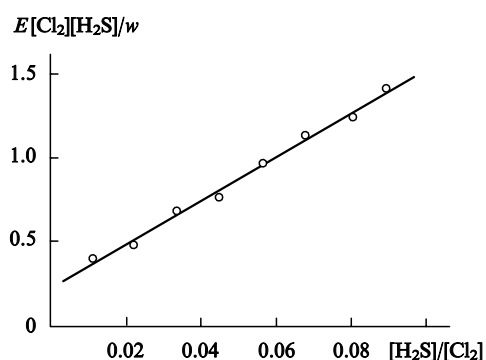
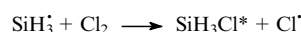
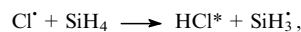


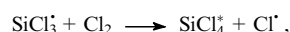
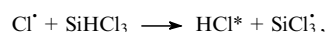
Figure 4. Dependence of inverse normalised rate of a chain reaction on the ratio of reagent concentrations.⁵²

It should be noted that an account of the vibrational relaxation complicates the determination of w from the observed luminescence signal. The formulas containing the necessary corrections are presented in Ref. 52.

Using the technique described above, the ratio of the rate constants for the chain growth stages in the chlorination of H_2S [reactions (8) and (9)] was determined: $k_1/k_2 = 16$.⁵² The chain reaction of the SiH_4 chlorination was studied using this method.⁵³ The ratio of rate constants for the reactions



was found to be 4.6. The chain reaction of the SiHCl_3 chlorination was studied.⁵⁴ The ratio of rate constants for the reactions



was found to equal 1.3. The same technique was applied to the study of the chain chlorination of butane and ethane.

Certainly, this procedure does not correspond to direct methods for the determination of rate constants. However, it provides rather reliable information, which is difficult to obtain by other methods. The advantage of using the time-resolved luminescence technique is that it is possible to avoid the complicating effect of chain termination reactions.

A method for the measurement of rate constants based on the study of chain reaction termination stages. The IR-CL signal of chain reaction products recorded after a sufficiently long period

since its initiation contains information on the rate of decay of active centres in chain termination reactions. If the elementary reaction the rate constant of which has to be determined can serve as the chain reaction termination stage, it becomes possible to measure its rate. In this approach, the chain reaction resulting in the formation of vibrationally excited molecules plays the role of a probe for tracing the time dependence of the concentration of atoms or radicals. This allows one to study reactions that do not produce vibrationally excited molecules by the IR-CL technique. A similar approach for non-chain reactions has been developed.^{50,51} The use of a chain reaction gives two additional benefits. First, the sensitivity of the method increases as the total number of vibrationally excited molecules formed in a chain reaction can be many times greater than the number of active centres. Second, this expands the range of reactive species whose reactions can be studied by this method.

A detailed analysis of the IR-CL kinetics of chain reaction products at various inhibitor concentration was carried out by Chesnokov.⁵⁵ The exact solution of this problem is rather cumbersome, but the results for reactions with a long chain are simple enough and have a simple qualitative interpretation.

A chain reaction in a mixture of compounds $\text{A} + \text{B}$ with active centres X^* and Y^* involves the following elementary steps:



In the initial instant of time, a pulse of laser irradiation creates a certain concentration of active centres X^* equal to x_0 . The active centres Y^* are absent in the initial instant, $[\text{Y}^*] = 0$. Then, during the chain reaction induction period, a quasi-steady-state equilibrium between the concentrations of X^* and Y^* is established; the X^* concentration decreases, while the Y^* concentration increases (Fig 5a). The overall concentration of the active centres $[\text{X}^*] + [\text{Y}^*]$ remains approximately equal to x_0 .

After a quasi-equilibrium has been established, the overall concentration of the active centres decreases owing to their decay in chain termination reactions. The fractions of X^* and Y^* in the overall concentration of active centres remain constant. The fraction of X^* in the overall concentration of active centres equals

$$\theta_2 = \frac{k_2[\text{B}]}{k_1[\text{A}] + k_2[\text{B}]}, \quad (20)$$

while the fraction of active centres Y^* equals

$$\theta_1 = \frac{k_1[\text{A}]}{k_1[\text{A}] + k_2[\text{B}]}. \quad (21)$$

The decay of active centres occurs with an weighted average rate constant

$$\kappa = \theta_1 k_4 + \theta_2 k_3. \quad (22)$$

If the active centres X^* disappear in a reaction with substance C added to the reaction mixture:



then the rate of decay of the active centres increases:

$$\kappa = \theta_1 k_4 + \theta_2 (k_3 + k[\text{C}]), \quad (24)$$

where k is the rate constant for reaction (23).

The formula (24) underlies the method discussed for the determination of rate constants. If the life time of active centres of a chain reaction τ is measured at various concentrations of reagent C, then the reciprocal value $\kappa = \tau^{-1}$ should linearly depend on the reagent concentration. The factors θ_1 and θ_2 depend

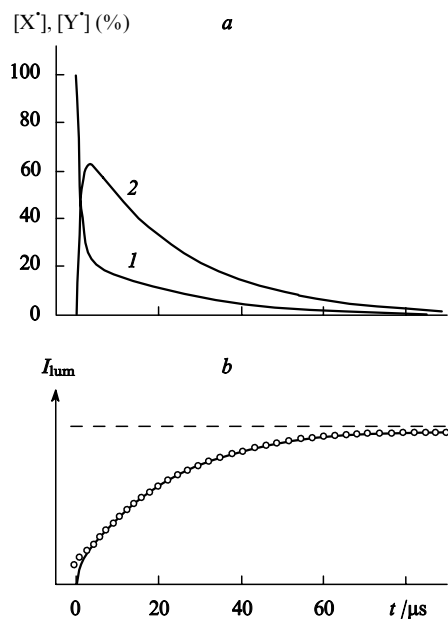


Figure 5. Theoretical luminescence signal of chain reaction products. (a) establishment of quasi-steady-state equilibrium between the concentrations of X' (1) and Y' (2); (b) luminescence intensity at quasi-steady-state equilibrium between X' and Y' .

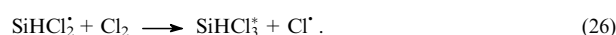
on the ratio of the starting concentrations of the original compounds A and B. If concentration B is chosen large enough, it is possible to reach the conditions where $\theta_2 \approx 1$ and $\theta_1 \approx 0$. If the reaction rate constant for the active centre Y' has to be measured, then, on the contrary, it is necessary to choose such conditions that $\theta_2 \approx 0$ and $\theta_1 \approx 1$.

The procedure for the determination of the life time of active centres from the luminescence signal of the reaction products remains the same. The curve $I(t)$ is described by a sum of exponential terms, which allow one to determine the time of vibrational relaxation and the life time of the active centres. One only has to exclude from consideration the initial period of the reaction, when the quasi-equilibrium between the concentrations of the active centres has not yet been established (see Fig. 5).

This method has been used for the measurement of the rate constants for a number of reactions.⁵⁵ Let us consider the measurement of the rate constants for the reactions $Cl' + NOCl$ with the use of this method.

First, one has to choose the chain reaction. Many chain reactions involving the chlorine atom and accompanied by the formation of vibrationally excited products are known. The reactions of chlorination of SiH_4 and its halogen derivatives are very convenient. These reactions give vibrationally excited hydrogen chloride molecules.^{23, 54} The stages of continuation in such reactions are fast,⁵⁶ hence the chain length can be significant even at low pressures. The inconvenience of the reaction of SiH_4 chlorination is that self-inflammation of its mixtures with Cl_2 occurs in the absence of an inhibitor. The reactions of SiH_2Cl_2 and $SiHCl_3$ chlorination are devoid of this drawback. Let us choose the faster reaction of SiH_2Cl_2 chlorination.

The chlorination of SiH_2Cl_2 involves the following chain growth steps:



The rate constant for reaction (25) is $1 \times 10^{-10} \text{ cm}^3 \text{ s}^{-1}$,⁵⁶ The rate constant for reaction (26) is $2 \times 10^{-11} \text{ cm}^3 \text{ s}^{-1}$.²³ Reaction (25) gives HCl^* molecules in the states $v = 0$ and $v = 1$ with probabilities of 0.67 and 0.33, respectively.²³

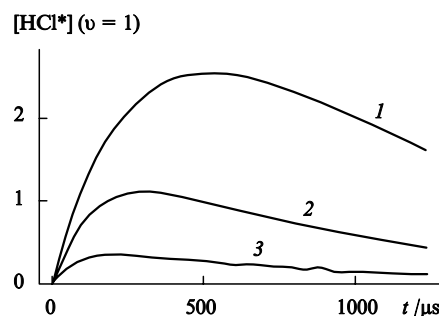


Figure 6. Examples of kinetic curves of luminescence of HCl^* molecules formed upon chlorination of SiH_2Cl_2 . Concentrations: SiH_2Cl_2 8×10^{14} ; Cl_2 2×10^{16} ; He $1.3 \times 10^{17} \text{ cm}^{-3}$; NOCl concentration/ cm^{-3} : (1) 2.2×10^{13} ; (2) 5.9×10^{13} ; (3) 15×10^{13} .

Figure 6 shows examples of IR-CL signals of excited hydrogen chloride molecules observed after reaction initiation in a $SiH_2Cl_2 + Cl_2$ mixture with addition of NOCl. An increase in the NOCl concentration decreases the amplitude of the luminescence signal. Such a dependence indicates that, under the conditions of the experiments, the time of vibrational relaxation exceeds the life time of active centres of the chain reaction. Figure 7 shows the dependence of the times of growth and decay of experimental curves on the NOCl concentration. It is evident that one of the characteristic times does not depend on the concentration of NOCl, while the other one varies over a wide range. The first time coincides with the time of vibrational relaxation and does not vary with the change in the NOCl concentration, since the concentrations of the other components of the mixture are much higher. The second time is the life time of the active centres of the chain reaction. At the concentrations $[NOCl] > 3 \times 10^{13} \text{ cm}^{-3}$, the life time of the active centres is smaller than the time of vibrational relaxation; at concentrations $[NOCl] < 3 \times 10^{13} \text{ cm}^{-3}$, the life time of the active centres becomes longer than the vibrational relaxation time. The inverse life time of active centres linearly depends on the NOCl concentration. The ratio of the projections of any segment of this linear dependence on the coordinate axes equals $(6.0 \pm 0.5) \times 10^{-11} \text{ cm}^3 \text{ s}^{-1}$.

In view of the above values of the rate constants for the steps of propagation of chain reaction under the conditions of the experiment, we obtain $\theta_2 = 0.85 - 0.9$; $\theta_1 = 0.1 - 0.15$. The parameter θ_1 cannot be regarded as negligibly small, hence it is necessary to take into account reactions of the active centres of both types

$$\kappa_2 = (\theta_2 k_3 + \theta_1 k_4)[NOCl] + \text{const}, \quad (27)$$

where k_3 and k_4 are the rate constants for the reactions

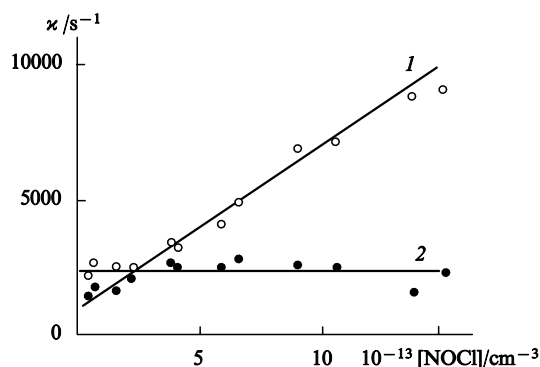
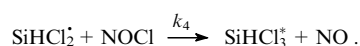
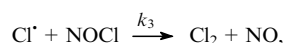


Figure 7. Dependences of reciprocal times of signal growth and decay on NOCl concentration; (1) life time of active centres; (2) vibrational relaxation time.



Thus, taking into account the slope of the straight line in Fig. 7, we obtain

$$\theta_2 k_3 + \theta_1 k_4 = (6.0 \pm 0.5) \times 10^{-11} \text{ cm}^3 \text{ s}^{-1}. \quad (28)$$

A mixture with a larger fraction of SiH_2Cl_2 was studied to estimate the contribution of the term $\theta_1 k_4$; in this case, $\theta_1 = 0.3-0.4$. It was found that the contribution of the second term in formula (28) did not exceed 10%–15%. The resulting rate constant k_3 equals $(6.5 \pm 0.5) \times 10^{-11} \text{ cm}^3 \text{ s}^{-1}$.

This method was used^{57,58} for measuring the rate constants for a number of reactions of the chlorine atom with silicon-containing radicals. The results of these studies and the available published data obtained by other methods are listed in Table 3. The prospects of this method for the measurement of the rate constants for a certain reactive particle are determined by whether a fast chain reaction accompanied by formation of vibrationally excited molecules can be found for this particle. The analysis carried out by Chesnokov⁵⁵ shows that is possible to expect a gain in sensitivity only in the case where the rates of the chain propagation steps of the chain reaction exceed the rate of vibrational relaxation. This condition is similar to that demanded for the chain reaction for a chemical laser.²

Table 3. Rate constants for some reactions of the chlorine atom with silicon-containing radicals.

Reaction studied	Auxiliary reaction	$10^{11} k / \text{cm}^3 \text{ s}^{-1}$	Ref.
$\text{Cl}^\bullet + \text{NOCl} \rightarrow \text{Cl}_2\text{NO}^\bullet$	$\text{Cl}_2 + \text{SiH}_2\text{Cl}_2$	6.5 ± 0.5	55
	$\text{Cl}_2 + \text{H}_2$	7.5 ± 1.0	55
		8.0	59
$\text{Cl}^\bullet + \text{ICl} \rightarrow \text{Cl}_2^\bullet + \text{I}^\bullet$	$\text{Cl}_2 + \text{H}_2$	1.2 ± 0.2	55
		0.8	60, 61
		1.0 ± 0.3	62
$\text{Cl}^\bullet + \text{Br}_2 \rightarrow \text{BrCl}^\bullet + \text{Br}^\bullet$	$\text{Cl}_2 + \text{SiH}_2\text{Cl}_2$	$(1.1 \pm 0.2) \times 10$	55
		1.2×10	50, 61
$\text{SiH}_3^\bullet + \text{NOCl} \rightarrow \text{SiH}_3\text{Cl}^\bullet + \text{NO}^\bullet$	$\text{Cl}_2 + \text{SiH}_4$	$(6.0 \pm 2.0) \times 10^{-1}$	55
		1.3 ± 0.3	63
$\text{SiH}_3^\bullet + \text{Br}_2 \rightarrow \text{SiH}_3\text{Br}^\bullet + \text{Br}^\bullet$	$\text{Cl}_2 + \text{SiH}_4$	6.5 ± 1.4	57
$\text{SiCl}_3^\bullet + \text{Br}_2 \rightarrow \text{SiCl}_3\text{Br}^\bullet + \text{Br}^\bullet$	$\text{Cl}_2 + \text{SiHCl}_3$	10.5 ± 1.7	57
$\text{SiHCl}_2^\bullet + \text{Br}_2 \rightarrow \text{SiHCl}_2\text{Br}^\bullet + \text{Br}^\bullet$	$\text{Cl}_2 + \text{SiH}_2\text{Cl}_2$	6.0 ± 0.9	57
$\text{Cl}^\bullet + \text{I}_2 \rightarrow \text{ICl}^\bullet + \text{I}^\bullet$	$\text{Cl}_2 + \text{SiHCl}_3$	$(2.5 \pm 0.7) \times 10$	58
$\text{SiCl}_3^\bullet + \text{I}_2 \rightarrow \text{SiCl}_3\text{I}^\bullet + \text{I}^\bullet$	$\text{Cl}_2 + \text{SiHCl}_3$	$(5.8 \pm 1.8) \times 10$	58

It should be noted that the idea of increasing the sensitivity by using a chain reaction as a ‘probe’ has been suggested and implemented by Orkin and Chaikin⁶⁴ for the thermometric detection of atoms. With the use of IR-CL, it was found possible to implement the same idea in a time-resolved version.

VII. The time-resolved Fourier-transform spectroscopy of IR chemiluminescence

In the last decade, time-resolved Fourier-transform spectroscopy is being used ever more frequently for the study of the IR luminescence of the products of gas phase reactions. This method makes it possible to obtain the luminescence intensity as functions of both frequency and time after the reaction initiation. In exceptional cases, it was also possible to obtain time-resolved IR-CL spectra by ordinary methods.⁶⁵

For the first time, the time-resolved version of Fourier-transform IR spectroscopy was used for the study of chemiluminescence in the gas phase by Aker and Sloan,⁶⁶ who studied the initial distribution over vibrational states of the $\text{OH}^\bullet$ radical formed in the reaction



A normal Fourier-transform spectrometer was used. The time resolution was achieved in these measurements by synchronisation of the pulse laser initiating the reaction under study with the instants of time when the spectrometer measures the values of the IR radiation interferogram.

Figure 8 illustrates the operation principle of a Fourier-transform IR spectrometer in the time-resolved mode. The directly measured characteristic is an interferogram, *i.e.*, dependence of intensity of IR radiation at the interferometer output on the difference between the ray paths in the two arms of the interferometer. The spectrum is obtained by Fourier transformation of the interferogram by a computer included in the set-up. The orientation of the moving mirror of the interferometer is determined using a helium–neon laser whose radiation passes through the auxiliary interferometer of the spectrometer combined with the main one. The controlling computer analyses the intensity of the ray of the helium–neon laser passed through the auxiliary interferometer and issues the commands for the measurement of the interferogram value. The moving mirror of the interferometer moves at a constant rate S , and the instants of time when the commands are issued are separated by identical time intervals T_0 (Fig. 8, curve 1)

$$T_0 = \frac{\lambda}{2S}, \quad (30)$$

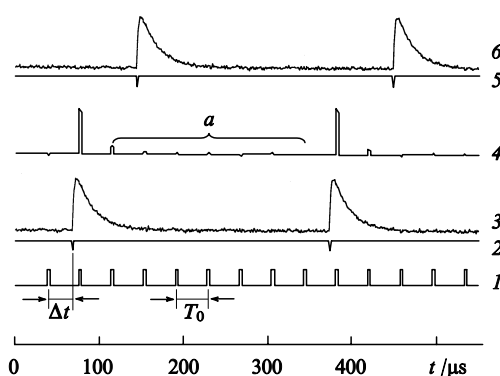


Figure 8. Diagram clarifying the operation of a Fourier-transform IR spectrometer in time-resolved mode;

(1) sequence of time instants of interferogram measurement; (2, 5) laser pulses; (3) IR radiation at interferometer output; (4) interferogram with discarded region *a*; (6) IR radiation in the next cycle of spectrometer operation.

where $\lambda = 0.6328 \times 10^{-4}$ cm is the wavelength of the helium-neon laser. To synchronise the pulse laser, the computer command for performing the measurements is used for starting the pulse generator, which after the time Δt triggers the pulse laser (Fig. 8, curve 2). If the delay Δt is equal to the duration of the measurement recurrence period T_0 or slightly smaller, the pulse laser will act immediately before the instant of the interferogram measurement. By decreasing the delay, one can obtain a luminescence spectrum for some definite time instant after the laser pulse.

A difficulty in the implementation of such a scheme arises due to the fact that the usual measurement frequency of an interferogram by a Fourier-transform spectrometer is several kHz or several tens kHz. The lasers used for reaction initiation cannot work with such a pulse repetition rate. This means that only a part of the interferogram measurements contain the signal, while the major part of the measurements, which do not contain the signal, should not be taken into account (see region *a* of curve 4). The missing points in the interferogram can be obtained in the subsequent cycles of mirror scanning; however special measures should be taken so that the interferogram contains no gaps. The measurements in Refs 66, 67 were carried out according to such a scheme. The gaps in the measurement of an interferogram can be avoided at high pulse frequency of the laser or at very small movement speed of the spectrometer mirror. An excimer laser with a repetition frequency of 316 Hz was used,^{68–70} and the interferometer mirror was moved very slowly (0.01 cm s^{-1}). At this movement speed of the mirror, the time interval between the interferogram measurements [formula (30)] is equal to the recurrence period of the laser pulses, and rejecting a part of the measurements is no longer necessary.

In the studies mentioned above,^{66–70} the Fourier-transform IR spectrometer was used without updating the IR radiation intensity measurement system. In later studies,^{71,72} advanced equipment was used that made it possible to make a measurement of the interferogram at several different delay times after each laser pulse, instead of one delay time as before. This required alteration of the standard measuring part of the spectrometer, which was replaced with a digital signal recorder connected to a computer with a sufficiently large memory size capable of simultaneous accumulation of interferograms for all time instants. This updating increases considerably the speed of recording spectra.

Additional specific noise appears in the time-resolved mode; this may result, e.g., from the power instability of the pulse laser. It was suggested⁷³ that this noise be decreased by normalising the measurement results in each pulse using the pulse power.

Let us consider several examples of studies carried out by time-resolved Fourier-transform IR spectroscopy.

The reaction of the electron-excited $\text{O}^*(^1\text{D})$ atom with the hydrogen molecule was studied.⁶⁶ The distribution of the radical $\text{OH}^\bullet$ formed in reaction (29) over vibration levels was determined and found to be as follows: $P(v = 1 : 2 : 3 : 4) = 0.29 : 0.32 : 0.25 : 0.13$. The time-resolved Fourier-transform IR spectroscopy made it possible to study the distribution undisturbed by relaxation processes. The distribution obtained is of intermediate type between that characteristic of reactions occurring through an intermediate complex and that characteristic of direct cleavage reactions. It was thus assumed that the reaction dynamics includes a stage of a very strongly excited water molecule, which decays after the time corresponding to several vibration periods.

The reaction of the $\text{CHF}^\bullet$ radical with the NO molecule was studied.⁷² The radical was obtained by multiphoton IR dissociation of CH_2FCl or CH_2F_2 . The luminescence of vibrationally excited HF molecules formed in the reaction was recorded. The addition of D_2 to the reaction mixture resulted in the excited DF molecules, which allowed the determination of the ratio of the pathways yielding HF and $\text{F}^\bullet$ for the reaction studied; this ratio was found to be 0.6 : 0.4.

Vibration relaxation of NO molecules excited to high vibration levels was studied.⁷⁴ The photolysis of N_2O (irradiation with a wavelength of 193 nm) gives $\text{O}^*(^1\text{D})$, which reacts with N_2O to

give the highly excited NO molecule. Twenty IR luminescence interferograms corresponding to various instants of time (step 30 μs) were obtained. Based on the interferograms, the spectra were reconstructed in the range from 2500 to 1500 cm^{-1} with a resolution of 4 cm^{-1} . By plotting the spectra calculated in this way, a time dependence of the population of vibration levels from $v = 1$ to $v = 11$ was obtained. The results were interpreted using a system of eleven kinetic equations that described the vibrational relaxation. The rate constants for the vibrational relaxation of separate vibration levels were determined. The relaxation constant for the level $v = 11$ is 40 times greater than that for the level $v = 1$.

In several publications, the initial distribution of photodissociation products of various molecules over vibration levels was studied using time-resolved Fourier-transform IR spectroscopy. For example, one of them⁶⁹ is devoted to the study of excitation processes of HF molecules formed upon the photodissociation of CH_2CClF (irradiation at the wavelength of 193 nm), while another one⁶⁷ deals with a study of distribution of the $\text{NH}_2^\bullet$ radical formed upon the photodissociation of NH_3 (irradiation with a wavelength of 193 nm) over vibration levels.

The studies using time-resolved IR chemiluminescence cannot be classified as purely kinetic ones, or to those where only the energy distribution in the reaction products is studied. The basic purpose of these works is to establish the distribution of products over vibration states. However, this can also provide quantitative information on the rates of vibrational relaxation processes and chemical reactions.

VIII. Conclusion

The time-resolved IR-CL method is used in gas-phase chemical kinetics in order to obtain quantitative information regarding the rates of elementary reactions. The application of this method for studying chain processes was found to be particularly fruitful.

However, it should be noted that the method is limited to a narrow range of molecules the luminescence of which can be observed. In fact, the luminescence of either HCl or HF was used in all of the studies. Attempts to overcome this restriction were undertaken. Reactions were found that gave polyatomic vibrationally excited molecules yielding intense luminescence. For example, luminescence of SiH_3Cl ⁷⁵ and of products of butane and ethane chlorination⁷⁶ was observed. The luminescence kinetics of SiH_3Cl was studied in detail;⁷⁵ this process is mostly determined by the transfer of vibration energy and vibrational relaxation. It was found of little use for obtaining information on the rates of chemical reactions. The difficulties are basically caused by the fast vibrational relaxation of highly excited polyatomic molecules.

Further prospects of the IR-CL method are related to the use of the time-resolved Fourier-transform spectroscopy.

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Mechanism of the directing influence of functional groups and the geometry of reactant molecules on peroxide epoxidation of alkenes

V G Dryuk, V G Kartsev

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Abstract. The influence of steric and electronic factors on the reactivity and the stereochemical outcome of epoxidation of cycloalkenes and prochiral alkenes by alkyl hydroperoxides, peroxy acids, oxaziridines, dioxiranes and dimethyl- α -peroxy lactone is analysed comparatively and generalised. The distinctive features of the directing influence of functional groups on the stereochemistry of the epoxide ring closure in the series of ionic, radical and molecular reactions are demonstrated. Some variants alternative to known reaction mechanisms are proposed. The bibliography includes 114 references.

I. Introduction

Stereochemical regularities of the epoxidation of alkenes by peroxide reagents have been the subject of detailed studies,^{1–8} because reactions of this type are widely used in asymmetric synthesis and for the preparation of a number of polyfunctional compounds of specified structures. In the last two decades, the knowledge of the stereochemistry of epoxidation has become much deeper due to the understanding of the role of stereo-electronic microeffects in the transition state^{2,5–9} and long-range macrostereochemical effects at the stage of coming together and coordination of reactants.^{10–13}

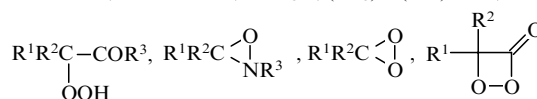
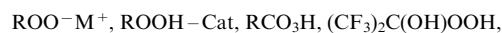
Thus it was found that the rate of epoxidation of aliphatic compounds by peroxy acids depends on the length and conformation of the hydrocarbon chain of the molecule.^{1,2} The dependence of the rate constants for epoxidation (k_{epox}) on the number of carbon atoms in the molecule of the peroxy acid RCO_3H or alkene is a broken curve (alternation effect).¹⁰ When the size of the peroxy acid molecule increases, the rate and contribution of epoxidation decrease; simultaneously, the loss of active oxygen in the alkene-induced decomposition of the peroxy acid becomes more significant.^{2,11,12} The rate of epoxidation of the first double bond in the diallyl dicarboxylates $\text{H}_2\text{C}=\text{CHCH}_2\text{OCO} \cdot (\text{CH}_2)_n\text{COOCH}_2\text{CH}=\text{CH}_2$ markedly decreases at $n > 2$,

although the electron-withdrawing influence of the ester group rapidly decays with an increase in n .¹³

The k_{epox} is substantially influenced by the solvation of functional groups far removed from the reaction centre. This solvation, like the increase in the size of the molecule, results in the loss of rotational degrees of freedom of reactant molecules and thus decreases the probability of their efficient collision.^{2,13}

The requirements for the spatial compatibility of reactants become more rigorous with an increase in the size of the substituents surrounding the CO_3H group up to the point when the steric factor becomes more significant than the electronic factor. *cis*-Alkenes better fit in the ‘niche’ of the shielded peroxy-acid site. As a consequence, the $k_{\text{cis}}:k_{\text{trans}}$ value becomes relatively high. An increase in the number of alkyl substituents at the double bond decreases the reaction rate.¹⁴

The stereo- and regioselectivity of epoxidation are largely associated with the influence of alkyl substituents and functional groups in the alkene (OH , COOH , CONH_2 , $\text{C}=\text{O}$, SiR_3 , etc.) on the epoxidising reagent and with the geometry of the reactant molecules.^{2,6–8,15} However, the features of the stereochemical influence of substituents and the stages responsible for this influence are still not quite clear. In particular, they have not yet been identified for the set of epoxidising reagents presented below.^{1,2,4,5,16}



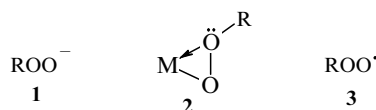
In this review, we attempt to generalise the accumulated data and to reveal new aspects concerning the mechanism of influence of the geometry of reactant molecules and the nature of functional groups on the rate, route and stereochemical outcome of epoxidation of alkenes with the above reagents. Using epoxidation by peroxy acids as an example, we describe systematically the general features of the behaviour of cycloalkenes and methylenecycloalkanes as functions of the strain and the degree of shielding of the double bond.

II. Epoxidation of alkenes with alkyl hydroperoxides

Epoxidation is normally carried out using alkyl hydroperoxide derivatives of types **1–3** shown below

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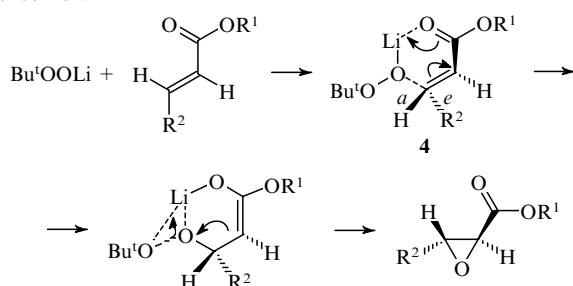
M is a transition metal in the highest oxidation state (Mo^{6+} , V^{5+} , Ti^{4+} , etc.).

Alkylperoxide anions **1**, like the hydroperoxide anion, oxidise polar $\text{C}=\text{C}$ double bonds conjugated with a carbonyl group in chalcones, quinones, naphthoquinones,^{17,18} α,β -unsaturated esters, sulfones, sulfoximines and amides^{19–22} at moderate temperatures (-20 to 0°C) with relatively high diastereoselectivity (20%–100%). These reactions are catalysed by bases (NaOH , Na_2CO_3). The use of salts (ROOK and ROOLi), which are formed on treatment of ROOH with the corresponding metal hydrides or alkylmetals, is also efficient. It is of interest that the use of the $\text{Bu}^t\text{OOH}-\text{RLi}$ oxidative system results in a side reaction, transfer of active oxygen to the carbanion, occurring in parallel with epoxidation.¹⁹

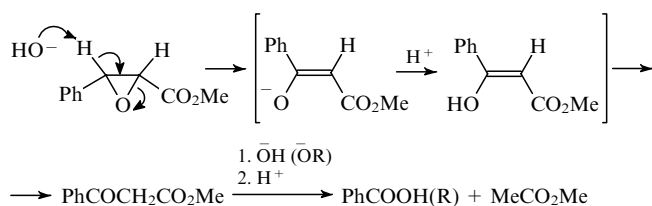


The regularities of the process have been studied most comprehensively in relation to epoxidation of α,β -unsaturated esters. This reaction is highly sensitive to steric restrictions, especially when the α - and β -positions in the substrate are substituted. The oxidation of *cis*-isomers is slower than that of *trans*-isomers. The reaction is completely stereospecific, except for oxidation of some sterically hindered esters of maleic acid. Di(*tert*-butyl) maleate is converted into the epoxide of di(*tert*-butyl) fumarate under the oxidation conditions.¹⁹

It is significant that epoxidation of α,β -unsaturated esters occurs diastereoselectively (the content of one isomer reaches 74%) only when lithium *tert*-butyl peroxide is used. When potassium *tert*-butyl peroxide is employed, the stereospecificity is lost. Apparently, the lithium cation, which has the most intense electromagnetic field among alkali metal cations, forms a stronger associative bond with the carbonyl oxygen atom in the substrate and thus stipulates the formation of cyclic transition state **4**. One of the two possible orientations of the unsaturated compound results in a more stable conformation of the transition state (TS) (with equatorial R^2); this ensures the predominant formation of one isomer.



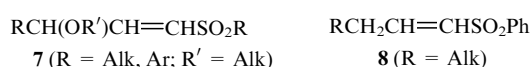
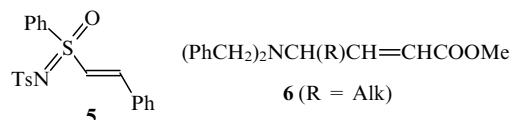
The reaction is accompanied by several side processes, in particular, transesterification and a rearrangement of the α,β -epoxy ester. Thus epoxycinnamate can rearrange to give the ester of an oxo acid, which then undergoes the Claisen cleavage.



Di(*tert*-butyl) maleate does not undergo stereocontrolled epoxidation.¹⁹ *N,N*-Dialkylamides of α,β -unsaturated acids undergo epoxidation with Bu^tOOLi with complete regio- and

stereo-control and a small extent of side reactions. This method is relatively ineffective for secondary amides and totally ineffective for primary amides. As in the case of esters, oxidation of *cis*-amides occurs more slowly than that of the corresponding *trans*-isomers. The reaction rate depends appreciably on the size of the substituent at the β -position.

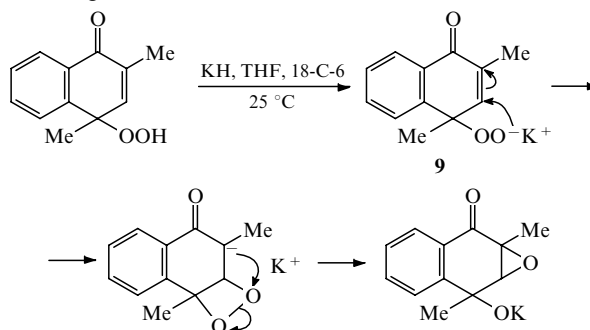
Phenyl *cis*-styryl sulfone is epoxidised according to the same rules as α,β -unsaturated esters. Epoxidation with potassium *tert*-butyl peroxide is not stereospecific (the ratio of *cis*- and *trans*-epoxides is 2:3), whereas treatment with lithium *tert*-butyl peroxide under the same conditions gives *cis*-epoxide as the only product in a high yield. The *trans*-isomer of this sulfone is epoxidised in a similar way. Asymmetric α,β -unsaturated sulfoximines **5** undergo epoxidation with 100% diastereoselectivity.



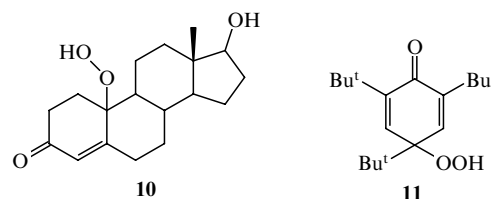
In this case, unlike the reactions described above,¹⁹ the use of potassium *tert*-butyl peroxide in a $\text{THF}-\text{NH}_3$ mixture permits stereoselective epoxidation of unsaturated compounds **6**.²⁰ The ratio of *syn*- and *anti*-diastereoisomers amounts to 95:5.

α,β -Unsaturated sulfones **7** undergo stereoselective epoxidation by Bu^tOOLi ,²¹ and analogous alkenyl sulfones **8** can be stereoselectively epoxidised by an alkaline solution of potassium *tert*-butyl peroxide.²² In the latter case, the product of addition of alkyl hydroperoxide at the double bond was isolated, apart from the corresponding epoxide.

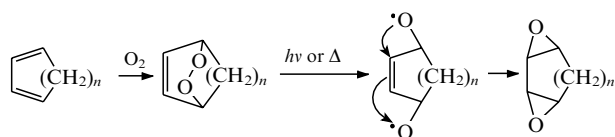
Intramolecular epoxidation of compound **9** simulates a stage of the biological oxidation of vitamin K.²³



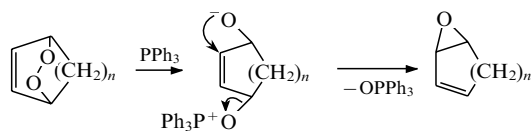
The alkaline intramolecular epoxidation of cyclic α,β -unsaturated ketones **10** and **11** occurs in a similar way, yielding *cis*-epoxy alcohols.^{24,25}



It can be easily understood that a coplanar arrangement of the p electrons of the peroxide anion and the π^* (antibonding) orbital of the double bond in the substrate is a necessary stereochemical condition for epoxide ring closure in the ketones **9–11** (stereoelectronic factor). This is also true for a large number of other heterolytic and radical reactions involving not only π^* orbitals^{23–26} but also $\sigma^*_{\text{O}-\text{O}}$,²⁷ and $\sigma^*_{\text{H}-\text{O}}$ ²⁸ type orbitals. In particular, this can be clearly seen in the case of photo or thermal isomerisation of *endo*-peroxides formed during oxygenation of cyclic 1,3-dienes by singlet oxygen.²⁶



Similar stereoelectronic effects are involved in the deoxygenation of *endo*-peroxides with triphenylphosphine.²⁶



The scheme of epoxidation of alkenes with alkylperoxy radicals with the intermediate formation of β -peroxyalkyl radicals^{1,27} is shown in Fig. 1.

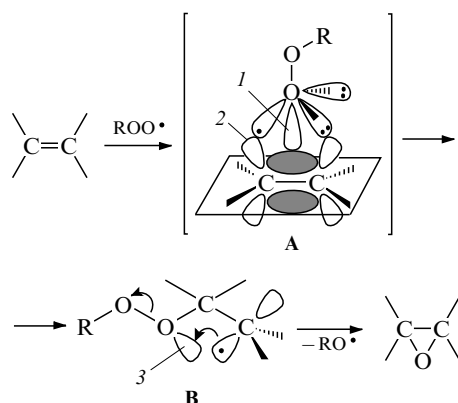
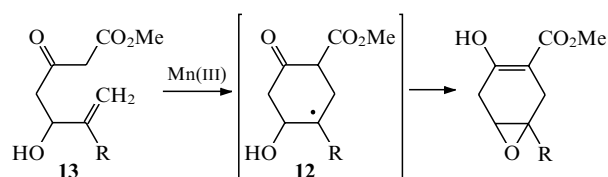
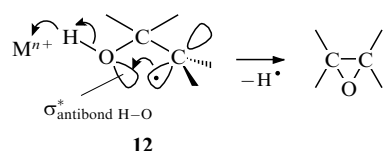


Figure 1. Epoxidation of alkenes with alkylperoxy radicals: **A** is the donor–acceptor complex; **B** is the β -peroxyalkyl radical; (1) the $\sigma_{\text{O}-\text{O}}^*$ orbital; (2) the $\pi_{\text{C}-\text{C}}^*$ orbital; (3) the $\sigma_{\text{antibond O}-\text{O}}^*$ orbital.

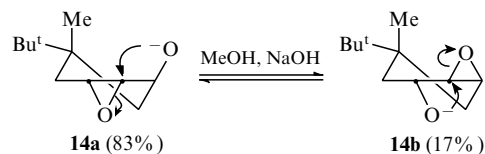
β -Hydroxy radicals **12** are generated during decarboxylation of β -hydroxy acids in the presence of lead tetraacetate and during oxidation of β -oxo esters **13** with manganese triacetate.²⁸



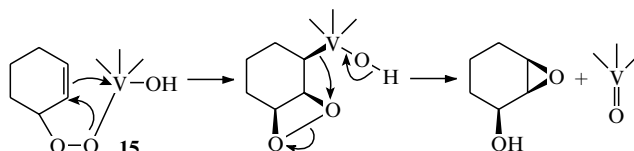
The epoxide ring closure occurring upon the oxidation of β -hydroxyl radicals by transition metal salts can be represented as follows:



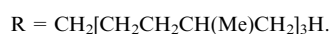
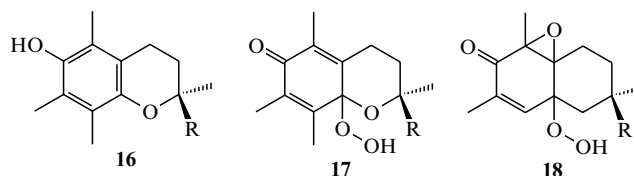
Isomerisation of α -hydroxy epoxide **14** in an alkaline medium occurs in a similar way.²⁹



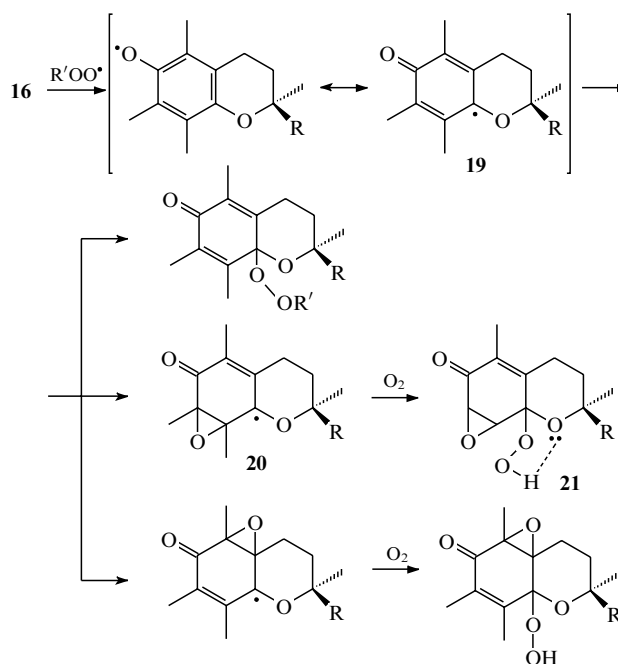
The generalisations made here can be invoked to interpret the mechanisms of some known reactions. Thus oxidation of alkenes with atmospheric oxygen on a vanadium catalyst^{5,30} gives allyl hydroperoxides, which undergo intramolecular epoxidation. This affords epoxy alcohols only as *cis*-isomers, which has been confirmed by simulation of the stage of self-oxidation of cyclo-alkenyl hydroperoxides.³¹ It is obvious that intramolecular *cis*-epoxidation rules out the possibility of the coplanar attack by the alkene π bond on the $\sigma_{\text{O}-\text{O}}^*$ orbital and the mechanism typical of epoxidation of inorganic acids by peroxy esters.^{5,7} Meanwhile, the structure of the substrate **15** is favourable for the nucleophilic attack by the outer peroxide oxygen atom on the π^* orbital of the alkene activated by the catalyst.



Yet another example of reaction the course of which can be predicted based on the above stereochemical regularity is oxidation of a biological antioxidant, vitamin E (D- α -tocopherol **16**).^{32,33} It was reported³² that the *tert*-butylperoxyl radical oxidises tocopherol **16** to give epoxy hydroperoxide **18** via the intermediate formation of hydroperoxide **17**.

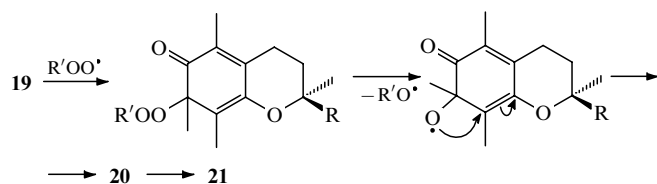


When tocopherol **16** is oxidised by the radicals formed upon thermolysis of azobis-2,4-dimethylvaleronitrile in oxygen-saturated acetonitrile, the hydroperoxide **17** is formed in only small amounts and, judging by kinetic data, it is not an intermediate compound.³³ It was suggested that the reaction follows the scheme shown below:

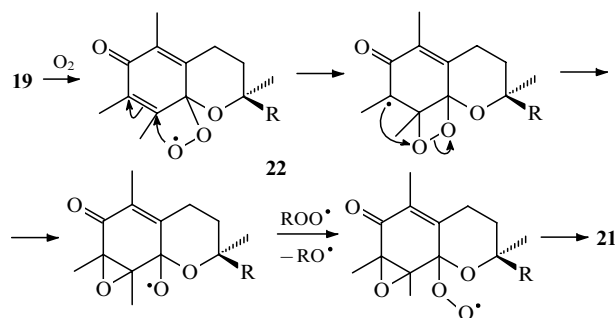


With allowance for the above-discussed stereoelectronic conditions for the closure of an epoxide ring, two ring formation mechanisms operating during the transformation of the radical **19**

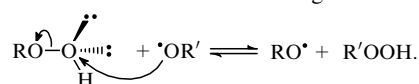
into **20** and then into the epoxide **21** can be conceived. In the case of direct attack by the alkylperoxyl radical $R'OO^\bullet$ on the π bond, the following transformations occur:



In the case where the radical **19** captures a triplet oxygen molecule, a different sequence of transformations is possible.



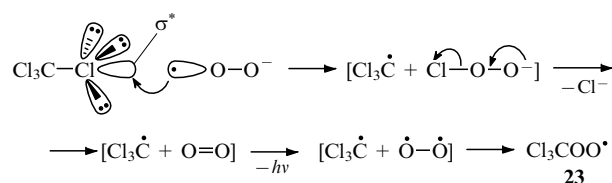
The epoxidation mechanism assuming the formation of the alkenylperoxyl radical **22** is possible in the case of either disproportionation of radicals or exchange interaction



One can expect that an equilibrium of this type in the reaction in question would be shifted towards the more stable hydroperoxide **21** having an intramolecular hydrogen bond.

It has been found that radicals formed from the superoxide ion ($O_2^{\bullet-}$) and polyhaloalkanes (CCl_4 , $CHCl_3$, F_3CCl_3 , $PhCCl_3$, $Cl_2C=CCl_2$, etc.)^{34,35} containing a halogen atom which can be homolytically eliminated possess epoxidising ability under mild conditions. For example, when CCl_4 is treated with potassium superoxide in acetonitrile in the presence of a phase transfer catalyst, the trichloromethylperoxyl radical $Cl_3COO^\bullet$ **23** acts as a species of this type.

In our opinion, the mechanism of generation of this radical includes radical decomposition of polyhaloalkanes initiated by the superoxide ion to give singlet oxygen.

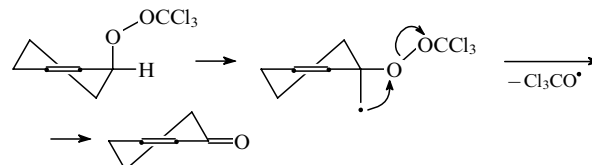


The fact that the yield of the epoxide does not depend on the concentration of $^3O_2$ indicates that the radical **23** is formed only from the initial compounds in a solvent cage.

The radical character of the process is confirmed by the loss of stereospecificity — *cis*-stilbene is mostly converted under these conditions into *trans*-stilbene oxide. Additives able to transform $Cl_3COO^\bullet$ into the anion inhibit the epoxidation.

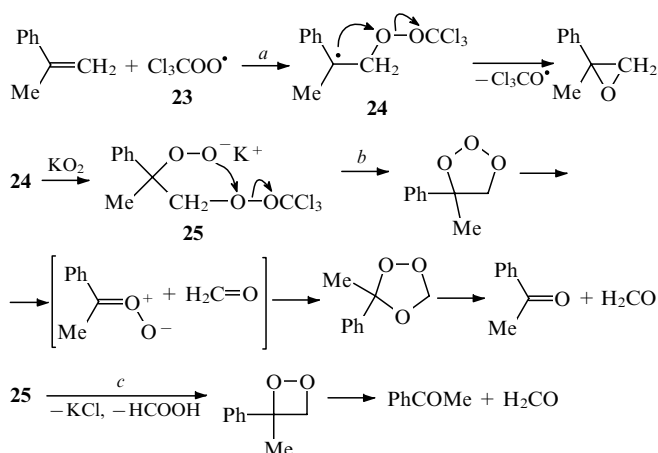
Oxidation of alkenes by radicals of the type **23** is a good model for the study of general, including stereochemical, regularities of the set of consecutive and competing transformations involved in epoxidation by alkylperoxyl radicals, oxometal complexes and triplet oxygen, which is usually accompanied by extensive oxidation of substrates with complete cleavage of the alkene double bond.^{2,5,36}

In particular, attention is attracted by the fact that in addition to oxirane (yield 73%), epoxidation of cyclohexene in the CCl_4-KO_2 system gives cyclohex-2-enone (yield 9%), whereas 1-methylcyclohexene is oxidised only to the corresponding oxirane. This difference is undoubtedly due to the higher nucleophilicity of the double bond in the latter compound. However, the steric factor also cannot be ignored; indeed, the methyl group introduced in the cyclohexene molecule decreases its conformational mobility. The stereochemistry of radical oxidation of cyclohexene at the α -C-H bonds requires that the $Cl_3COO^\bullet$ radical **23** be inserted into the axial position; this should be followed (at the stage of formation of the carbonyl group) by ring inversion and migration of the substituents to the equatorial position.



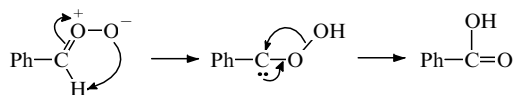
In addition to epoxides, the reaction affords products of complete cleavage of alkenes at the double bond (which are formed *via* a parallel route rather than in subsequent transformations). For example, acetophenone (19%) is formed in the oxidation of α -methylstyrene apart from the epoxide (73%). The highest yield of acetophenone is attained much earlier than that of the epoxide. It was found in special experiments that epoxide itself is not converted into acetophenone under the reaction conditions. It is also noteworthy that α -methylstyrene is oxidised more readily when taken as an equimolar mixture with styrene rather than in a pure state, although it is more nucleophilic.

The character of the observed transformations implies that in addition to the classical epoxidation of the alkene *via* β -peroxyalkyl radical **24** (pathway *a*),^{2,36} transformations in this system include more extensive oxidation involving a second KO_2 molecule, yielding intermediate **25** and resulting in complete rupture of the alkene bond. This brings about the fundamentally important question of what is the route leading to the oxo compound. Indeed, this product could be formed either *via* the ozonide and then the Criegee intermediate (pathway *b*) or *via* dioxetane (pathway *c*).

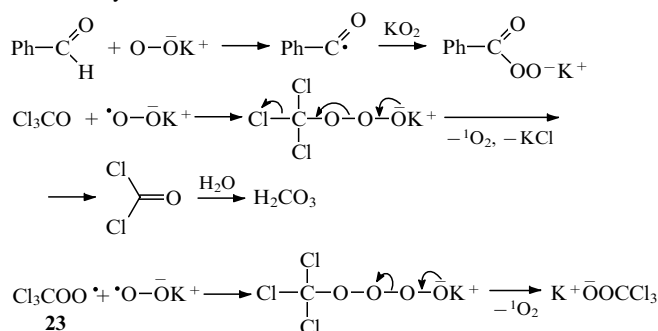


Pathway *b* is a result of the transfer of oxygen from the peroxide group $R-O-O-R'$ to the peroxyalkyl anion, by analogy with self-oxidation of peroxide compounds.² This seems more likely than pathway *c*, which assumes reversible nucleophilic substitution giving a strained dioxetane ring at an initial stage.

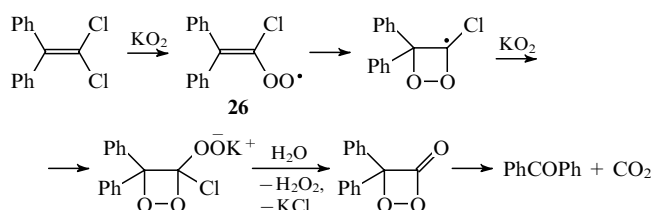
Pathway *b* involving the formation of a carbonyl oxide accounts for the fact that during oxidation of styrene, benzoic acid, formed in parallel with benzaldehyde, is accumulated in the reaction mixture.³⁵



However, in the presence of KO_2 , oxidation of aldehydes, in particular benzaldehyde, is also possible; this gives rise to the benzoylperoxide anion, the oxidative capacity of which exceeds that of the radical **23**. It is this fact that accounts for the promotory influence of styrene on the epoxidation of α -methylstyrene. The $\text{Cl}_3\text{CO}^\bullet$ radical formed in epoxidation is neutralised apparently by excess KO_2 . The epoxidising radical **23** can be consumed in a similar way.



If the polyhalide molecule contains a double bond, cyclisation of the intermediate peroxy radical **26** during the reaction becomes possible.³⁴



Epoxidation of alkenes by peroxy esters of inorganic peroxy acids has been studied fairly comprehensively.^{1, 2, 5, 7, 37, 38}

A peculiar feature of the ROOH –Cat epoxidising system (Cat is a transition metal complex) is that the hydroperoxide molecule enters the coordination sphere of the central atom as a nucleophile; this is accompanied by displacement of one ligand (acetylacetonate, OR, RCO_2 , CO, *etc.*). Apparently, the alkene also participates in the ligand exchange. The rate of these reactions can be comparable with the epoxidation rate. Consequently, the overall rate of the process is controlled by the rate of diffusion and exhibits self-acceleration or, conversely, self-deceleration effects.^{2, 39}

When the alkene contains a nucleophilic functional group (for example, an allylic hydroxy group), both the alkylperoxide fragment and this functional group get into the coordination sphere of the catalyst.^{5, 7} Thus, the stereodirecting influence of the hydroxy group in alkenes on the attack by alkyl hydroperoxide is exerted at the stage of construction of a highly ordered multiligand donor–acceptor complex. It has been found that the stereoselectivity of formation of the corresponding oxiranes in the epoxidation of allylic alcohols decreases upon an increase in the degree of shielding of the hydroxy group.⁴⁰

Compound				
ee (%)	> 95	85	25	5
Yield (%)	52	43	77	75

The geometry of the chiral environment of the catalytic center, which has a sort of matrix effect on the orientation of the prochiral double bond, is a crucial factor for the occurrence of stereocontrolled synthesis in the presence of the ROOH –Cat system. In

particular, the Sharpless reagent ensures not only high diastereoselectivity but also enantiofacial selection caused by the ligand configuration (D- or L-tartrate). The strict spatial orientation of the molecular orbitals participating in the construction of the intermediate complex also makes a certain contribution to the matrix effect (stereoelectronic factor).

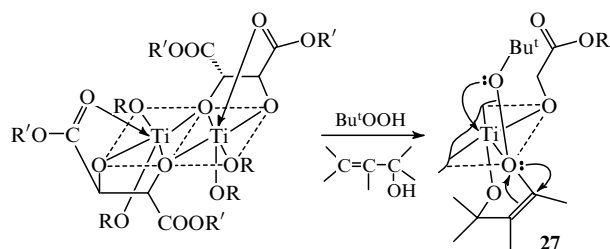
The extent to which a hydroxy group is involved in the epoxidation of cyclic alkenes and alkadienes is determined not only by its position relative to the double bond but also by the conformation of the molecule as a whole. This can be judged by examining the relative rates of epoxidation of the double bonds [$\text{Bu}^\text{t}\text{OOH}$, $\text{VO}(\text{acac})_2$, C_6H_6 , 40 °C] in the following sequence of substrates:⁴¹

Compound					
k_{rel}	100	2.1	0.09	40	19

The introduction of a bulky trimethylsilyl group (*e.g.* at the 3-position) in the unsaturated alcohol molecule increases the stereoselectivity of epoxidation.⁴²

The higher stereoselectivity observed in the presence of alkyl hydroperoxides and the greater versatility of these reagents compared to peroxy acids is due to the formation of a fairly strong donor–acceptor bond between the hydroxy group of alkenol and the central metal atom.

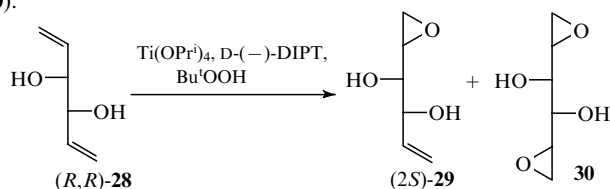
Detailed investigation of the $\text{Bu}^\text{t}\text{OOH}$ –diethyl tartrate–Ti(IV) epoxidising system permitted the researchers^{7, 39} to conclude that epoxidation occurs in binuclear complex **27** with six-coordinate titanium.



$\text{R} = \text{Pr}^\text{i}$, $\text{R}' = \text{Et}$.

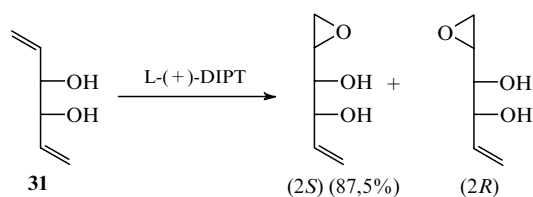
Change in the ligand nature, in particular, the use of titanium complexes containing chloride ions or amides of tartaric acid results in inverted stereoselectivity.⁴³

It has been shown⁴⁴ that opposite enantiofacial selectivities are observed for allylic and homoallylic alcohols. This finding might suggest a synergistic effect of the two hydroxy groups in the optically active (1*R*,2*R*)-1,2-divinylethylene glycol **28**. However, epoxidation of this compound by $\text{Bu}^\text{t}\text{OOH}$ led to an unexpected result,⁴⁰ namely, the inversion of enantioselectivity and enantiofacial selectivity was observed. Depending on the amount of the oxidant used, this reaction yielded either mono- (**29**) or di-epoxide (**30**).

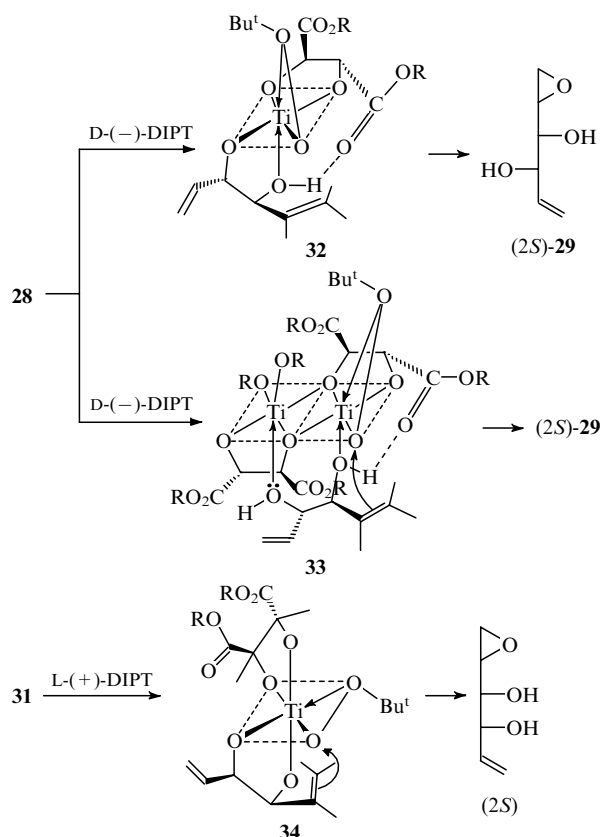


DIPT is diisopropyl tartrate

Diisopropyl L-(+)-tartrate [L-(+)-DIPT], which should have been used according to the empirical rule formulated by Rossiter and Sharpless,⁴⁴ proved to be inapplicable. However, epoxidation of the monobenzyl ether of glycol **28** occurred in conformity with this rule.⁴⁵ The *meso*-form of 1,2-divinylethylene glycol **31** was epoxidised in a similar way.



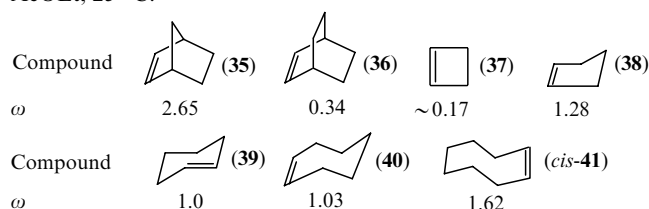
The result of the asymmetric epoxidation of the stereoisomeric glycols **28** and **31** was interpreted by assuming that the (*R,R*)-substrate **28** reacted as a monomeric (**32**) or dimeric (**33**) complex, in which the peroxide oxygen atoms are arranged as in the complex **27**, whereas the *meso*-form reacted in complex **34**, in which the oxygen atoms are arranged horizontally.



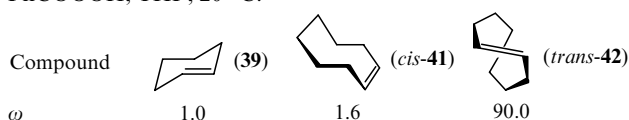
III. Specific features of epoxidation of cycloalkenes and methylenecycloalkanes with peroxy acids

Cycloalkene molecules are characterised by various types of strain: cisoid stretching or compression strain and out-of-plane, one-sided, torsional and transannular strain.^{12, 46–48} The three last mentioned types of strain are most typical of methylenecycloalkanes.^{47, 48} The real contributions of the components to the total strain can be estimated based on thermochemical data and quantum-chemical calculations.^{12, 46–49} Qualitative estimates can be made by comparing the relative rates of epoxidation (ω) of several cycloalkenes under conditions A and B.

A. Reaction conditions for cycloalkenes **35–40**: AcOOH, AcOEt, 25 °C.⁴⁷



B. Reaction conditions for cycloalkenes **39**, **41** and **42**: PhCOOOH, THF, 20 °C.⁴⁶



It can be seen that the reactivity of five- and six-membered rings increases in the sequence **39** < **38** < **35**. This was attributed to the increase in the cisoid compression strain and out-of-plane strain.^{47, 49}

The higher reactivity of the double bond of the norbornene fragment compared to that in the cyclopentene fragment is manifested when dicyclopentadiene is oxidised with peracetic and monoperoxyphthalic acids⁵⁰ and with geminal hydroxyalkyl hydroperoxides.⁵¹

The reaction of norbornene **35** is characterised, in addition to the typical *exo*-selectivity of the attack on the double bond, by a high rate of electrophilic addition, observed irrespective of the reagent used or the reaction mechanism. A certain contribution to the relatively high reactivity of norbornene is made by the out-of-plane deformation and hyperconjugation.⁵² PMX calculations showed that the =C–H bonds in norbornene **35**, unlike those in cyclohexene **39** and bicyclo[2.2.2]octene **36**, are bent by 4.2° to the *endo*-region. In view of this result, which has been confirmed by *ab initio*⁵³ calculations, the preferred *exo*-attack by the electrophile is explained by the fact that in the *exo*-region, the π orbital of norbornene is turned outwards due to the repulsion from the occupied orbitals of the methylene bridge,^{53, 54} whereas in the *endo*-region, the orbital is shielded by the carbon skeleton of the molecule. In cyclopentene, this effect is less pronounced.⁵²

The replacement of the *endo*-methylene bridge in norbornene **35** by an *endo*-ethylene bridge relieves the cisoid compression strain and, apparently, enhances shielding of the double bond, which results in a markedly lower reactivity of bicyclo[2.2.2]octene **36**.

Upon replacement of the six-membered ring by an eight-membered ring, the system becomes more flexible and the reaction rate increases. Unlike other cycloalkenes, *cis*-cyclooctene **41** is readily converted into the epoxide on treatment with various oxidants including molecular oxygen. This leads to the conclusion that both the intermediate states and species and the epoxide formed from the cycloalkene **41** are highly conformationally stable.

trans-Cyclooctene **42** occupies a special place in the series of cycloalkenes.^{46, 55} It typically exists in a *twist*-conformation with highly pronounced out-of-plane torsional strain, favourable for *syn*-addition reactions. The electrophilic attack is directed only at one face of the double bond, which is rotated outwards due to twisting of the molecule.

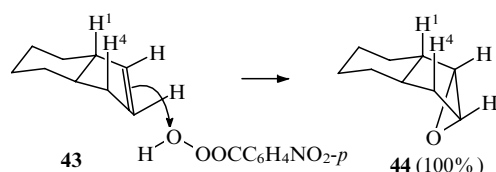
The general pattern of the electrophilic addition to double bonds in cycloalkanes is as follows: as the substrate becomes more strained, the formation of a cyclic transition state is facilitated, because this releases strain.^{46, 47, 56} The more atoms incorporated in the transition state, the greater the decrease in the strain of the system; consequently, the reaction rates can differ by 2–3 orders of magnitude.⁵⁶ The fact that the rates of epoxidation of norbornene and cyclohexene differ by a factor of less than three attests to the formation of three-membered transition states in both cases.

It should be noted that in the case of typical 1,3-dipolar addition of phenyl azide (in CCl₄ at 25 °C) to *trans*-cyclooctene **42**, norbornene **35** and cyclohexene **39**, the relative reaction rates are 2.1×10^5 , 5.7×10^3 and 1.0.

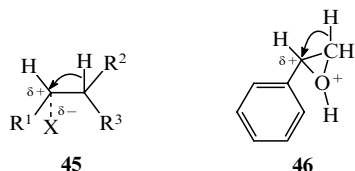
Apparently, the rate of epoxidation depends on the strain not only in the initial alkene but also in the final product, oxirane. It is the high conformational distortions in the latter in combination with steric shielding that account for the facts that 3,5-dibromocyclopentene and 3,6-dibromocyclohexene are much more difficult to epoxidise than their open-chain analogue, 1,4-dibromobut-

2-ene, and that cyclobutene **37** is much less reactive than cyclopentene **38**.²

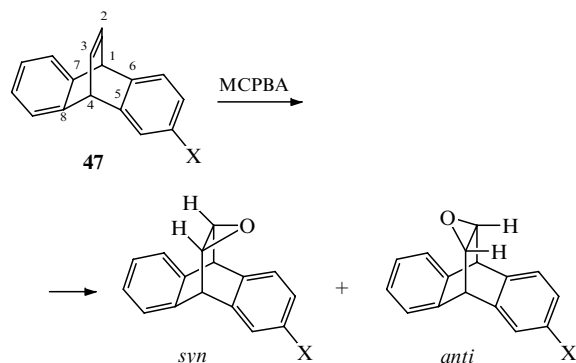
An important factor governing the stereochemistry of epoxidation of cycloalkenes is the principle of the least conformational strain formulated by Toromanoff.⁵⁷ By means of dynamic conformational analysis of the probable transition states with allowance for the Curtin–Hammett principle, the researcher showed that insertion of the epoxide oxygen during the epoxidation of mono- and bicyclic alkenes follows predominantly the direction that ensures the least conformational distortions (thermodynamic control). However, the notion of conformational distortion is ambiguous and can comprise several components. The concepts of torsional,^{10,58} hyperconjugative⁵⁹ and electrostatic⁶⁰ effects controlling the stereochemistry of epoxidation are being debated in the literature. It has been reported^{57,61} that bicyclononene **43** reacts with peroxy acids to give exclusively *endo*-epoxide **44**.



This reaction route is apparently facilitated by shielding of the double bond by the axial H¹ and H⁴ atoms at the stage when the reactants approach each other, by the torsional strain in the transition state, which would have been generated by an attack by the peroxy acid from the side of these atoms and, finally, by stabilisation of the transition state formed in the case of the *anti*-attack by RCO₃H due to the interaction of the C–H¹ and C–H⁴ σ bonds with the electron-deficient sites arising in the bicyclononene complex **43**. The latter type of interaction is involved in initial stages of classical rearrangements of carbenium ions of the type **45** and in the isomerisation of oxiranes **46** to oxo compounds,⁶² associated with hydride shifts.



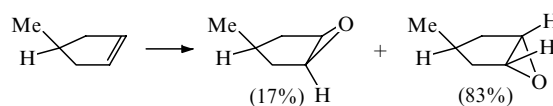
The combined action of all these factors in the reaction of bicyclononene **43** results ultimately in the generation of a conformationally more stable (see Section V) and, hence, energetically more favourable transition state. The (σ–δ⁺) type interaction (in the σ–σ* variant) has been invoked⁶³ to explain the stereochemical outcome of epoxidation of the bicyclo[2.2.2]octene derivative **47** by *m*-chloroperbenzoic acid (MCPBA).



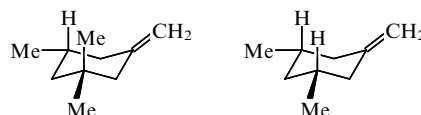
It was found that the proportions of the *syn*-isomer obtained with X = OMe, H, F and NO₂ are 48%, 50%, 58% and 77%, respectively. In other words, the introduction of an electron-withdrawing substituent (F, NO₂) decreases the σ-donor capacity

of the C(1)–C(6) and C(4)–C(5) bonds and thus makes the *syn*-attack by the peroxy acid more favourable.

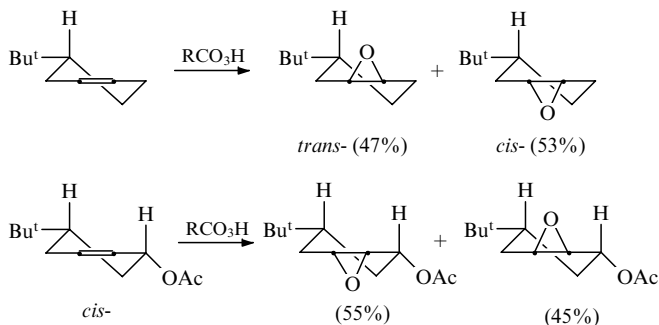
The presence of an alkyl substituent in the five-membered ring and in polycyclic molecules^{6,50} can hamper the attack on the double bond from one side.



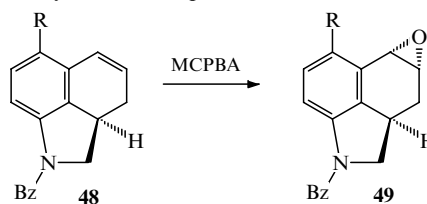
The presence of an axial methyl group at C(3) in 3,3,5-trimethyl-1-methylenecyclohexane decreases the proportion of the axial attack by RCO₃H on the double bond to 17% (compared to 64% observed for 3,5-dimethyl-1-methylenecyclohexane).¹⁵



However, in flexible systems, for example, in cyclohexene derivatives direct steric shielding can be removed or minimised due to the conformational mobility of the molecule,²⁹ because the most substantial steric restrictions are created by an axial substituent.



Alkene **48**, having a rigid alkenyl system, forms epoxide **49** with high diastereospecificity (93%–99%),¹⁸ in this case, the *anti*-attack by the oxidant predominates.



R = H, Br, CN, OMe.

Conformational analysis of diastereoisomeric transition states (**A** and **B**, Fig. 2) permits the conclusion that *gauche*-structure **A**, leading to the *anti*-epoxide, is more favourable than eclipsed

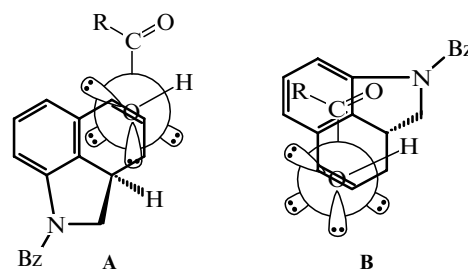
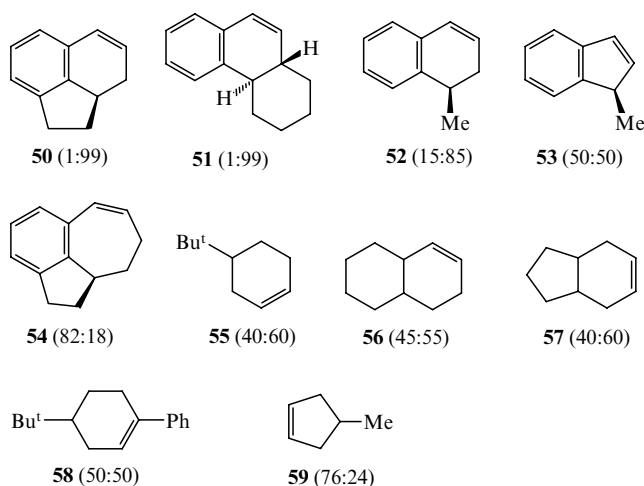


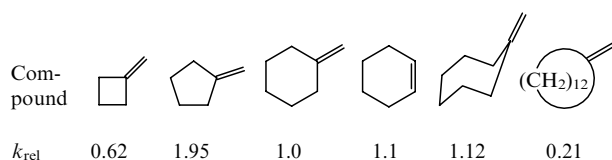
Figure 2. Newman projections of the transition state formed in the oxidation of the alkene **48** with *m*-chloroperbenzoic acid: **A** is the *gauche*-conformation; **B** is the eclipsed conformation.

structure **B**, in which the orientation of the benzamide group in one direction with the peroxy-acid fragment increases the torsional strain in the transition state. In the Newman projections, the line of sight of the observer is directed along the peroxide bond from the side of the attack of the alkene, the π bond passing through one of the two lone pairs of the active oxygen atom; this is a necessary condition for the occurrence of dative interaction at the stage of the epoxide ring formation.²

The composition of the products of epoxidation of two series of compounds, alicyclic compounds **50–54** with conformationally fixed styrene fragments, and more flexible structures, cyclohexene derivatives **55–58** and cyclopentene derivative **59**, by peroxy acids shows that high diastereofacial selectivity is manifested only in the series of compounds **50–54** (the ratio of *syn*- to *anti*-epoxides is given in parentheses). This may be explained by the conformational stability of the transition state with allowance for all factors which ensure this stability.



The regularities of epoxidation of methylene- and alkylidenecycloalkanes have been briefly considered.⁶⁴ The relative rates of epoxidation of monocyclic compounds with *exo*-double bonds by peracetic acid in ethyl acetate at 40 °C were determined.¹²

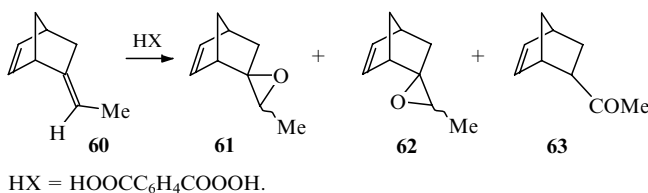


Terminal double bonds in aliphatic compounds are known to be substantially less reactive than symmetrically dialkyl-substituted bonds.^{2,14} In the series of alicyclic compounds, the relative reactivities of *exo*- and *endo*-double bonds are substantially affected by cyclic strain. This is indicated by kinetic and activation parameters. As noted above, more strained cycloalkenes are more reactive. However, methylenecyclobutane, which has the most strained molecule in the series of its analogues, is the least reactive compound. It may be expected that the rate of epoxidation would be correlated with the HOMO energy of the alkene, calculated by a quantum-chemical method: the higher this energy, the easier the interaction between the π orbital and the σ_{O-O}^* orbital of the peroxy acid. In the case of cycloalkenes, this correlation actually holds.⁴⁷ In fact, E_{HOMO} increases in parallel with the decrease in the ring size and with the enhancement of strain. In the series of methylenecycloalkanes, the opposite dependence is manifested.¹⁰ Methylenecyclohexane is epoxidised at a lower rate and with a higher activation energy than more strained methylenecyclopentane, although the data of photoelectron spectra indicate that they have close π -ionisation potentials. However, the low reactivity of methylenecyclobutane correlates with the fact that it has the highest ionisation potential in the series of compounds under study.¹⁰

Nevertheless, the differences in the reactivity found in the series of medium rings ($C_4–C_7$) are relatively small, because in all these cases, a strained three-membered transition state is formed.

Methylenecyclododecane occupies a special place in this series. Its low reactivity is inconsistent with the views on the ring strain and leads to the conclusion that the reaction rate is also influenced by the probability of effective collision of the reactant molecules, which varies depending on the size of the molecules.^{2,10,13}

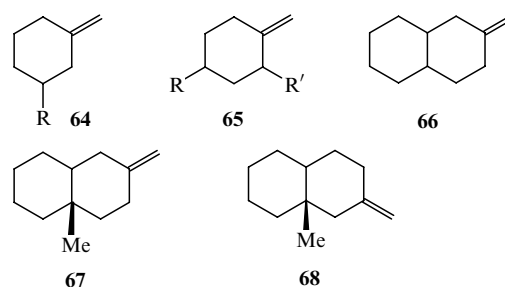
Epoxidation of alicyclic compound **60** presents interest because this compound contains both norbornene and ethylidene fragments. The reaction with monoperoxyphthalic acid affords nearly equal amounts of compounds **61–63**, i.e. only the exocyclic double bond is involved in the reaction.⁵⁰



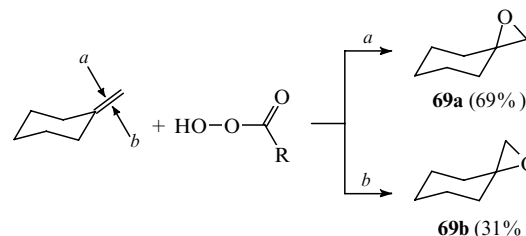
The ratio of the epoxide **61** to the epoxide **62** is 1.9 after 1 h, and 0.9 after 2 h. When peracetic acid is used, this ratio does not change during the reaction and lies in the range 1.6–1.7.

It was found in special experiments that the ketone **63** is formed only from the oxirane **61** during oxidation by monoperoxyphthalic acid. When peracetic acid is used, this isomerisation does not occur. This might be due to the lower acidity of the medium.

Study of epoxidation of substituted methylenecyclohexanes **64–68** revealed fine stereochemical features of this reaction.^{15,64–67}



The addition of an oxygen atom to an alkene can be directed at either axial (*a*) or equatorial (*e*) positions. Epoxide **69a** in which the methylene group is equatorial is 0.6–1.1 kJ mol^{–1} thermodynamically more favourable than the product **69b**.



The compositions of the isomeric epoxide mixtures formed from the alkenes **64–68** were determined using low-temperature ¹H NMR spectroscopy or stereochemical analysis of the alcohols formed upon hydride reduction of the epoxides.

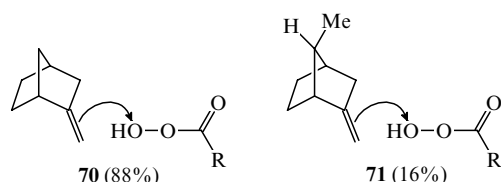
In the majority of cases, when peracetic, *m*-chloroperbenzoic and peroxyphthalic acids are used, the axial attack proved to be preferred. The inversion of the epoxidation stereochemistry was observed in the case of the alkene **68**, due to the shielding of the double bond by the methyl group, and in the case where the methylenecycloalkanes **64–68** were epoxidised with peroxybenzimidic acid ($C_6H_5CN + H_2O_2 + KHCO_3$). It has been reported⁶¹

that the change in the predominant direction of the attack in the latter case is due to the larger size of the peroxy-carboimide group compared to the CO_3H group. It should also be noted that the presence of an active proton and a basic imide nitrogen atom in the peroxyimide acid molecule changes significantly the solvation conditions and may be the reason for the change in the optimum spatial orientation of the reactants.

The predominance of the axial attack^{66, 68} in the epoxidation of methylenecycloalkanes is mainly explained by hyperconjugation effects. The axial attack is facilitated by some stabilisation of the transition state attained due to interaction of the $\alpha\text{-C-H}$ bond electrons with electron-deficient sites, similar to what has been observed in the epoxidation of the bicycloalkene **43**.

The axial attack of the oxidant predominates in the epoxidation of methylenenorbornane **70**.^{64, 69}

The introduction of a *syn*-7-methyl group in methylenenorbornane (compound **71**) results in inverted stereoselectivity. The selectivity of epoxidation of methylenenorbornane **70** is lower than that for norbornene (98%) because the double bond is further removed from the methylene bridge.



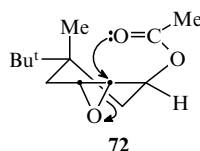
The increase in the size of the exocyclic group in the series $=\text{CH}_2 < =\text{CHMe} < =\text{CMe}_2$ increases the rate of epoxidation by a large factor.

Meanwhile, the rate of oxidation of the exocyclic double bond depends on the ring size and decreases in the order cyclohexane > cycloheptane > cyclopentane.

Electrophilic addition to alicyclic alkenes is typically accompanied by participation of neighbouring atoms and groups, in particular, by migration of C-C and C-H σ bonds.^{70, 71} From the theoretical viewpoint, it is significant to distinguish the few cases in which the neighbouring nucleophilic groups directly participate in the transfer of active oxygen to the substrate.

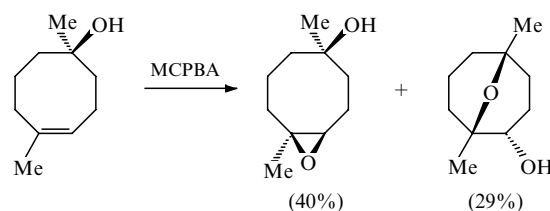
The nucleophilic assistance of the *endo*- CONH_2 and *endo*- CH_2OH groups to the epoxidation of norbornene has been considered in a review.² Participation of this type of hydroxy group in the reaction has been noted in other studies.^{1, 70, 71} In particular, 5-hydroxymethylbicyclo[2.2.1]hept-2-ene reacts with perbenzoic acid 30 times faster than its methyl ether and 40 times faster than the corresponding acetate.⁷⁰ Most often, however, the formation and opening of an epoxide ring in cycloalkenes occur as consecutive reactions.

It is noteworthy that epoxy alcohol acetate **72** proved to be unstable on silica gel, its epoxide ring being cleaved, apparently due to participation of the neighbouring acetoxy group.

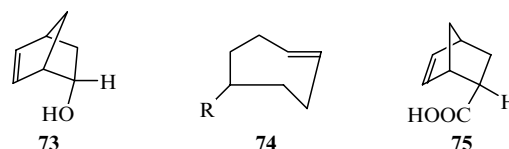


As noted above, the corresponding alcohol **14** exists in an alkaline solution of methanol in an equilibrium with its isomer. The exceptional instability of *trans*-2,3-epoxycyclohexanol acetate under conditions of epoxidation of cyclohex-2-enol with hexafluoro-2-hydroperoxypropan-2-ol has also been noted.⁷² Epoxycyclohexane containing a *trans*-benzamide group in the α -position behaves in a similar way.⁴

Epoxidation of 1,5-dimethylcyclooct-4-en-1-ol is accompanied by partial transannular cyclisation.⁷³

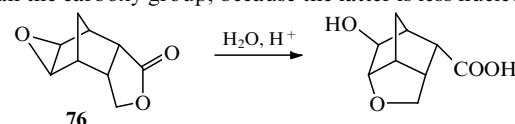


The hydroxy group at the 5-position of the compound **73** has no influence on the course of epoxidation.⁷⁴ However, cycloheptene derivatives **74** are epoxidised by *m*-chloroperbenzoic acid to give products of the transannular cleavage of the epoxide ring.



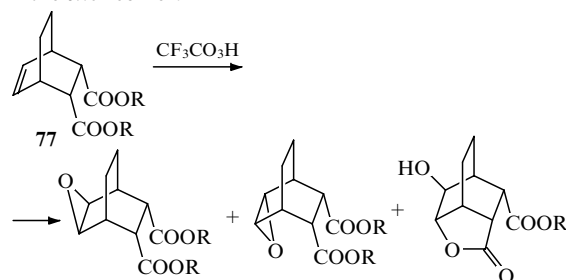
R = CH_2OH , COOH .

Epoxidation of the acid **75** of the norbornene series also affords initially the epoxy acid; however, due to the fast isomerisation to hydroxy lactone, the acid has not been isolated. Kinetic data rule out the possibility of participation of the carboxy group in the rate-determining step of transfer of the active oxygen to the alkene,⁶⁹ because the hydroxy group is more nucleophilic than the carboxy group.⁷⁶ In the case of lactone **76**, the cleavage of the epoxide ring during hydrolysis involves the hydroxy group rather than the carboxy group, because the latter is less nucleophilic.⁷⁶

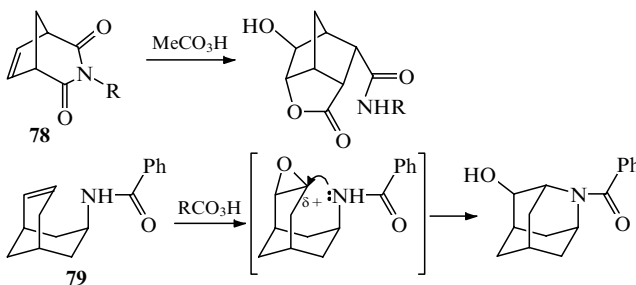


Unlike norbornene, bicyclo[2.2.2]octene derivatives are epoxidised without *exo*-stereospecificity, which is due to the lower strain and the higher conformational mobility of the cage.

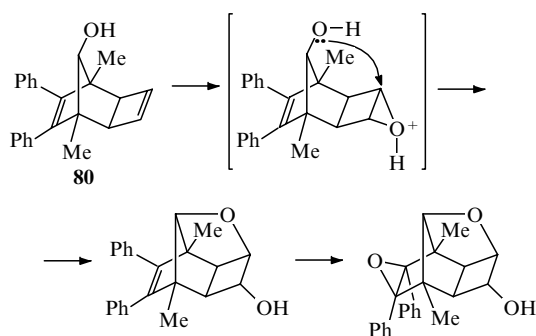
endo-Acids and esters of the bicyclo[2.2.2]octene series **77** form *endo*- and *exo*-epoxides together with the lactones derived from the *exo*-isomer.⁷⁶



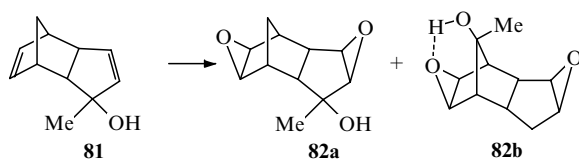
Oxidation of bicyclic imide **78** is accompanied by intramolecular cyclisation involving the oxygen atom of the carbonyl group,⁷⁷ as has been observed for *endo*-amides of the norbornene series.² In the oxidation of amide **79**, the structure of the intermediate epoxide is favourable for the intramolecular cyclisation involving the nitrogen atom to give an azaadamantane derivative.⁷⁸



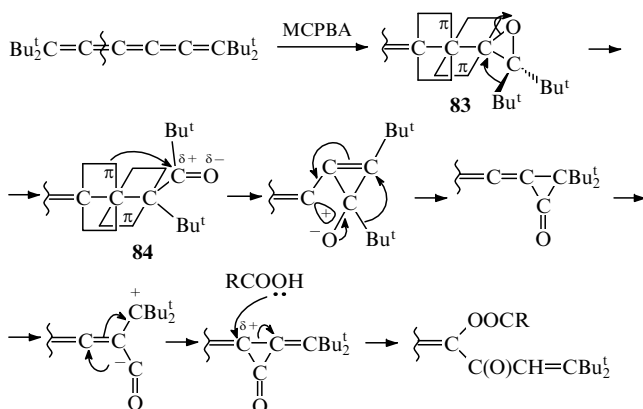
Epoxidation of diene **80** occurs chemoselectivity according to the following scheme:⁷⁹



During epoxidation by monoperoxyphthalic acid, tricyclic diene **81** partially isomerises, diepoxides **82a,b** being formed in a ratio of 65 : 35.⁸⁰



Sterically hindered cumulenes, which are converted into cyclopropanes upon a rearrangement of intermediate oxiranes, represent a peculiar system as regards epoxidation by peroxy acids.⁸¹ A probable mechanism for this reaction is shown below:

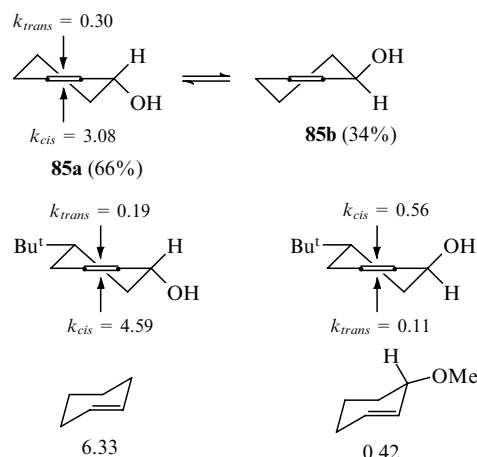


The formation of the intermediate epoxide **83** was not detected; therefore, the isomeric ketone **84** might also arise upon disproportionation of the alkene-RCO₃H complex in the transition state.

IV. Mechanism of the directing influence of functional groups during epoxidation of alkenes with peroxy acids

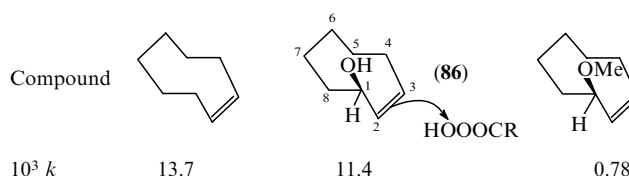
The stereodirecting influence of the hydroxy group in 2-, 3- and 4-alkenols on the attack by RCO₃H has been discussed in numerous publications.^{1,2,6,82,83} Possible variants of the transition state geometry have been discussed. Stereochemical features of the epoxidation of cyclohex-2-enols have been considered.²⁹ It was found that the directing influence is exerted by a pseudo-equatorial (compound **85**) rather than axial hydroxy group.²⁹

The relationship between the rate and the route of epoxidation and the structure of cyclohexenols is clearly illustrated by the scheme given below, in which $k_{\text{epox}} \times 10^3$ (perbenzoic acid, benzene, 5 °C) is resolved into components, k_{cis} and k_{trans} , with respect to the hydroxy group.



It is significant that in the epoxidation of C₆–C₉ cycloalkenols with *m*-chloroperbenzoic acid, the direction of the attack by the reagent changes on passing from seven- to eight-membered ring; the yields of *cis*-epoxides from the above cycloalkenols are 95.0%, 61.0%, 0.2% and 0.2%, respectively.⁴¹ When an alkyl hydroperoxide and a vanadium catalyst are used in this reaction, the coordination of the hydroxy group to the metal is so strong that it leads to a change in the conformation and ensures the *cis*-attack in the two latter cases.

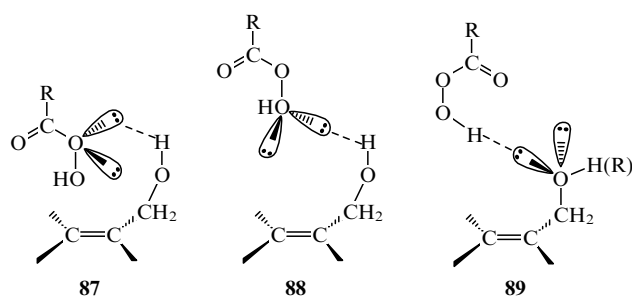
It is notable that not only *cis*-cyclooct-2-enol **86** but also its methyl ether are epoxidised by RCO₃H stereospecifically into the *trans*-position. However, the difference in the reaction rates (perbenzoic acid, benzene, 5 °C) implies active assistance from the hydroxy group of the cyclooctenol **86**.²⁹



When cyclooctenol **86** occurs in a pseudo-chair conformation, electrophilic assistance to the peroxy acid comes, as in the case of cyclohexenol **85**, from the pseudo-equatorial OH group; however, in epoxycyclooctanol, unlike epoxycyclohexanol, this group gets into *trans*-position with respect to the oxirane ring. It was suggested that the rear attack by the peroxy acid is hampered by the hydrogen atoms at C(5) and C(8), similarly to the situation observed in the epoxidation of the bicycloalkene **43** and methylenecyclohexane.

The mechanism of interaction of the directing hydroxy group with a peroxy acid is not so unambiguous as that for alkyl hydroperoxides. It is clear that a peroxy acid is capable of forming hydrogen bonds with basic groups, including the hydroxy group. However, it is significant to elucidate not only the nature of these bonds but also the stage at which their role is manifested. On the one hand, a hydroxy group can be involved at the stage when the reactants approach each other and are coordinated; on the other hand, this group can stabilise the leaving RCO₂[−] anion at the stage of decomposition of the alkene-peroxy acid activated complex.

Several schemes have been proposed describing the hydrogen bonds formed between allylic alcohols and peroxy acids, in particular, **87**,^{2,6} **88**⁷³ and **89**.^{2,78}



Evaluation of the relative strengths of the hydrogen bonds and stereoelectronic analysis of the structures **87**–**89** lead to several conclusions. In conformity with the views on the acid–base properties of the reaction participants, the strength of the hydrogen bond must substantially decrease in the sequence **89** > **88** > **87**. Moreover, the formation of a hydrogen bond between an allylic hydroxy group and an RCO_3H molecule in the ground state according to the associate **87** pattern is relatively unlikely, because the p electrons of the $\text{O}(2)$ atom are involved in conjugation and are difficult to displace. In addition, the corresponding n orbitals are arranged at an angle relative to the $\text{O}–\text{H}$ bond of the alcohol. When the associates **88** and **89** are formed, the reaction sites ($\pi_{\text{bonding}} \text{C}–\text{C}$ and $\sigma_{\text{antibonding}}^* \text{O}–\text{O}$) are too far removed from each other for the epoxidation proper to occur. This rules out participation of the hydroxy group directly in the step of transfer of the active oxygen to the alkene.

The problem of efficiency of the directing action of the hydroxy group at the stage when the reactants approach each other was solved based on the data on epoxidation of cyclohexene containing an axial OR group ($\text{R} = \text{Me}, \text{Bz}$) in the allylic position.⁷⁴

It was found that when *m*-chloroperbenzoic acid is used as the oxidant, the hydrogen bond formed between the acid and the OR group, similar to that in **89**, is not sufficiently strong to exert a *syn*-directing influence; steric effects of the OR groups induce predominantly *anti*-epoxidation. Only replacement of *m*-chloroperbenzoic acid by CF_3COOOH , which is the strongest peroxy acid having a relatively high $\text{p}K_a$ value, results in *syn*-epoxidation. This mechanism for the assistance by the OR group is supported by the fact that replacement of the inert solvent (CH_2Cl_2) by a basic solvent (THF) capable of solvating CF_3COOOH changes the stereochemical outcome of epoxidation, which yields predominantly the *anti*-isomer. The hypothesis that the reactants approach each other through the formation of species like **87** and **88** seems even less likely.

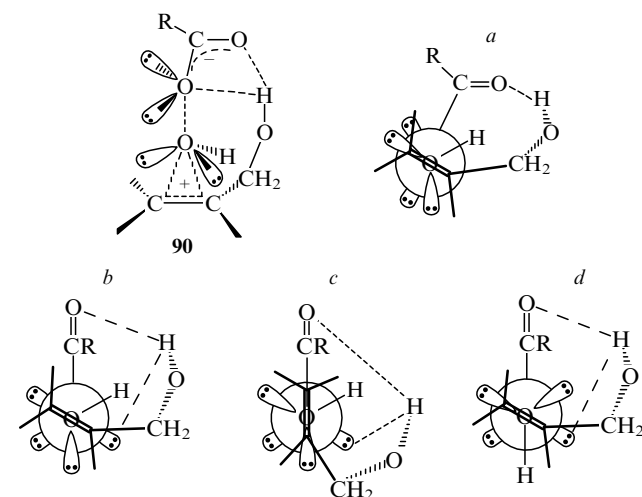


Figure 3. Activated complex **90** formed in the oxidation of allylic alcohols by peroxy acids; (*a*, *b*, *c*, *d*) are the Newman projections.

Orbital consideration and quantum-chemical calculations^{2,84} allow the conclusion that the directing influence of a hydroxy group is due to the interaction of the leaving anion of the acid with the hydrogen atom of the hydroxy group during decomposition of the activated complex **90** (Fig. 3).

It can be seen from Fig. 3 that in this case we are dealing not with a classical hydrogen bond, formed as a hydrogen bridge between two proton acceptors, but with interaction of the proton with a delocalised negative charge in a fairly polarised intermediate complex. When constructing Newman projections *a*–*d* for the transition state **90**, we assumed that any of the two p -electron pairs of the active oxygen atom can participate in the formation of the oxirane ring.

Analysis of projections *a*–*d* with allowance for the Curtin–Hammett principle demonstrates that structures *b* and *d* are the most favourable. The actual occurrence of structure *b* is confirmed by a comparison of the epoxidation mechanism with the closely related mechanism of aziridination of cyclohex-2-enol by 3-acetoxyamino-2-ethylquinazoline.⁸⁵ The latter reacts more stereoselectively than peroxy acids. In our opinion, this is due to the more rigorous steric requirements imposed on the transition state. Unlike the peroxide oxygen atom in RCO_3H , nitrogen carries two substituents. This appreciably hampers the electrophilic attack on the alkene and makes it more strictly directed. In addition, the nitrogen atom has only one pair of p electrons. As a result, the optimum orientation of the reactants is attained only in structure **91** (Fig. 4), in which the bulkiest substituents occupy transoid positions and the NH group proton deflects from the plane of the $\text{O}–\text{C}=\text{O}$ fragment.

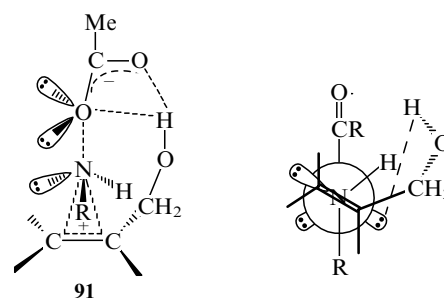
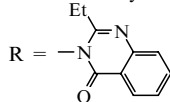


Figure 4. Activated complex **91** and its Newman projection for aziridination of cyclohex-2-enol with 3-acetoxyamino-2-ethylquinazoline

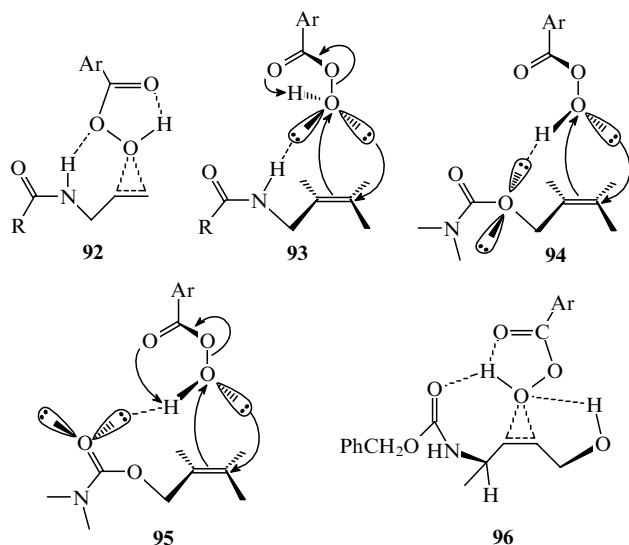


The transoid species *d*, which is energetically even more favourable, is sterically less strained than structure *b*; its active proton participates in the stabilisation of the leaving RCO_2^- anion through interaction with both p -electron pairs of the $\text{O}(2)$ atom. In structures *b* and *d* (Fig. 3) and **91** (Fig. 4), the allylic hydroxy group and the carboxy group are optimally removed from each other.

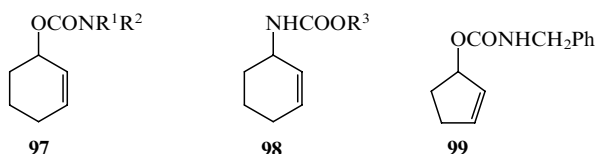
The close arrangement of the hydroxy and carboxy groups in the energetically unfavourable eclipsed conformation *a* diminishes or even completely rules out the possibility for assistance of the hydroxy group to the leaving RCO_2^- anion; in the case of planar structure *c*, the allylic hydroxy group is removed too far from the leaving anion.

The *syn*-directing effect is manifested in epoxidation of not only alkenols but also unsaturated carboxylic acids,^{86,87} amides,^{88,89} urethanes, urea derivatives,^{6,90} acetals, sulfones, sulfoxides,⁶ sulfamides⁹¹ and ketones of the aliphatic and aromatic series.⁹² In some cases, concerted or competing action of two groups has been observed.^{6,89,90}

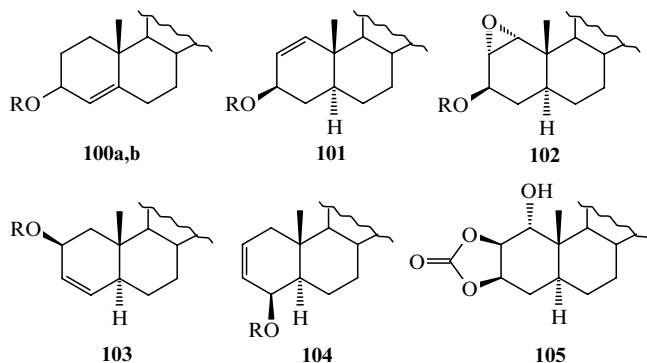
Several variants have been considered for the mechanism of the directing influence of some groups, for example, those involving the formation of structures **92**,⁸⁹ **93**⁹⁰ and **94–96**.⁶



Kocovsky and Stary,⁶ who studied a broad range of unsaturated (allylic and homoallylic) carbamates, amides, urethanes and esters, in particular, cyclohexene (**97**, **98**) and cyclopentene (**99**) derivatives and steroid type compounds **100–105**, including those differing in the position of the double bond, concluded that the stereodirecting influence exerted by the functional groups present in these substrates is due to involvement of the carbonyl oxygen atom, which carries the highest electron density into the hydrogen bond (see structure **95**).

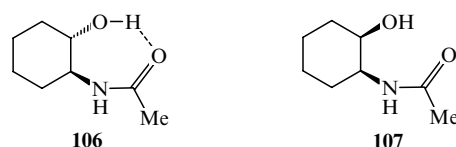


$R^1 = \text{H, Me; } R^2 = \text{Me, CH}_2\text{Ph}$ (**97**); $R^3 = \text{Alk, NH}_2, \text{EtO}$ (**98**).



$R = \text{PhCH}_2\text{NHCO}$ (**100a**, **101**, **102**); $R = \text{Me}_2\text{NCO}$ (**100b**, **103**, **104**).

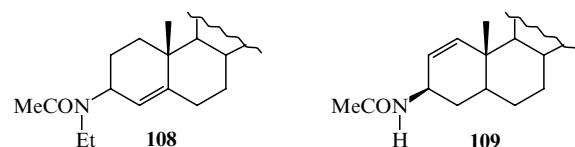
The lower basicity of the carbonyl oxygen atom in esters compared to that in amides or carbamates accounts for the lower stereoselectivity of their epoxidation; however, *syn*-epoxidation of dimethyl *trans*-1,2-dihydrophthalate occurs to more than 90%.⁹³ The assumption that it is the carbonyl group that participates in the reaction was confirmed by the IR spectroscopy data obtained for *trans*- (**106**) and *cis*-hydroxy amides (**107**) used as model compounds. In the latter case, it was found that no intramolecular hydrogen bond is formed.



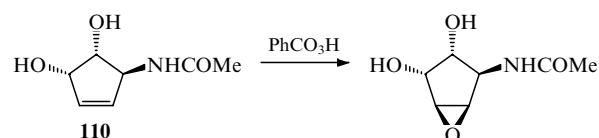
The directing influence of the carbonyl oxygen atom in the type **95** transition state, unlike that of the hydroxy group in the transition state **90**, appears most likely at the stage of coordination of the reactants. The two mechanisms acting through the transition states **90** and **95** are based on the formation of a hydrogen bond; however, they differ significantly regarding the stereochemical features and, hence, the general substrate selectivity. Thus allylic alcohol **101** ($R = \text{H}$) is converted into a mixture of *cis*- and *trans*-epoxy alcohols in a ratio of 3 : 1, whereas in the case of the corresponding *N*-benzylcarbamate, *cis*-epoxidation is prevented by the spatial shielding of the β -side, *trans*-epoxide **102** and compound **105**, resulting from intramolecular opening of the epoxide ring, being isolated as the major reaction products.

Carbamates **103** and **104**, like the corresponding alcohols ($R = \text{H}$), are mainly converted into *trans*-epoxides. The mere replacement of the benzyl group in the structure **100** by a phenyl group or the introduction of an additional substituent, for example, a methoxy group, into the carbamate **104** can result in the reversed stereoselectivity.⁹⁴ The *N*-ethylacetamide prevents epoxidation of amide **108**, which is consistent with the data reported in another publication.⁹⁵

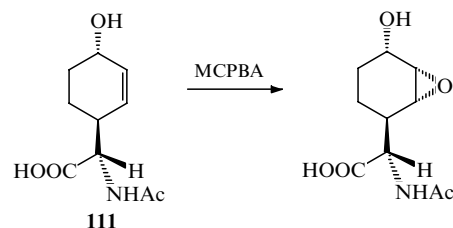
However, the acetamide group in the molecule **109** exerts a *syn*-directing influence exceeding that of a hydroxy group.⁶



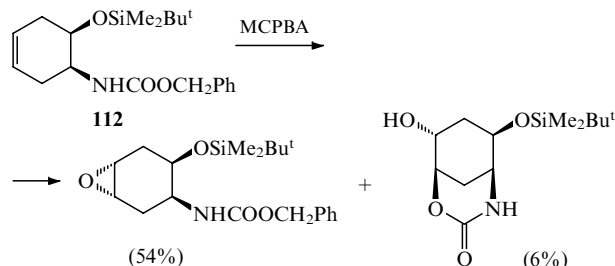
The competition of the acetamide and hydroxy groups⁷⁸ in amide **110** also results in the predominance of the stereodirecting influence of the former.⁸⁷



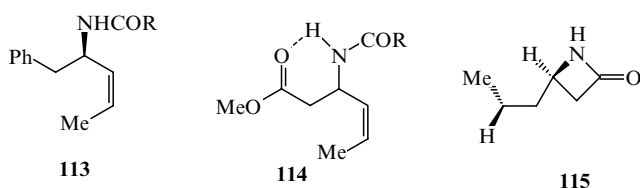
The distant acetamide and allylic hydroxy groups in the molecule of acid **111** exert a concerted influence.⁹⁶



The trialkylsilyloxy group in *cis*-cyclohexylcarbamate **112** stipulates the *trans*-attack by a peroxy acid. The reaction product undergoes partial intramolecular cyclisation.⁹⁷

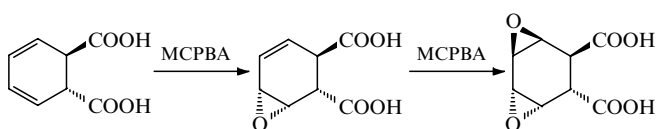


Acyclic allyl *Z*-amides **113** are epoxidised by peroxy acids and *tert*-butyl hydroperoxide in the presence of $\text{Mo}(\text{CO})_6$ with a high *threo*-selectivity (75%–95%).⁸⁷ The corresponding *E*-isomers are less sensitive to this reagent and to the influence of the amide group, the yield of the *threo*-isomer amounting to 60%–78%. The general regularity is violated in the case of amides **114**. The low stereoselectivity of the reaction, in which the *erythro*-isomers slightly predominate in the reaction products, is apparently due to the unfavourable structure of the major conformation, which is fixed by an intramolecular hydrogen bond. In the case of amide **115**, participation of the carbonyl group in the orienting influence is relatively unlikely; nevertheless, the stereoselectivity of epoxidation is fairly high. This is apparently accounted for by the directing influence of the NH group, which has been postulated by Davies and Whitham.⁸⁷ This type of electrophilic assistance to the epoxidising agent is also preferable for the toluenesulfamide group.⁸⁸



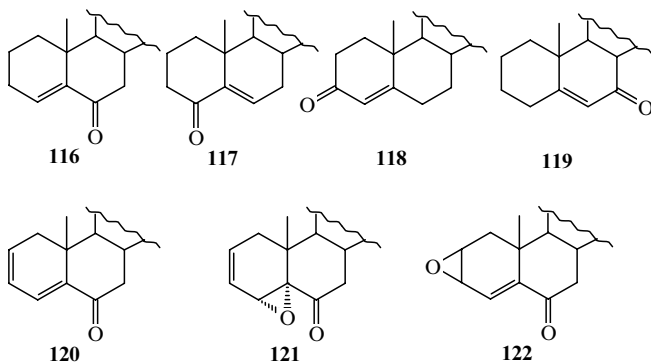
R = CCl_3 , Ph, OMe, NHPh.

An α -carboxy group exerts a strong orienting influence on the attack by RCO_3H . Oxidation of both *trans*-1,2-dihydrophthalic acid and dimethyl *trans*-1,2-dihydrophthalate affords only mono- and diepoxides with *cis*-arrangement of the neighbouring epoxy and carboxy groups even in a basic solvent (ethyl acetate),⁸⁶ capable of solvating carboxy groups. It still remains unclear how the carboxy groups affect the course of the process, either similarly to a homoallylic hydroxy group or in accordance with the transition state **95**.



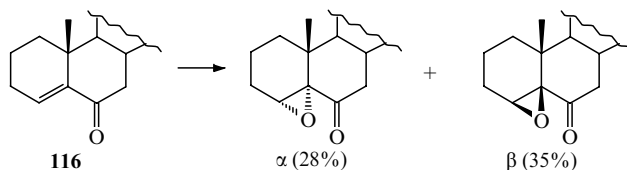
The *syn*-stereoselectivity of epoxidation of *trans*-5-*tert*-butylcyclohex-2-enecarboxylic acid in inert solvents is not very high (54%–79%). Meanwhile, the epoxidation of the corresponding methyl ester affords predominantly the *trans*-isomer irrespective of the solvent used.⁹⁸ Apparently, the *tert*-butyl substituent diminishes the coordination mobility of the ring and hampers the formation of the conformation optimum for the carbonyl group to be involved in the active oxygen transfer.

It has been reported⁹² that the carbonyl group in α,β -unsaturated steroid ketones **116**–**119** and dienone **120** influences the rate and regioselectivity of their epoxidation by MCPBA *via* the formation of a hydrogen bond.

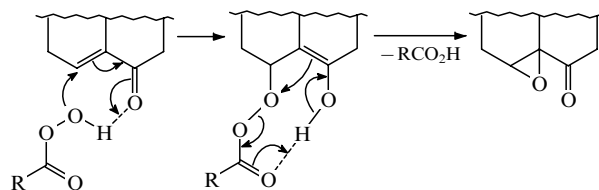


The mere fact that these compounds do undergo epoxidation seems quite unexpected, because the double bond conjugated with a carbonyl group is usually inert to peroxy acids. Moreover, when the dienone **120** is oxidised in a non-polar solvent (benzene), the epoxidation involves the α,β -double bond rather than the remote double bond. In a polar solvent (acetonitrile), the efficiency of participation of the carbonyl group of the ketone **120** in the formation of the hydrogen bond decreases, the yields of the isomeric monoepoxides **121** and **122** becoming comparable. The *S*-*cis*-ketones **116** and **117** react with an oxidant faster and give the oxiranes in higher yields (63% and 51%) than the *S*-*trans*-isomers **118** and **119** (the yields of the corresponding oxiranes are 8% and 27%).

In this connection, it is pertinent to consider the possible epoxidation mechanisms. Stereoelectronic analysis shows that in this reaction, there are no stereochemical prerequisites for the mechanism based on the transition state **95**. The RCO_3H molecule, associated with the carbonyl group through a hydrogen bond, is unable to attack the π electrons of the alkenyl fragment. Therefore, if the classical epoxidation mechanism is realised, the carbonyl group of a cycloenone can render assistance only at the stage when the reactants approach each other, thus increasing the probability of their efficient collision. However, epoxidation of the ketone **116** affords α - and β -oxiranes in comparable amounts, although, by analogy with the epoxidation of the methylenecycloalkane **68** and alkyl-substituted cycloalkenes,^{6,15} one could have expected that the methyl substituent would shield the β -side and promote the formation of the α -isomer.

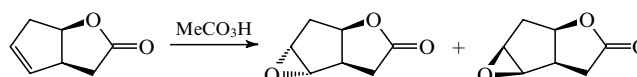


The geometry of the molecules of the cycloenones **116**, **117** and **120** and the whole set of the available experimental data suggest that the process follows a mechanism including a nucleophilic attack on the antibonding $\pi_{\text{C}=\text{O}}$ orbital and 1,4-addition of RCO_3H .



The structure of the *S*-*trans*-isomers **118** and **119** excludes the possibility of a similar synchronous nucleophilic addition of RCO_3H . In addition, the formation of only α -oxirane (27%) from the ketone **119** is evidence supporting the ordinary epoxidation mechanism, which assumes the electrophilic attack by the peroxy acid on the less shielded side of the double bond.

A fairly unusual effect of the nature of the solvent on the stereochemistry of epoxidation of 2-hydroxycyclopent-4-enylacetolactone has been observed.⁹⁹



The ratio of the *cis* to *trans* isomers in the resulting epoxides changes from 8.1 in acetic acid and 4.0 in hexane to 0.89 in benzene and 0.67 in CCl_4 . Since the carbonyl oxygen atom in the lactone is far removed from the double bond, its association with the peroxy acid molecule cannot influence significantly the epoxidation route. Apparently, solvation of the ester group, which determines the character of shielding of the double bond and the conformational stability of the diastereoisomeric transition states, is the

crucial factor governing the stereochemical outcome of the reaction. The pronounced difference between the reaction outcomes in inert solvents, for example, in hexane and benzene, indicates that the process stereochemistry depends substantially on the structural features of the solvent cage.

A similar type of dependence of the enantioselectivity on the solvent nature is displayed in the epoxidation of a number of cyclohexene derivatives by dimethyldioxirane.⁴ It might be this factor that is responsible for the enantioselectivity of some enzyme-catalysed reactions⁹⁸ and for the difference between the yields of glycols in epoxidation of diallyl dicarboxylates¹³ and phenylcyclohexene⁶² in solvents with close basicities — tetrahydrofuran and diethyl ether.

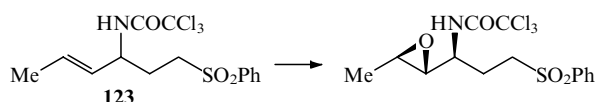
V. Complementarity of reactants as a factor of stereodirected epoxidation

As shown above, the presence in the alkene of a functional group capable of association with an epoxidising agent (ROOH, RCO₃H) is not always a sufficient condition for an efficient directing influence. Spatial compatibility of the reactants favourable for the reaction is also needed. This is ensured, on the one hand, by an appropriate molecular geometry and the environment of the reaction sites and, on the other hand, by a coplanar arrangement of the vacant and occupied orbitals which overlap during the reaction (stereoelectronic factor).

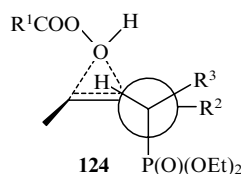
In cycloalkenes and, especially, in polycycloalkenes, the optimum direction of the attack by the oxidant is provided by the rigidly fixed structure of the carbon framework.^{8, 64}

In alkenes, which are normally characterised by relatively low barriers to the rotation around σ bonds, stereodirected epoxidation can be attained in those cases where the two diastereoisomeric transition states of the reaction have substantially different energies. According to the Curtin–Hammett principle, the reaction proceeds *via* the more favourable transition state. This transition state often arises upon transformation of the most stable conformation with a transoid arrangement of the bulkiest substituents.

The simultaneous influence of bulky groups such as SiR₃ or OSiR₃ and the corresponding functional group results in a single diastereoisomer being formed in an almost quantitative yield.^{42, 100} Only one diastereoisomer is produced, for example, in the epoxidation of amide **123**,¹⁰¹ which contains a bulky sulfonyl group in addition to the directing amide group.

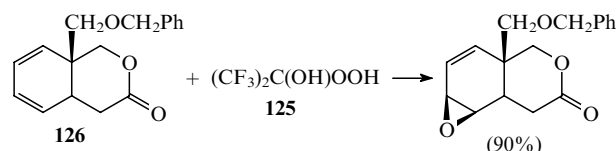


In some cases, the stereoselectivity of the reaction can be ensured without the formation of a hydrogen bond with the peroxy acid but only due to the ordinary spatial shielding of one side of the π bond by bulky groups such as SiR₃ in a fixed conformation of the alkene.⁴² This can account for the *erythro*-selectivity of epoxidation of alkenylphosphonates.¹⁰² The bulky phosphonate group and the peroxy acid occupy transoid positions in the transition state **124** formed in this reaction.



The factors that govern the mutual arrangement of the reactants in space can be judged from a comparison of the stereochemical outcome of epoxidation of alkenes by peroxy acids and by hexafluoro-2-hydroperoxypropan-2-ol **125**.⁷² Whereas cyclohex-2-en-1-ol reacts with *m*-chloroperbenzoic acid to give *cis*- and *trans*-epoxycyclohexanols in 93 : 7 ratio, the reaction

with hydroperoxide **125** yields only the *cis*-isomer. Furthermore, on treatment with the hydroperoxide **125**, cyclohex-2-en-1-ol acetate is converted into the corresponding *cis*-epoxide by 80%, whereas the use of *m*-chloroperbenzoic acid results in a mixture of *cis*- and *trans*-isomers of epoxycyclohexyl acetate in a ratio of 2 : 3. Hexafluoro-2-hydroperoxypropan-2-ol oxidises bicyclic diene **126** to give only one monoepoxide. Other oxidants, namely, peroxy acids, ROOH–Cat and singlet oxygen combined with trimethyl phosphite, react with the diene **126** to give all four isomers of monooxirane.



The specific behaviour of the hydroperoxide **125** can be explained by the fact that its molecule, unlike RCO₃H, is tetrahedral, the hydroperoxide group occupying a vertex of the tetrahedron which has two bulky trifluoromethyl groups at the base (Fig. 5). Shielding of the peroxide site restricts the sphere of the attack on the alkene and imposes stringent steric requirements on the transition state caused by the torsional strain between the substituents in the hydroperoxide and the alkene.

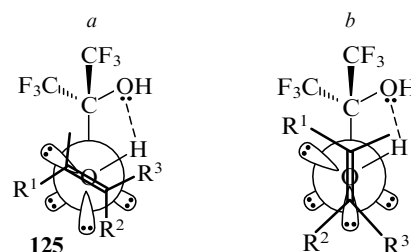


Figure 5. Newman projections of the transition state formed in the oxidation of alkenols with hexafluoro-2-hydroperoxypropan-2-ol (**125**); (a) spiro structure; (b) eclipsed conformation.

Of the two transition state structures *a* and *b* (see Fig. 5), possible due to the presence of two lone electron pairs at the active oxygen atom, spiro structure *a* is preferred, in which the pseudo-axial electron pair in relation to the five-membered chelate ring of the hydroperoxide participates in ring formation.

Epoxidation of the cycloalkene **126** involves the double bond removed further from the benzyloxymethyl substituent. The *syn*-orientation of the oxidant with respect to the substituent ensures the formation of the most favourable transoid conformation of the transition state (Fig. 6*a*). The *anti*-orientation would result in *gauche*-conformation (Fig. 6*b*).

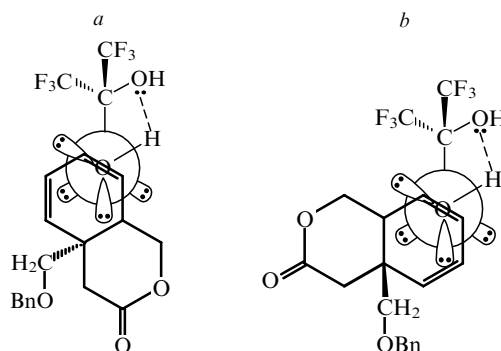


Figure 6. Newman projections of the transition state formed in the oxidation of the diene **126** by hexafluoro-2-hydroperoxypropan-2-ol (**125**); (a) transoid conformation; (b) *gauche* conformation.

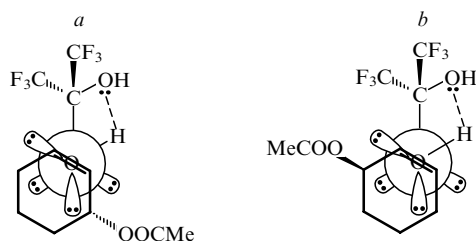
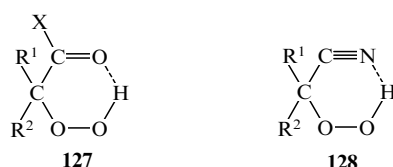


Figure 7. Newman projections (*a* and *b*) of the transition state formed in the oxidation of cyclohex-2-enol acetate with hexafluoro-2-hydroperoxypropan-2-ol (**125**).

From this standpoint, it becomes clear why acylated cyclohex-2-enol is converted into the *syn*-epoxide. Evidently, conformation *a* is more stable than conformation *b* (Fig. 7).

Epoxidation of the same alkene by a peroxy acid affords mostly the *anti*-epoxide. When cyclohex-2-enol is epoxidised by hexafluoro-2-hydroperoxypropan-2-ol, the role of complementarity is enhanced by the directing influence of the hydroxy group, thus making this reagent more selective than peroxy acids.

The stereochemistry of the epoxidation of alkenes by α -hydroperoxides **127** and α -hydroperoxy nitriles **128** has been described in reviews.^{1,2}



R¹ = Me, R² = Ph; X = OR³, NR³, Alk.

The hydroxy group in cyclohex-2-enol has a *syn*-directing influence on epoxidation. However, unlike peroxy acids, the hydroperoxide **127** (X = OR) oxidises *trans*-stilbene more easily than *cis*-stilbene and oxidises *trans*- β -methylstyrene more easily than cyclohexene.

Interpretation of the *trans*-selectivity should be sought in a comparison of the electronic and steric features of the transfer of active oxygen from the hydroperoxide **127** to the alkene with those for peroxy acids. The latter are known to be characterised by low energies of the O–O bond and high mobility of the OOH-group proton. The RCO₃H–alkene transition state is extended along the reaction coordinate, and, in conformity with the Bell–Evans–Polanyi principle, its structure is closer to the final products than to the initial compounds. This means that loosening of the peroxide bond in RCO₃H starts at an early stage of insertion of the alkene π orbital into the antibonding $\sigma_{\text{O–O}}^*$ orbital before the O–H bond is cleaved. The proton transfer does not limit the overall rate of the process.^{1,2} In addition, in the case of peroxy acids, there is no torsional strain, involved in the transition state with hexafluoro-2-hydroperoxypropan-2-ol and the hydroperoxides **127**. This accounts for the low sensitivity of the RCO₃H molecule to the alkene structure; the *cis*-alkene is epoxidised slightly more readily than the *trans*-isomer,¹⁴ which can be easily explained by the higher thermodynamic stability of the latter isomer.

Regarding the α -hydroperoxides **127**, it should be noted that they are several orders of magnitude weaker oxidants than peroxy acids.² The peroxide proton in the hydroperoxides **127** is substantially less active than that in RCO₃H. Therefore, the α -hydroperoxide–alkene transition state **129** is compact and the intramolecular proton transfer on the leaving alkoxy anion is necessarily included in the step determining the overall rate of the process (Fig. 8). This, in turn, places certain steric demands on the orientation of the OH group in the hydroperoxide **127**. On the one hand, this group tends to be coplanar with the axial lone electron pair of the neighbouring peroxide oxygen atom and, on the other hand, it tends to escape the eclipsed position with respect to the

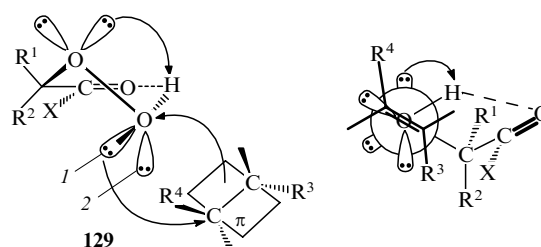
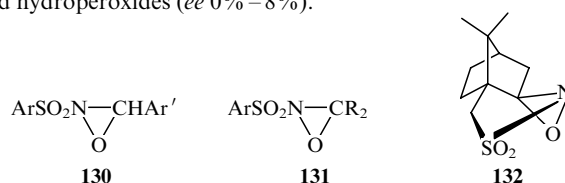


Figure 8. Transition state **129** formed in the oxidation of alkenes by the hydroperoxide **127** and its Newman projection: (1) equatorial lone pair of the oxygen atom; (2) axial lone pair of the oxygen atom.

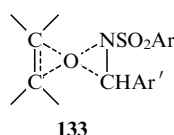
bulky substituents at the alkene double bond. These requirements are satisfied in the case where the coplanar alkene π bond and chelated hydroperoxide molecule approach each other with the R³ substituent of the alkene being removed from the eclipsed position with respect to the OH group (under the π -bond plane) and the R⁴ substituent being located above the plane. This determines the *trans*-selectivity of the reaction.

In the case of *cis*-alkene, the substituents R³ and R⁴ should be directed below the plane of the chelated hydroperoxide; this increases the strain in the transition state due to the interaction of these groups with R². If the transition state had a spiro structure in which the alkene π plane passed through the n_{O} orbital of the active oxygen atom, the shift of the proton into the axial position and its interaction with the leaving alkoxy anion would be hampered. In this connection, it is noteworthy that the transition state formed in the epoxidation of alkenes by hexafluoro-2-hydroperoxypropan-2-ol **125** has a spiro structure (see Fig. 6*a*). In this case, the problem of the proton transfer to the leaving alkoxy anion is eliminated because the process is synchronous.

The complementarity factor, which determines the direction of the attack on the electrophilic site of the alkene, becomes significant when substituted oxaziridines are used as epoxidising agents.^{103–107} Diastereoisomeric 2-sulfonyloxaziridines **130–132** epoxidise alkenes containing no directing functional groups with higher enantioselectivity (*ee* 12%–65%) than chiral peroxy acids and hydroperoxides (*ee* 0%–8%).



Based on kinetic and thermodynamic parameters, correlation analysis of the effects of substituents present in the phenyl groups of oxaziridines, a synchronous mechanism of epoxidation of alkenes including transition state **133** has been proposed. In accordance with this mechanism, the oxaziridine ring and the π bond are coplanar, the process stereochemistry being controlled by the configuration of substituents.^{104–107}



Similar conclusions have been drawn from quantum-chemical calculations.¹⁰⁸ Experimental data cited above^{103–107} can be interpreted in a different way by invoking general theoretical views on the stereoelectronic features of reactions of this type, in particular, epoxidation of alkenes by hydroperoxides^{1,2,5} and dioxiranes.^{4, 109, 110}

The oxidising capacity of oxaziridines is due most of all to the N–O bond, which is similar to the peroxide bond. The nitrogen atom is less electronegative than oxygen but the $E_{\text{N–O}}$ value in the oxaziridines **130–132** decreases owing to the strong electron-

withdrawing influence of the SO_2 group. The difference between the O–N and O–C bond energies results in the loosening and rupture of the O–N bond at the stage of oxygen transfer to the substrate occurring somewhat ahead of the O–C bond cleavage. The asynchronous cleavage of bonds is apparently a general feature of small rings similar to oxaziridine, in particular, dioxirane and dioxetane.

The nucleophilic attack by the alkene π electrons on the oxygen atom of the oxaziridine ring is directed at the antibonding orbital of the O–N bond along its axis (transition state **134**, Fig. 9). In the initial interaction event, transfer of the π -electron density on the oxygen atom loosens the N–O bond and, simultaneously, the axial lone electron pair of oxygen n_a interacts with the π^* orbital of the alkene. As in the case of hydroperoxides, the combination of two types of interaction — donor-acceptor and dative interaction — is a necessary condition for the synchronous formation of the C–O bonds in the oxirane ring.

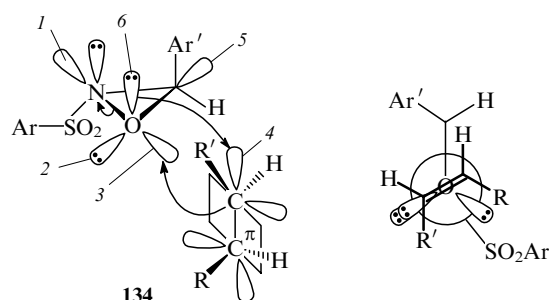


Figure 9. Transition state **134** formed in the epoxidation of alkenes with oxaziridines and its Newman projection; (1) $\sigma_{\text{N-O}}^*$; (2) equatorial lone pair of the oxygen atom (n_e); (3) $\sigma_{\text{N-O}}^*$; (4) π^* ; (5) $\sigma_{\text{C-O}}^*$; (6) axial lone pair of the oxygen atom (n_a).

The localisation of excess electron density at the nitrogen atom creates conditions for the overlap of the partially occupied $\sigma_{\text{N-O}}^*$ orbital (or the nitrogen n orbital) with the vacant $\sigma_{\text{C-O}}^*$ orbital, which, in turn, induces loosening of the C–O bond.

It is clear that the angle between the attack on the alkene π bond and the plane of the oxaziridine ring is about $180^\circ - 109^\circ = 71^\circ$, the most significant restrictions hampering the approach of the reactants and construction of the transition state being caused by the carbon atom and its substituents rather than by the substituents at the nitrogen atom in the epoxidising agent. Therefore, the epoxidation transition state **134** in which the ring formation involves the *cis*-alkene and the axial lone electron pair of oxygen seems to be the least sterically hindered.

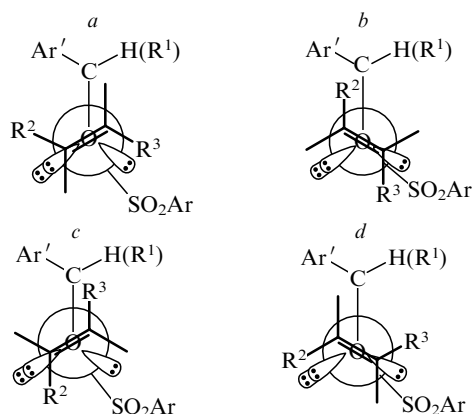
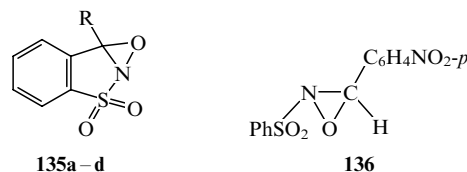


Figure 10. Newman projections (*a–d*) of the transition state of epoxidation of *trans*-alkenes with sulfonyloxaziridines.

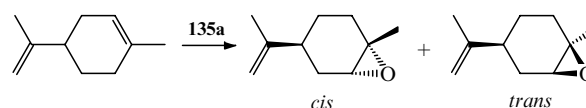
The best transition state for the epoxidation of *trans*-alkenes should be chosen out of the four possible structures *a–d* (Fig. 10) (in the Newman projections, the observer looks along the O–N bond from the side of the alkene attack).

Analysis of the stereochemical outcome of epoxidation of *trans*-stilbene with (*R,R*)-(+)-sulfonyloxaziridines **135a–d** shows that the (*R,R*)-(+)-oxirane is formed with *ee* 34.9%. Hence, the reaction occurs mainly *via* transition state *a*. Indeed, transition state *b* is sterically much more strained and transition states *c* and *d* would lead to the (*S,S*)-oxirane.



R = Me (**a**), Buⁿ (**b**), Buⁱ (**c**), Bu^t (**d**).

Our conclusions are also consistent with other experimental data.^{105–108} Thus epoxidation of (*R*)-(+)-limonene by sterically shielded oxaziridine **135a** is 20.7 times slower than that by oxaziridine **136**.¹⁰⁴ This reaction is fairly *cis*-selective (60%–74%), the selectivity increasing with an increase in the size of the group R.



Note for comparison that oxidation of limonene by *m*-chloroperbenzoic acid yields the isomers in 1:1 ratio. It is also noteworthy that the rates of limonene epoxidation by the oxaziridines **135a–c** are related as 1:0.93:0.3, and the compound **135d** barely enters into this reaction.

The replacement of the oxaziridine **136** by its analogue containing a nitro group in the *ortho*-position rather than in the *para*-position decreases the rate of epoxidation of 1-methylcyclohexene by a factor of more than 6.¹⁰⁷

To summarise the foregoing, we can conclude that the reaction in question occurs by an S_{N} -type mechanism assuming the formation of a spiro transition state. The fact that the bonds in the oxaziridine ring are cleaved asynchronously induces some charge separation. The negative charge on the nitrogen atom is highly delocalised due to the electron-withdrawing influence of the SO_2 group. The buffer function of this group markedly decreases the sensitivity of the reaction to the polar influence of the substituent X in the $\text{XC}_6\text{H}_4\text{SO}_2$ group. Hence, the Hammett constants of the reaction (ρ) found upon variation of substituents in the benzene nucleus at the carbon atom and in the sulfamide moiety of the sulfoxaziridine molecule are nearly equal and amount to 1.07 and 1.09, respectively.

Dioxiranes are very close to oxaziridines regarding the character of their reactions with alkenes.^{4, 109, 110} In the case of dimethyldioxirane, the reaction is highly sensitive to steric restrictions caused by the interaction of the methyl groups with the substituents at the double bond. Branched alkenes, *trans*-4,4-dimethylpent-2-ene and *trans*-2,2,5,5-tetramethylhex-3-ene, are epoxidised much more slowly than *trans*-hex-3-ene. In the series of ordinary dialkyl-substituted alkenes, *cis*-isomers are an order of magnitude more reactive than the corresponding *trans*-alkenes.

Based on the kinetic and thermodynamic parameters, it was concluded that the reaction proceeds *via* a bimolecular complex having a spiro structure.¹¹⁰

By analogy with the transition state **134**, it can be assumed that the attack by the alkene is directed at the antibonding $\sigma_{\text{O-O}}^*$ orbital of the dioxirane along the peroxide bond, the π -electron plane passing through the pseudo-axial non-bonding orbital of oxygen as has been shown in the structure **137** (Fig. 11).

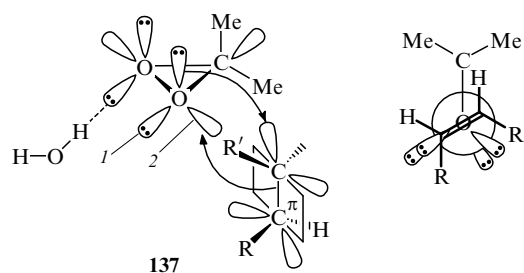


Figure 11. Transition state **137** formed in the epoxidation of alkenes with dioxiranes and its Newman projection; (1) n_e of oxygen, (2) σ_{O-N}^* .

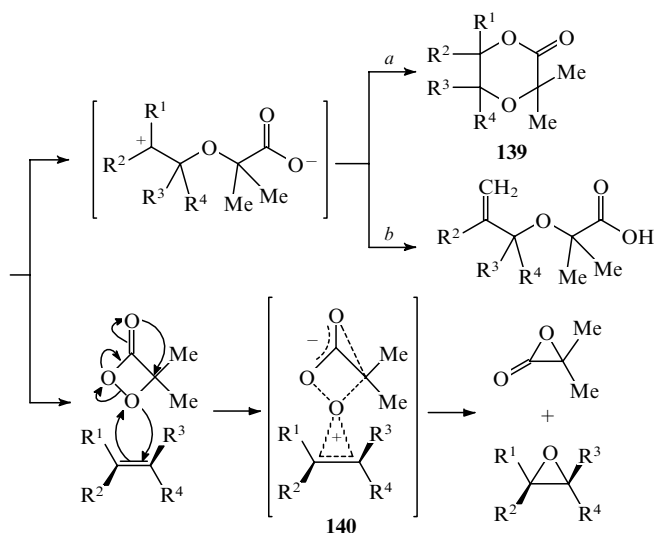
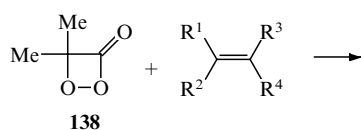
The loosening and rupture of the O–O bond in dioxirane at an initial stage of its reaction with the alkene occurs ahead of the C–O bond cleavage, a partial negative charge being created on the leaving oxygen atom. Unlike oxaziridine, dioxirane is unable to delocalise the excess charge and in the transition state **137**, the leaving anion is solvated, which is typical of the S_N -type reactions. It is due to this fact that the allylic hydroxy group has a directing influence on the oxidant during epoxidation of cyclohex-2-enol.⁴ It has also been found that admixtures of water in acetone catalyse the process.¹⁰⁹ The decrease in the effect of water admixtures in the case of epoxidation of low-reactivity alkenes by dioxiranes is, apparently, due, as in the case of epoxidation by peroxy acids,^{1,2} to the ability of the oxidant to undergo self-oxidation to give singlet oxygen in media favourable for the formation of hydrogen bonds. Reactive alkenes normally suppress decomposition of the epoxidising agent thus increasing the rate of formation and the yield of oxiranes. Chiral dioxiranes, prepared from chiral ketones and oxone ($KHSO_5$), epoxidise alkenes with a substantial asymmetric induction (up to 87%).¹¹¹

Correlation analysis and thermodynamic parameters point to a common character of electron density distribution in the transition states formed when dioxiranes, oxaziridines and peroxy acids are used as epoxidising agents.

Epoxidation of di-, tri- and tetrasubstituted alkenes by dimethyl- α -peroxy lactone **138**, the structure of which is similar to that of dimethyldioxirane, is controlled by absolutely different stereochemical factors.

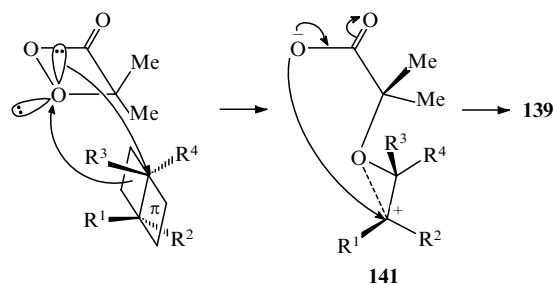
First, attention is attracted by the high *trans*-selectivity of epoxidation by peroxy lactone **138**. *cis*-But-2-ene is virtually not epoxidised; instead, it is converted into cycloaddition product **139**. However, *trans*-but-2-ene is transformed only into the epoxide. As the number of alkyl substituents at the double bond increases, the overall rate of the process increases, indicating that the alkene acts in this reaction as a nucleophile. Simultaneously, the contribution of cycloaddition, which is known to be highly sensitive to steric restrictions, diminishes. In the case of tetraalkyl-substituted alkenes, cycloaddition hardly occurs. Yet another characteristic feature of this process is the relatively high polarity of the intermediate complex. This is indicated by the fact that it can be efficiently neutralised by methanol, acting as a carbocation trap.

The formation of the oxirane ring implies a concerted mechanism for the electron density redistribution in transition state **140**, which, judging from experimental data, is conformationally stable only for *trans*-alkene, as in the epoxidation of α,β -unsaturated carbonyl compounds **4**.¹¹²



(a) Cycloaddition; (b) ene reaction, $R^1 = \text{Me}$.

It turns out that the *cis*-orientation of substituents in the alkene, which is favourable for the reactants to come together, prevents the formation of a planar, conformationally stable transition state **140** with delocalised charges. In this case, zwitter-ionic transition state **141** with sterically non-hindered rotation around the σ -bonds, needed for 1,4-dioxane ring closure, becomes more preferable.



The principle of complementarity of reactants underlies the asymmetric epoxidation of simple, non-functionalised alkenes by oxometal complexes containing Schiff's bases, porphyrins or other oxygen- and nitrogen-containing compounds as ligands.^{112–114} The geometry of the environment of the reaction site determines the predominant orientation of the prochiral alkene at the stage when the reactants approach each other. For example, epoxidation of a number of alkenes with an oxygenated manganese complex gives the corresponding oxiranes in very high optical yields (92%–98%).¹¹² However, detailed consideration of reactions of this type is beyond the scope of our review.

VI. Conclusion

Conformational analysis of the diastereoisomeric transition states (TS) with allowance for the stereochemical conditions for the closure to give an oxirane ring is an efficient method for substantiation and prediction of the route and the stereochemical outcome of epoxidation of alkenes with various peroxide reagents. The integral stereocontrolling factor in these reactions is the conformational stability of the TS, which is determined, in its turn, by the spatial compatibility (complementarity) of the reactants, torsional strain, influence of the neighbouring functional groups, hyperconjugation and other effects.

The directing influence of allylic and homoallylic hydroxy groups in the case of alkyl hydroperoxides, which require metal complex catalysis, is attained at the stage of construction of a multiligand complex and the formation of a donor-acceptor bond between the OH group and the central atom. When epoxidation is carried out by an epoxy acid, the role of these groups is to stabilise the carboxylate anion, which is eliminated at the stage of decomposition of the transition state, whereas carbonyl groups in alkenyl-containing amides, esters, carbamates and urethanes exert a similar stereoeffect due to the formation of a hydrogen bond with RCO_3H at the stage of coming together and coordination of the reactants.

Epoxidation of α,β -unsaturated *S-cis*-ketones of the steroid type occurs apparently by a non-classical mechanism assuming 1,4-addition of the peroxy acid.

The stereochemistry of the non-catalysed epoxidation involving active alkyl hydroperoxides is largely determined by the formation of more compact transition states than those in the case of peroxy acids and by the substituents attached to the sp^3 hybridised carbon atom of the C–OOH group.

Some general regularities of the formation of planar transition states and spiro structures were established. The spiro type TS, which are less sterically strained, are formed in the epoxidation of alkenes with RCO_3H and $(\text{CF}_3)_2\text{C}(\text{OH})\text{OOH}$. Under these conditions, the stage of transfer of the active oxygen to the substrate does not depend on the rate of proton transfer. Meanwhile, the epoxidation of alkenes with α -hydroperoxy-derivatives of esters is controlled by the transfer of the OOH group proton on the axial pair of p electrons of the neighbouring oxygen atom. The orientation of molecular orbitals participating in this process induces the formation of a planar transition state and requires a transoid configuration of the alkene molecule.

trans-Selectivity is also typical of other epoxidation reactions involving the formation of planar TS, in particular, those using dimethyl- α -peroxy lactone as the epoxidising reagent and in the alkaline alkyl-peroxide oxidation of α,β -unsaturated esters. In the latter case, the reaction occurs stereoselectively because of the two possible conformations of the cyclic transition state, the more stable conformation with an equatorial orientation of the bulkiest substituent in the alkene molecule is formed preferentially.

cis-Selectivity is an indication of a spiro configuration of the compact transition states formed in epoxidation of alkenes with oxaziridines and dimethyldioxirane. The process stereochemistry is controlled by the substituents at the carbon atom in these heterocycles; in the case of oxaziridines, this ensures a fairly high enantioselectivity.

The overall effect of various types of strain in cycloalkenes and methylenecycloalkanes stipulates the predominance of the epoxidation pathway that relieves the strain in cycloalkene and results in the formation of the transition state and the oxirane with the least conformation distortion.

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Fluorine-containing 2,4-dioxo acids in the synthesis of heterocyclic compounds[†]

V I Saloutin, Ya V Burgart, O N Chupakhin

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Abstract. The review surveys the data on the synthesis, tautomerism, electronic structures and chemical transformations of 4-polyfluoroalkyl- and 4-pentafluorophenyl-2,4-dioxo acids and their derivatives. The reactions yielding fluorinated heterocyclic compounds and their further conversions are considered. The bibliography includes 86 references.

I. Introduction

Fluorine-containing α -oxo esters,¹⁵ α -diketones,¹ β -oxo esters^{4–6} and β -diketones^{7–9} are used in studies of tautomerism, carbonotropy, stereoisomerism and reactivity of dicarbonyl compounds (DCC). Fluorinated DCC often serve as building blocks for the preparation of various heterocyclic compounds.^{1, 6, 7, 10} Particularly impressive progress has been achieved in the design of drugs of the fluoroquinolone series with unique antibacterial activity, which are analogues of nalidixic acid.^{11–16} These antibiotics contain a fluorobenzoylacetic acid structural fragment; for a number of these compounds, fluorinated β -DCC serve as starting compounds.^{11–16}

The use of fluorinated DCC is not confined to their application as biologically active compounds. Certain fluorine-containing DCC and their derivatives can be used as catalysts of various reactions, surfactants, shift reagents, analytical reagents, including those used for the determination and separation of a number of metals by gas chromatography, extractive agents for various metals, dyes and oil and composite additives.^{1, 6, 7, 17} Therefore, further progress in the chemistry and practical application of fluorinated dicarbonyl compounds seems to be very promising.

Polyfluorinated 2,4-dioxo acids and their derivatives containing simultaneously α - and β -dicarbonyl fragments are convenient starting compounds for the preparation of fluorinated heterocycles. Therefore, the development of procedures for the synthesis

of these compounds and investigation of their reactivity are topical problems. Although the chemistry of nonfluorinated 2,4-dioxo acids has been well studied (see, for example, Refs 18–21), this class of fluorine-containing compounds was not known until our first publications.^{22–25}

II. Synthesis and structures of esters of polyfluorinated 2,4-dioxo acids

Nonfluorinated 2,4-dioxo acids and their esters had been first prepared at the end of the 19th century. Esters of 4-polyfluoroalkyl- (**1a–d**)²² and 4-pentafluorophenyl-2,4-dioxo acids (**1e,f**)^{23–25} were first synthesised by the Claisen condensation starting from fluoroalkyl- and pentafluorophenyl ketones, respectively, and dialkyl oxalates. Lithium hydride was used as a condensing reagent. The target compounds were isolated *via* copper chelates **2a–f** (Scheme 1).

Copper chelates of esters **2a–d** are quite stable compounds.²² However, chelates of pentafluorobenzoylpyruvates **2e,f** undergo cyclisation in DMSO or DMF to 2-alkoxycarbonyl-5,6,7,8-tetrafluorochromones **3a,b**.^{23–25} Chromones **3a,b** are also formed upon heating of pentafluorobenzoylpyruvates **1e,f** above 25 °C.^{23–25} Cyclisation occurs through intramolecular replacement of the *ortho*-fluorine atom of the pentafluorophenyl group.

In the design of syntheses on the basis of polyfluoroacyl(pentafluorobenzoyl)pyruvates, it is necessary to have an idea of keto–enol tautomerism, charge distribution on atoms and frontier-orbital electron density in these compounds.

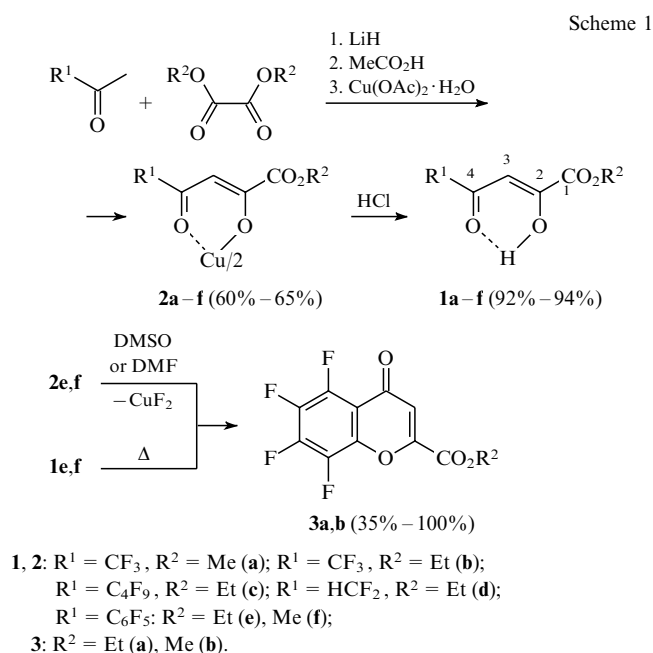
As for enolisation, the tautomerism of nonfluorinated analogues of dioxo esters **1** has been reported in a series of publications. Thus ¹H NMR spectral studies demonstrated²⁸ that aroylpyruvates exist mainly as enols. It was also concluded²⁸ that the intramolecular hydrogen bond in the β -dicarbonyl fragment of the molecule is strengthened as the electron-accepting ability of substituents increases. On the basis of the ¹H and ¹³C NMR spectral data, it was concluded that there was no tautomerism between two possible enol forms.^{28, 29} The proton is delocalised between two potential wells due to tunnelling. This agrees with the results of quantum-chemical SCF MO LCAO calculations by the CNDO/2 method.³⁰ In going from one substituent to another, ¹³C chemical shifts are changed due to

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[†] Dedicated to the memory of our teacher Academician I Ya Postovskii on the occasion of his 100th birthday.



the electron density redistribution in the dicarbonyl fragment.³¹ It was attempted to determine the position of the proton in a series of β-DCC (including the acetylpyruvate molecule) by comparing the ¹³C chemical shifts for β-DCC and their BF₂ chelates.^{32,33} Presumably,^{32,33} insignificant changes in the chemical shifts on going from β-DCC to their BF₂ chelates indicate that the structures are nearly quasi-symmetrical and that the proton is delocalised between the two oxygen atoms to approximately the same extent.

It was established by X-ray diffraction analysis that ethyl acetylpyruvate is enolised at the C(2) atom.³⁴ A comparative analysis of the ¹³C NMR spectra of ethyl acetylpyruvate and ethyl trifluoroacetylpyruvate (**1b**) demonstrated that compound **1b** is also enolised at the C(2) atom.³⁵ It was found that polyfluoroacyl(pentafluorobenzoyl)pyruvates **1** are completely enolised.^{22,23}

It is remarkable that, unlike fluoroacyl(aroyl)pyruvates under consideration, fluorinated β-diketones and β-oxo esters are only partially enolised.^{6,7} The degree of enolisation reaches 100% only in fluorine-rich β-DCC. In this case, enolisation occurs at the carbonyl group bound to the fluorinated substituent.^{6,7}

With the aim of discussing the reactivity of fluoroacyl(aroyl)pyruvates **1**, quantum-chemical SCF MO LCAO calculations of charges and Fukui indices were performed for (fluoro)acylpyruvates³⁵ by the CNDO/2 method and for pentafluorobenzoylpyruvic acid and methyl pentafluorobenzoylpyruvate[†] by the AM-1 method³⁷ using the MNDO-89 program.³⁶ The calculations demonstrated that the largest positive charge in fluoroacyl(aroyl)pyruvates is localised on the C(1) atom. The Fukui indices for the lowest unoccupied molecular orbitals (LUMO) in fluoroacylpyruvates and methyl pentafluorobenzoylpyruvate have the maximum values for the C(2) and C(4) atoms, respectively. In pentafluorobenzoylpyruvic acid, the values of the Fukui indices for LUMO of the C(2) and C(4) atoms have close values. Therefore, under kinetically controlled conditions the attack of a nucleophilic reagent occurs preferentially on the C(1) atom according to the charge control. According to the orbital control, the reactions of fluoroacylpyruvates should occur at the C(2) atom, while the reactions of methyl pentafluorobenzoylpyruvate should occur at the C(4) atom. In the case of pentafluorobenzoylpyruvic acid, the orbital-controlled process is approximately equally probable for the C(2) and C(4) reaction centres (Table 1).

[†] V I Saloutin, Ya V Burgart, O N Chupakhin, unpublished data.

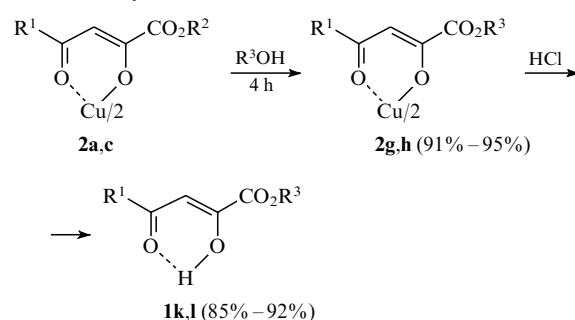
Table 1. Charges and Fukui indices for the electrophilic centres in acyl(aroyl)pyruvates.

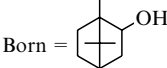
Compound	R ¹	R ²	Charges (Fukui indices)			
			H	C(1)	C(2)	C(4)
1g	Me	Me	+0.2586	+0.3609 (0.1880)	+0.2076 (0.5250)	+0.2996 (0.3613)
1h	HCF ₂	Me	+0.2561	+0.3624 (0.1459)	+0.2123 (0.5170)	+0.2429 (0.4306)
1a	CF ₃	Me	+0.2549	+0.3628 (0.1289)	+0.2128 (0.5134)	+0.2216 (0.4540)
1i	C ₄ F ₉	Me	+0.2558	+0.3630 (0.1240)	+0.2128 (0.5661)	+0.2502 (0.4624)
1f	C ₆ F ₅	Me	+0.2651	+0.3302 (0.0271)	+0.1456 (0.1630)	+0.3252 (0.1740)
1j	C ₆ F ₅	H	+0.2665	+0.3378 (0.0365)	+0.1439 (0.1862)	+0.3245 (0.1858)

III. Transesterification reactions

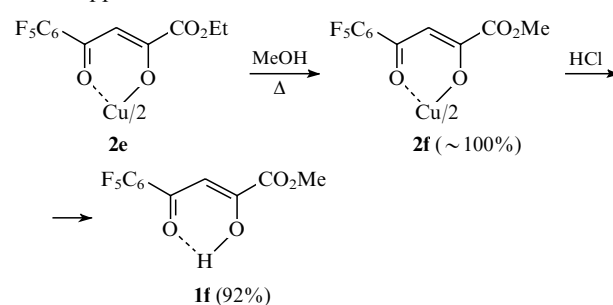
Esters are prone to transesterification. This property substantially enhances the synthetic potential of fluoroacyl(aroyl)pyruvates when using them as the starting compounds for constructing various heterocyclic systems.

Copper chelates of ethyl(methyl) acylpyruvates **2a,c** can be readily transesterified with a higher alcohol (borneol) even in the absence of catalysts.³⁸



R¹ = CF₃, R³ = Born (**2g**, **1k**), where Born = 
R¹ = C₄F₉, R³ = Born (**2h**, **1l**).

Boiling the copper chelate of ethyl pentafluorobenzoylpyruvate **2e** in methanol also results in transesterification to form the chelate of methyl pentafluorobenzoylpyruvate **2f**.³⁹ Thereafter methyl pentafluorobenzoylpyruvate (**1f**) can be readily prepared from the copper chelate **2f**.

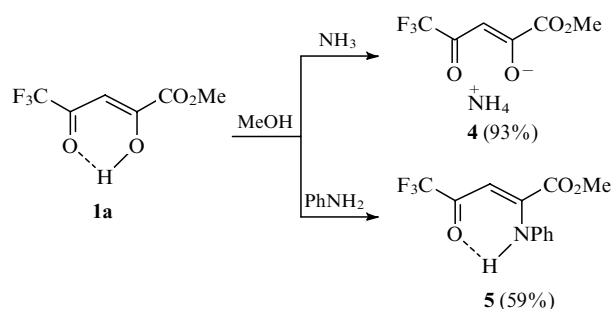


It should be noted that this reaction is common to copper chelates of β-oxo esters because the chelates of esters of both aceto- and trifluoroacetoacetic acids enter into this reaction.³⁸ However, the time required to achieve high degrees of conversion of the latter compounds is an order of magnitude larger than in the

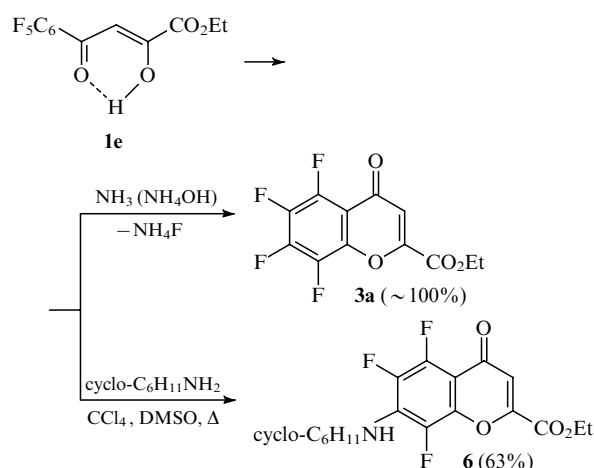
case of copper chelates of acylpyruvates **2a,c**. Apparently, this is associated with the involvement of the ester group of β -oxo ester in intrachelate conjugation. Free ligands can also undergo transesterification; however, the selectivity of the reaction decreases sharply and substantial resinification of the reaction mixture occurs. Apparently, copper(II) ions favour the reaction by orienting an alcohol molecule through coordination and suppress side processes.

IV. Reactions with amines

The reaction of methyl acetopyruvate with ammonia affords an enamine at the carbonyl C(2) atom.⁴⁰ The reaction of methyl trifluoroacetopyruvate (**1a**) with ammonia yields [methyl (trifluoroacetopyruvato)]ammonium (**4**), which remains unchanged on boiling in toluene.^{41, 42} However, compound **1a** reacts with a softer base (aniline) at the C(2) centre to form an enamine, *viz.*, methyl 2-anilino-5,5,5-trifluoro-4-oxopent-2-enoate (**5**),^{41, 42} according to orbital control over the reaction.



Treatment of pentafluorobenzoylpyruvate **1a** with gaseous or aqueous ammonia affords chromone **3a**. Apparently, the corresponding ammonium salt is initially formed, which is followed by intramolecular substitution of the aromatic *ortho*-fluorine atom.^{42, 43}

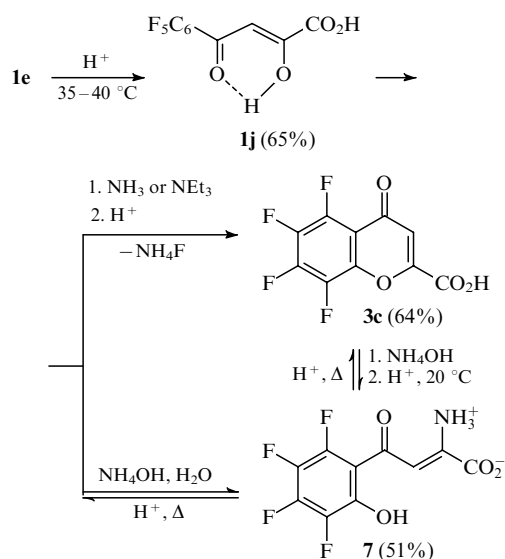


The reaction of pentafluorobenzoylpyruvate **1e** with cyclohexylamine proceeds analogously. However, in this case cyclisation is accompanied by the orbital-controlled replacement of the fluorine atom at position 7 of chromone to form 7-cyclohexylamino-2-ethoxycarbonyl-5,6,8-trifluorochromone (**6**).^{42, 43}

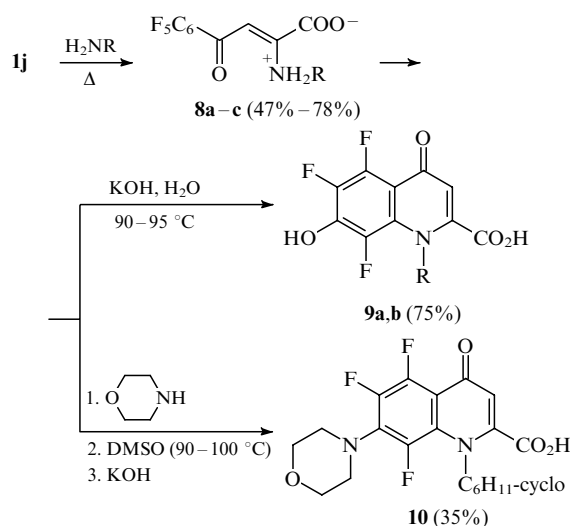
Thus, in the reactions of compound **1e** with ammonia or cyclohexylamine, intramolecular cyclisation dominates over addition of the nucleophile at the C(2) centre regardless of the solvent.

Pentafluorobenzoylpyruvic acid (**1j**) prepared by hydrolysis of ester **1e** reacts with anhydrous ammonia in dioxane or with tertiary amines (triethylamine) to form 2-carboxy-5,6,7,8-tetrafluorochromone (**3c**).^{41, 42} The reaction of acid **1j** with ammonium hydroxide affords 2-amino-3-(3,4,5,6-tetrafluoro-2-hydroxybenzoyl)acrylic acid (**7**), which exists as a zwitterion.^{41, 42} When heated in an acidic medium, the amino acid **7** is hydrolysed to the acid **1j** or undergoes cyclisation to form the chromone **3c**.

When treated with aqueous ammonia followed by acidification, the latter, in turn, gives the amino acid **7**.^{41, 42} Consequently, in these cases intramolecular cyclisation also prevails.



The reactions of the acid **1j** with primary amines (aniline, isopropylamine or cyclohexylamine) yield addition-elimination products at the C(2) centre, *viz.*, 2-alkylamino(anilino)-2-pentafluorobenzoylacrylic acids **8a-c**, which indicates that this reaction is an orbital-controlled process. In an alkaline medium, compounds **8a,b** undergo cyclisation and nucleophilic replacement of the fluorine atom at the C(7) atom by the hydroxy group, which is typical of these fluorine-containing systems, to form 5,6,8-trifluoro-7-hydroxy-1-R-4-quinolone-2-carboxylic acids **9a,b**.^{41, 42} The fact that it was the fluorine atom at position 7 of quinolone that has been replaced was established by X-ray diffraction analysis of a complex of compound **9a** with DMSO.^{44, 45} Cyclisation of compound **8a** in the presence of morpholine affords 1-cyclohexyl-5,6,8-trifluoro-7-morpholino-4-quinolone-2-carboxylic acid (**10**).^{41, 42}



$\text{R} = \text{cyclo-C}_6\text{H}_{11}$ (**8a**, **9a**), Pr^i (**8b**, **9b**), Ph (**8c**).

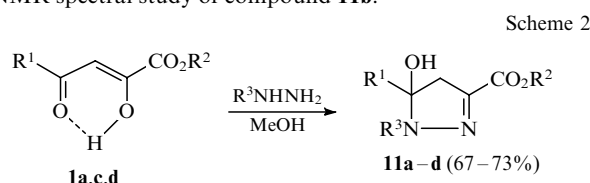
V. Reactions with dinucleophiles

Various heterocyclic systems can be constructed by reactions of 2,4-dioxo esters with bifunctional nucleophiles. The reactions of acyl(aroyl)pyruvates can involve both the α -dicarbonyl and β -dicarbonyl fragments depending on the nature of the nucleophile.

1. Reactions with hydrazines and hydroxylamine

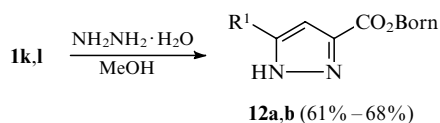
The reactions of acetyl(aryl)pyruvates with hydrazines give 3-alkoxycarbonyl-5-methyl(aryl)pyrazoles.^{26, 27, 46–48} The reactions of ethyl acetylpyruvates with hydroxylamine yield 3-ethoxycarbonyl-5-methylisoxazole, isomeric 5-ethoxycarbonyl-3-methylisoxazole or a mixture of isoxazoles depending on conditions.^{26, 49} Ethyl benzoylpyruvate reacts with hydroxylamine to afford 3-ethoxycarbonyl-5-phenylisoxazole, the reaction proceeds *via* intermediate α -oxime.^{27, 50}

Ethyl(methyl) fluoroacetylpyruvates **1a,c,d** react with hydrazine hydrate and phenylhydrazine at the β -dicarbonyl fragment like hydrocarbon analogues and fluorine-containing β -oxo esters⁶ and β -diketones.⁷ However, unlike the latter compounds, the reactions with **1a,c,d** give stable 3-alkoxycarbonyl-5-fluoroalkyl-5-hydroxy- Δ^2 -pyrazolines **11a–d** (Scheme 2). The position of the hydroxy group in the pyrazoline ring was established by ¹³C NMR spectral study of compound **11b**.³⁵



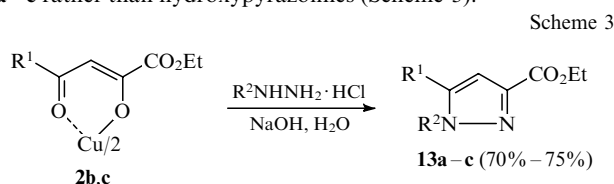
11: R¹ = CF₃, R² = Me; R³ = H (**a**), Ph (**b**);
R¹ = C₄F₉, R² = Et, R³ = H (**c**); R¹ = HCF₂, R² = Et, R³ = H (**d**).

Unlike methyl(ethyl) fluoroacetylpyruvates **1a,c,d**, the reactions of bornyl esters **1k,l** with hydrazine hydrate give 3-bornyloxycarbonyl-5-fluoroalkylpyrazoles **12a,b**.³⁸



12: R¹ = CF₃ (**a**), C₄F₉ (**b**).

The reactions of chelates **2b,c** with hydrazine and phenylhydrazine hydrochlorides in water or methanol afford pyrazoles **13a–c** rather than hydroxypyrazolines (Scheme 3).⁵¹

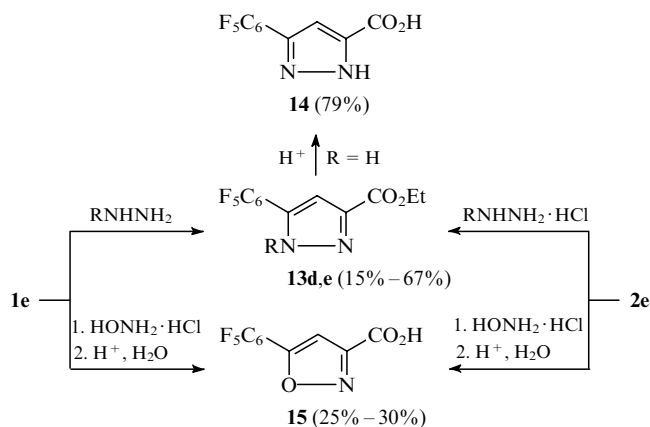


R¹ = C₄F₉, R² = H (**2c**, **13a**); R¹ = CF₃, R² = H (**2b**, **13b**), Ph (**13c**).

The reactions of copper chelates of trifluoroacetylacetone and ethyl trifluoroacetylacetate with hydrazine hydrochloride in DMF, which were studied for comparison, yielded 3-methyl-5-trifluoromethylpyrazole and 5-hydroxy-3-trifluoromethylpyrazole, respectively.⁵²

Pentafluorobenzoylpyruvate **1e** and its copper chelate **2e** react with hydrazine hydrate to give 3-ethoxycarbonyl-5-pentafluorophenylpyrazole **13d**, which can be readily hydrolysed in an acidic medium to 5(3)-pentafluorophenylpyrazole-5(3)-carboxylic acid (**14**).⁵¹

Pentafluorobenzoylpyruvate **1e** reacts with phenylhydrazine and copper chelate **2e** reacts with phenylhydrazine hydrochloride to form pyrazole **13e**.⁵³ The reactions of hydroxylamine hydrochloride with compounds **1e** and **2e** afford 5-pentafluorophenylisoxazole-3-carboxylic acid (**15**).⁵³

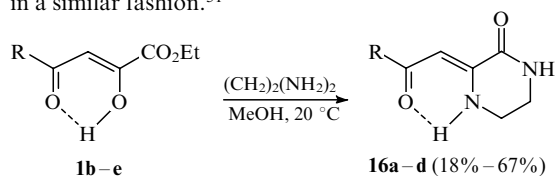


The formation of pyrazole and isoxazole derivatives in the reactions with hydrazines and hydroxylamine is typical also of both pentafluorobenzoylacetate ester⁵⁴ and derivatives of non-fluorinated aroylpyruvic acids.⁵⁵

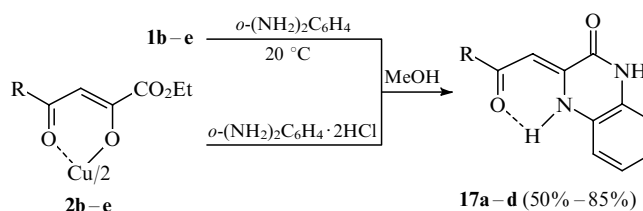
2. Reactions of 2,4-dioxo esters with aliphatic and aromatic 1,2-dinucleophiles

Acyl(aryl)pyruvates react with 1,2-dinucleophiles at the α -oxo ester fragment. The reactions with ethylenediamine, *o*-phenylenediamine or *o*-aminophenol as dinucleophiles give piperazinone derivatives,⁵⁶ substituted quinoxalinones^{57–63} or benzoxazinones, respectively.^{63–65}

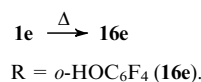
The reactions of polyfluoroacetylpyruvates **1b–d** with ethylenediamine and *o*-phenylenediamine give 3-(2-oxofluoroalkylidene)piperazin-2-ones **16a–c** and 3-(2-oxofluoroalkylidene)-1,2,3,4-tetrahydroquinoxalin-2-ones **17a–c**, respectively.³⁵ Copper chelates **2b–d** react with *o*-phenylenediamine hydrochloride in a similar fashion.⁵¹



16: R = CF₃ (**a**), C₄F₉ (**b**), HCF₂ (**c**), C₆F₅ (**d**).

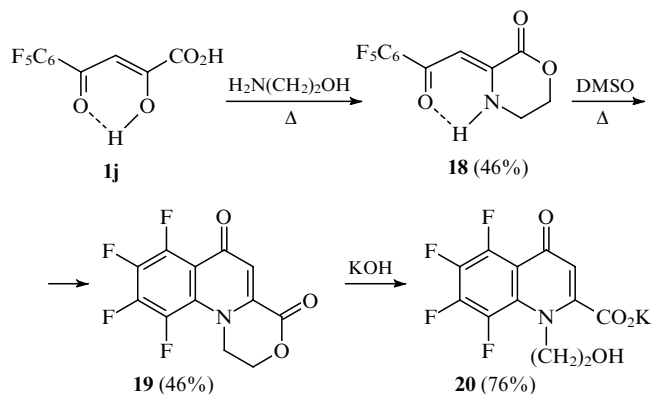


17: R = CF₃ (**a**), C₄F₉ (**b**), HCF₂ (**c**), C₆F₅ (**d**).

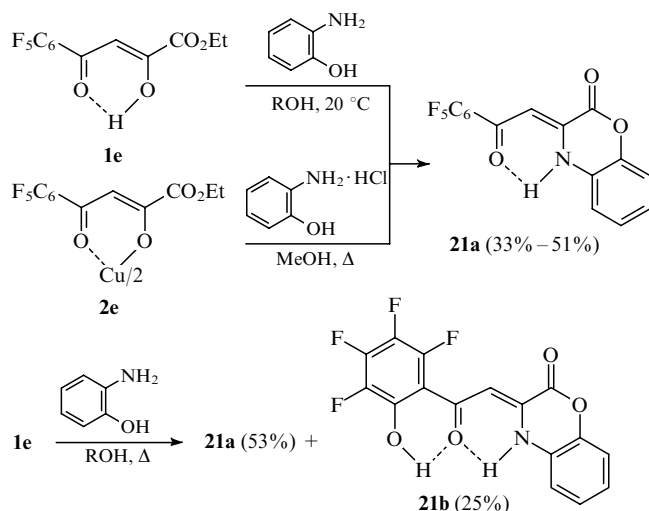


Under mild conditions, pentafluorobenzoylpyruvate **1e** reacts with ethylenediamine to form piperazinone **16d**. However, heating of the reaction mixture affords piperazinone **16e** containing the tetrafluoro-2-hydroxyphenyl substituent.⁵³ The mechanism of formation of the latter is discussed below. The reactions of compound **1e** and its copper chelate **2e** with *o*-phenylenediamine or its hydrochloride yield quinoxalone **17d**.^{51, 53}

The reaction of pentafluorobenzoylpyruvic acid (**1j**) with ethanolamine yields 3-pentafluorobenzoylmethylidenemorpholin-2-one (**18**).^{41,42} When refluxed in DMSO, the morpholinone **18** undergoes cyclisation to form 7,8,9,10-tetrafluoro-4-oxo-1,2,4,6-tetrahydro[1,4]oxazino[4,3-*a*]-4-quinolone (**19**). Treatment of compound **19** with an aqueous KOH solution affords potassium 5,6,7,8-tetrafluoro-1-(2-hydroxyethyl)-4-quinolone-2-carboxylate (**20**).^{41,42} This procedure is one of a few methods for the synthesis of fluorine-containing 2-carboxyquinolones.

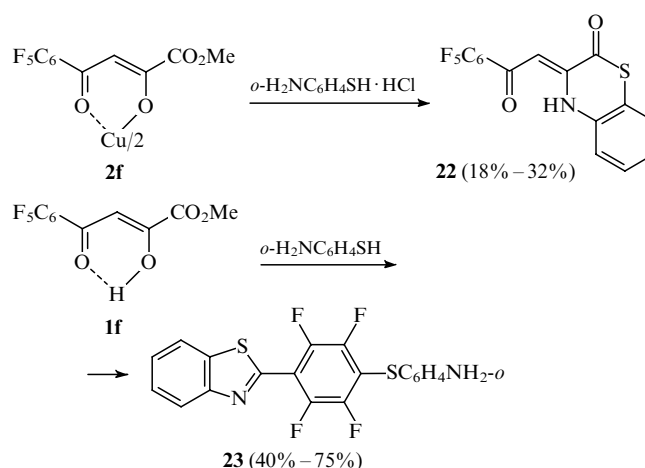


Pentafluorobenzoylpyruvate **1e** and its chelate **2e** react with *o*-aminophenol and its hydrochloride under mild conditions to form 3-pentafluorobenzoylmethylidene-2*H*-1,4-benzoxazin-2-one (**21a**). Under more severe conditions, this reaction, like the reaction of compound **1e** with ethylenediamine,⁵³ yields 3-(3,4,5,6-tetrafluoro-2-hydroxybenzoylmethylidene)-2*H*-benzoxazin-2-one (**21b**) containing the tetrafluoro-2-hydroxyphenyl substituent as a minor product in addition to compound **21a**.^{53,66} Apparently, the product **21b** is formed either from 2-ethoxycarbonyl- (**3a**) or from 2-carboxy-5,6,7,8-tetrafluorochromone (**3c**), which are generated under the reaction conditions. This suggestion was confirmed by the synthesis of compound **21b** directly from the chromones **3a** or **3c**.^{53,66}



R = Me, Et, Prⁱ.

The reactions of pentafluorobenzoylpyruvate **1f** and its copper chelate **2f** with *o*-aminobenzenethiol were studied. It was demonstrated that the chelate **2f** reacted with 2-aminobenzene-thiol hydrochloride at the α -oxo-ester fragment to form 3-pentafluorobenzoylmethylidene-2*H*-1,4-benzothiazin-2-one (**22**). In the reaction with *o*-aminobenzenethiol under mild conditions, the ester **1f**, unlike the chelate **2f**, undergoes acid scission accompanied by nucleophilic replacement of the fluorine atom in the pentafluorobenzoyl fragment of the molecule by the 2-aminophenylthio group to form 2-[4-(2-aminophenylthio)-2,3,5,6-tetrafluorophenyl]benzothiazole (**23**).³⁹



Thus, polyfluoroacylpyruvates react with hydrazines at the β -dicarbonyl fragment, while their reactions with ethylenediamine and *o*-phenylenediamine proceed at the α -oxo-ester fragment. Apparently, the first stage of the reactions with HN-dinucleophiles, as in the case of aniline, involves the attack of one amino group on the electrophilic C(2) centre according to the orbital control over the reaction. Subsequent attack of the second amino group can occur on two centres, *viz.*, either on the electrophilic C(1) centre or on the C(4) atom. Apparently, the nucleophilic attack on the C(4) centre to form five-membered rings in the case of hydrazines and on the C(1) centre to form six-membered rings in the case of ethylenediamine and *o*-phenylenediamine is governed by thermodynamic factors.

In the reactions of pentafluorobenzoylpyruvate **1e** with amines, intramolecular cyclisation to 2-ethoxycarbonylchromone **3a** is the dominant reaction route. Reactions at the β -dicarbonyl fragment are typical of the reactions of pentafluorobenzoylpyruvates with hydrazines and hydroxylamine, while reactions at the α -oxo-ester fragment are characteristic of the reactions with ethylenediamine, *o*-phenylenediamine and *o*-aminophenol. It is believed that the main regularities manifested in these reactions are similar to those observed in the case of polyfluoroacylpyruvates.

The use of copper chelates of β -di- and tricarbonyl compounds instead of free ligands in the reactions with nucleophiles does not necessarily lead to the formation of identical products. Thus the reactions of copper acylpyruvates **2b,c** with hydrazines afford pyrazoles **13a–c** rather than hydroxypyrazolines **11** (see Schemes 2 and 3). Apparently, this is due to the template role of the copper cation. In some instances, for example, in the reactions of β -DCC chelates with hydrazine hydrochlorides as well as in the reactions of copper acylpyruvates with hydroxylamine hydrochlorides and *o*-phenylenediamine hydrochlorides, identical products were obtained in comparable yields.

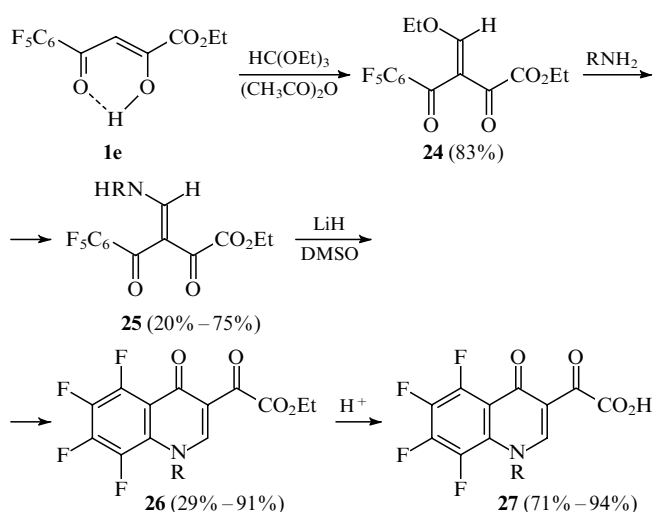
In addition, the use of the copper chelate of pentafluorobenzoylpyruvate **2f** allows one to obtain substituted benzothiazinone **22** by the reaction with *o*-aminobenzenethiol, while pentafluorobenzoylpyruvate **1f** as such undergoes acid scission under the reaction conditions.

VI. Preparation and reactions of 3-substituted polyfluorinated 2,4-dioxo acids

Preparation of fluorine-containing 3-substituted chromones and quinolones by cyclisation of aroylpyruvates requires that an alkoxymethylene group be introduced at the C(3) atom of the initial pyruvates.

Ethyl pentafluorobenzoylpyruvate (**1e**), like other β -DCC,^{11, 12, 23, 24, 67} readily reacts with ethyl orthoformate to form ethyl 3-ethoxymethylidene-2,4-dioxo-4-pentafluorophenylbutyrate (**24**). The reactions of compound **24** with amines followed by cyclisation of the resulting ethyl 3-

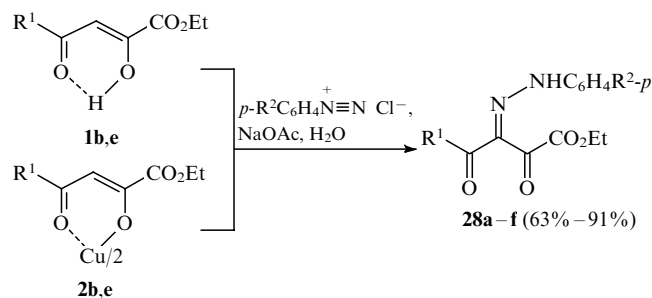
alkylaminomethylidene-2,4-dioxo-4-pentafluorophenylbutyrate (**25**) afford 3-ethoxalyl-1-*R*-5,6,7,8-tetrafluoro-4-quinolones (**26**). 2-(1-*R*-5,6,7,8-Tetrafluoro-4-oxo-1,4-dihydroquinolin-3-yl)glyoxylic acids (**27**) were prepared by hydrolysis of the esters **26**.⁶⁸



$R = H, Me, Et, cyclo-C_3H_5, C_6H_{13}, C_2H_4OH, o-MeC_6H_4$.

The active methylene group in compounds containing a β -dicarbonyl fragment is the reaction site for azocoupling with aryldiazonium salts to form the corresponding arylhydrazones.⁶⁹ Until recently, the data on the participation of fluorine-containing β -DCC in azocoupling have been limited to only a few examples of the reactions of fluorinated β -diketones,^{70, 71} trifluoroacetates⁷⁰ and pentafluorobenzoylaceticates.⁷² Recently, the synthesis of fluorinated 2-arylhydrazono-1,3-dicarbonyl compounds was reported and their reactivity with respect to N,O-dinucleophilicities was studied.⁷³ Data on the possibility of the synthesis of arylhydrazones using fluorine-containing acyl(aryl)pyruvates are lacking in the literature although nonfluorinated analogues of acyl(aryl)pyruvate arylhydrazones were reported.⁷⁴

3-Arylhyaones of 5,5,5-trifluoro-2,3,4-trioxopentanoates and 4-pentafluorophenyl-2,3,4-trioxobutyrate **28a–f** were first prepared by the reactions of trifluoroacetyl(pentafluorobenzoyl)pyruvates **1b,e** and their copper chelates **2b,e** with aryldiazonium chlorides in an aqueous medium.⁷⁵



28: $R^1 = CF_3$; $R^2 = H$ (**a**), Me (**b**), OMe (**c**);
 $R^1 = C_6F_5$; $R^2 = H$ (**d**), Me (**e**), OMe (**f**).

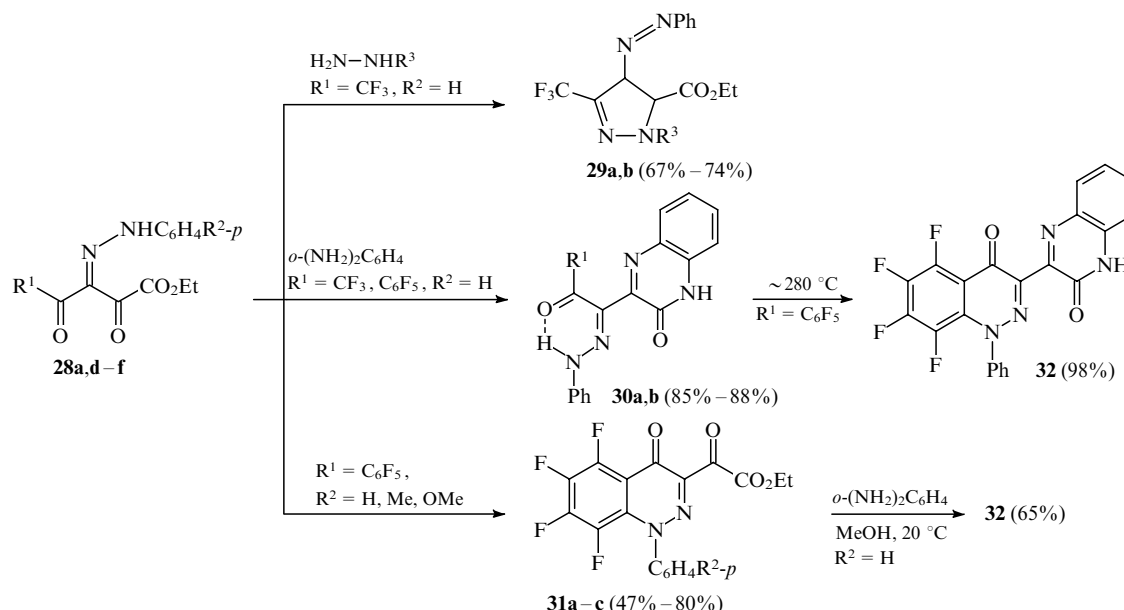
Arylhyaones **28a,d** were subjected to heterocyclisation with hydrazines and *o*-phenylenediamine. Compound **28a** reacts with hydrazine hydrate and phenylhydrazine to give 1-*R*³-5-ethoxycarbonyl-4-phenylazo-3-trifluoromethyl- Δ^2 -pyrazolines **29a,b**, unlike pentafluorobenzoyl-substituted arylhydrazone **28d**, which reacts with hydrazine hydrate to form a mixture of products which are difficult to separate. 3-(2-*R*-Ethyl-2-oxo-1-phenylhydrazono)-1,2-dihydroquinoxalin-2-ones **30a,b** were synthesised from arylhydrazones **28a,d** and *o*-phenylenediamine by boiling in diethyl ether (Scheme 4).⁷⁵

Thus, arylhydrazones of fluoroacyl(aryl)pyruvates, like their nonsubstituted analogues, react with hydrazines and *o*-phenylenediamine at the β -dicarbonyl and α -oxo-ester fragments, respectively.

The presence of a pentafluorobenzoyl substituent in arylhydrazones **28d–f** makes it possible to use them for constructing heterocyclic compounds of the cinnolone series. Thus when heated in DMSO in the presence of K_2CO_3 or refluxed in chloroform with a twofold excess of triethylamine, arylhydrazones **28d–f** give 3-ethoxalyl-5,6,7,8-tetrafluoro-1-(4-*R*²-phenyl)-1,4-dihydrocinnolin-4-ones **31a–c**.⁷⁵

Cyclisation of quinoxalinone **30b** upon heating affords 5,6,7,8-tetrafluoro-3-(2-oxo-1,2-dihydroquinoxalin-3-yl)-1-phenyl-1,4-dihydrocinnolin-4-one (**32**). Compound **32** is also formed in the reaction of cinnolinone **31a** with *o*-phenylenediamine.

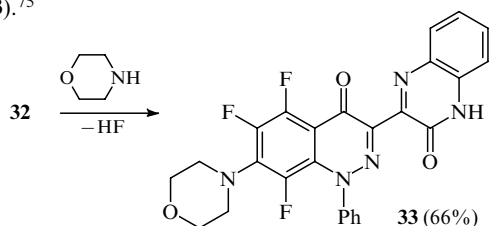
Nucleophilic replacement of the fluorine atom at position 7 in the reactions with various alkylamines is typical of fluorine-containing cinnolinones, fluorochromones and quinolones.¹² For example, the reaction of cinnolinone **32** with an excess of



29: $R^3 = H$ (**a**), Ph (**b**); **30**: $R^1 = CF_3$ (**a**), C_6F_5 (**b**); **31**: $R^2 = H$ (**a**), Me (**b**), OMe (**c**).

Scheme 4

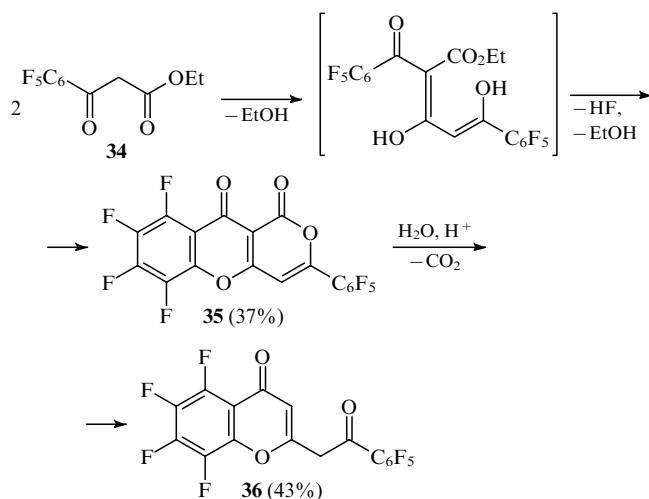
morpholine in DMSO yields a product of replacement of the fluorine atom, *viz.*, 5,6,8-trifluoro-7-morpholino-3-(2-oxo-1,2-dihydroquinoxalin-3-yl)-1-phenyl-1,4-dihydrocinnolin-4-one (**33**).⁷⁵



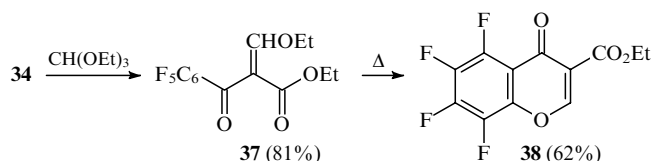
From the aforesaid it may be concluded that modification of fluoroacyl(aroyl)pyruvates by introducing alkoxyethylidene and arylhydrazone fragments at position 3 qualitatively changes and substantially extends synthetic possibilities of the compounds under consideration.

VII. Reactions of 2-ethoxycarbonyl(carboxy)-5,6,7,8-tetrafluorochromone

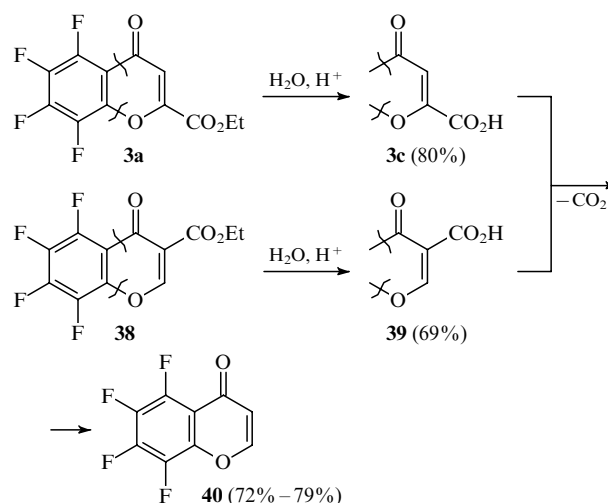
A characteristic feature of pentafluorobenzoylpyruvate **1e** and its chelate **2e** (see Scheme 1) is their conversion into 2-ethoxycarbonylchromone **3a** due to their ability to undergo intramolecular cyclisation to form a six-membered ring.^{23,24} Under analogous conditions, ethyl pentafluorobenzoylacetate (**34**) undergoes self-condensation. The latter reaction is accompanied by the Dieckmann condensation and intramolecular cyclisation of an intermediate product to yield 1-oxo-3-pentafluorophenyl-1*H*-pyrano[4,3-*b*]-6,7,8,9-tetrafluorochromone (**35**).⁷⁶ 2-Pentafluorobenzoylmethyl-5,6,7,8-tetrafluorochromone (**36**) was prepared by acid hydrolysis of compound **35**. It should be mentioned that self-condensation is typical of both fluorinated⁷⁷ and nonfluorinated β -oxo esters.⁷⁸ However, in the case of pentafluorobenzoylpyruvate **1e**, intramolecular cyclisation dominates.



It should also be noted that ethyl 2-ethoxymethylidenepentafluorobenzoylacetate (**37**), like the ester **1e**, undergoes cyclisation to form 3-ethoxycarbonyl-5,6,7,8-tetrafluorochromone (**38**).^{23,24}



Chromones **3a** and **38** are readily hydrolysed to the corresponding acids **3c** and **39**, which undergo decarboxylation upon heating to form 5,6,7,8-tetrafluorochromone (**40**).^{23,24}



The reactivity of fluorochromones was discussed⁷⁹ with recourse to quantum-chemical AM-1³⁷ calculations of the charges and Fukui indices for tetrafluoro-2-methoxycarbonylchromone, 2-carboxytetrafluorochromone and its anion and their nonfluorinated analogues using the MNDO-90 method³⁶ (Table 2).

The calculated data make it possible to reveal the following regularities. The introduction of fluorine atoms into the aromatic ring of chromone has virtually no effect on the charge distribution in the pyrone ring. The maximum positive charges in the pyrone and fluorine-containing aromatic rings are localised on the C(9) and C(5) atoms, respectively.⁷⁹

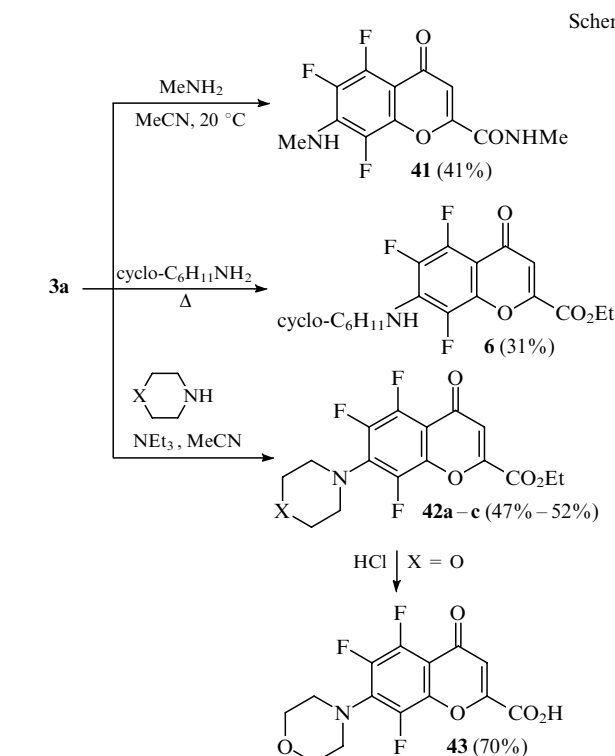
In the pyrone rings, the maximum values of the Fukui indices for LUMO correspond to the C(2) atom in the fluorine-substituted ester and acid and to the C(4) atom in the anion. In the fluorine-containing aromatic rings of the ester, acid and anion, the maximum values of the Fukui index correspond to the C(7) atom.⁷⁹

Thus, according to the charge control, the kinetically controlled reactions of chromones with nucleophilic reagents should occur predominantly at the C(9) atom of the ester fragment, carboxyl group and the anion of the acid. According to orbital control, the reactions of the ester and acid should occur at the C(2) atom of the pyrone ring, while the reactions of the anion should occur at the C(4) atom. The orbital-controlled nucleophilic replacement of the fluorine atom should occur predominantly at the C(7) atom.⁷⁹

2-Ethoxycarbonyl- **3a** and 2-carboxychromones **3c** possess different reactivity with respect to ammonia and primary amines.⁴³ Thus 2-ethoxycarbonylchromone **3a** does not react with ammonia or aniline. Methylamine reacts with the ester group and the C(7) atom of the fluorinated ring of compound **3a** to form *N*-methyl-5,6,8-trifluoro-7-methylaminochromone-2-carboxamide (**41**) (Scheme 5). This behaviour is untypical of the known nonfluorinated chromones. Under these conditions, the latter add a nucleophile at the C(7) atom with the opening of the heterocycle.⁷⁸ Under the action of cyclohexylamine, only the fluorine atom at the C(7) atom of chromone **3a** is replaced to form chromone **6** (see Scheme 5).⁷⁹ It should be noted that the replacement at the C(7) atom is an orbital-controlled reaction, while the formation of methylamide at the C(9) atom is a charge-controlled process.

Table 2. Charges and Fukui indices for the electrophilic centres in substituted chromones.

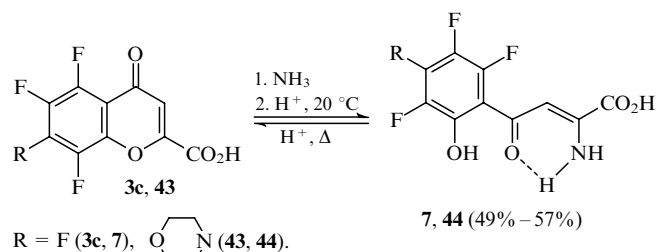
R	X	Charges							Fukui indices						
		C(2)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(2)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)
Me	F	+0.0564	+0.3041	+0.1618	+0.0060	+0.1015	+0.0429	+0.3454	0.197	0.186	0.312	0.00158	0.365	0.207	0.0406
H	F	+0.0543	+0.3033	+0.1620	+0.0072	+0.1019	+0.0440	+0.3531	0.224	0.192	0.300	0.00026	0.333	0.197	0.0521
Sec. ^a	F	+0.0754	+0.3184	+0.1539	+0.0306	+0.0748	+0.0297	+0.3916	0.0246	0.0676	0.338	0.0165	0.564	0.370	—
Me	H	+0.0567	+0.3039	−0.0451	−0.1630	−0.0748	−0.1536	+0.3439	0.476	0.237	0.124	0.00650	0.0959	0.0743	0.153
H	H	+0.0547	+0.3036	−0.0449	−0.1622	−0.0742	−0.1531	+0.3514	0.480	0.226	0.114	0.00710	0.0837	0.0672	0.171
Sec. ^a	H	+0.0836	+0.3162	−0.0553	−0.1973	−0.0977	−0.1669	+0.3861	0.0567	0.153	0.333	0.0154	0.542	0.285	—

^a Anion of 2-carboxychromone.

The reactions of chromone **3a** with secondary amines (morpholine, *N*-methylpiperazine or piperidine) proceed analogously without the opening of the heterocycle (which is typical of the reactions of nonfluorinated chromones with secondary amines) to form the corresponding 2-ethoxycarbonyl-7-*R*-5,6,8-trifluorochromones **42a–c**. Boiling of chromone **42a** with HCl gives 5,6,8-trifluoro-7-morpholinochromone-2-carboxylic acid (**43**) (see Scheme 5).⁴³

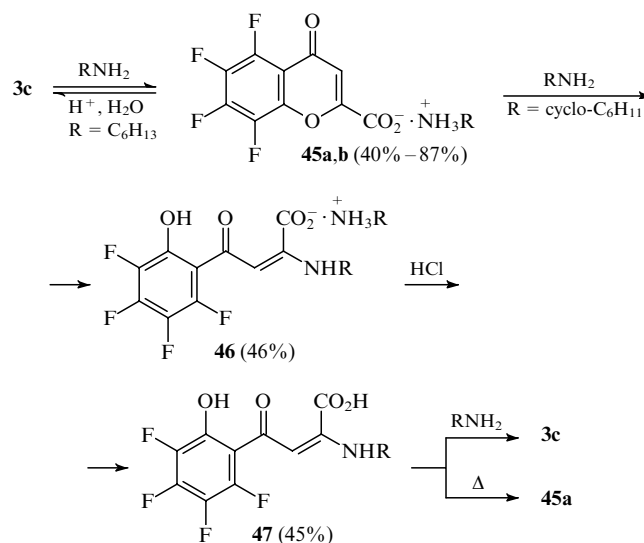
Thus, the reactions of 2-ethoxycarbonylchromone **3a** with primary and secondary amines are orbital-controlled and yield products of replacement at the C(7) atom.

In contrast to 2-ethoxycarbonylchromone **3a**, the reactions of 2-carboxychromones **3c** and **43** with ammonia are accompanied by the opening of the pyrone ring, which is typical of the known chromones.⁷⁸ These reactions afford 2-amino-3-(4-*R*-3,5,6-trifluoro-2-hydroxybenzoyl)acrylic acids **7** and **44**, which can undergo recyclisation to form the initial compounds **3c** and **43** upon boiling in an acidic medium.⁴³

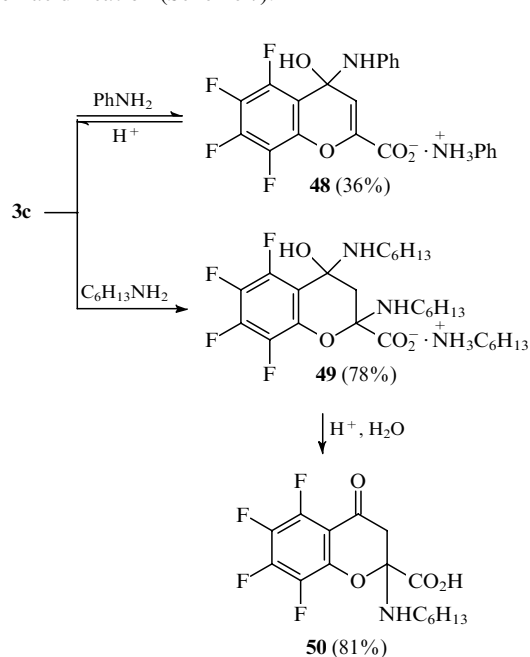


The reactions of 2-carboxychromone **3c** with primary amines are governed by both the nature of the amine and the reaction conditions.⁷⁹ Thus boiling of chromone **3c** with an equimolar amount of amine (cyclohexylamine or hexylamine) in dioxane affords cyclohexylammonium (hexylammonium) 5,6,7,8-tetrafluorochromone-2-carboxylate (**45a,b**). Salts **45a,b** are stable on prolonged boiling in toluene. In the presence of an excess of amine, the pyrone ring in compound **45a** is opened to form 2-cyclohexylamino-3-(3,4,5,6-tetrafluoro-2-hydroxybenzoyl)acrylate (**46**). Acidification of the salt **46** affords 2-cyclohexylamino-3-(3,4,5,6-tetrafluoro-2-hydroxybenzoyl)acrylic acid (**47**). Treatment of the hexylammonium salt **45b** with hydrochloric acid affords the initial chromone **3c** (Scheme 6).⁷⁹

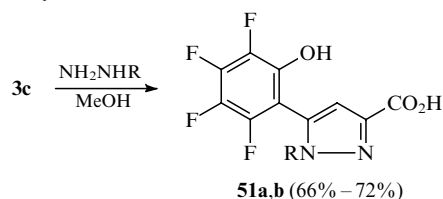
Scheme 6

45: R = cyclo-C₆H₁₁ (a), C₆H₁₃ (b).

The reactions of chromone **3c** with hexylamine and aniline in a mixture of chloroform and water at 30–35 °C can proceed both as nucleophilic addition of the amine at the activated C = C bond and as the reaction at the carbonyl group of the chromone. Thus chromone **3c** reacts with aniline to form anilinium 4-anilino-5,6,7,8-tetrafluoro-4-hydroxychromene-2-carboxylate (**48**). The reaction of chromone **3c** with hexylamine affords hexylammonium 2,4-bis(hexylamino)-5,6,7,8-tetrafluoro-4-hydroxychromene-2-carboxylate (**49**), which is converted into 5,6,7,8-tetrafluoro-2-hexylamino-4-oxochromane-2-carboxylic acid (**50**) upon acidification (Scheme 7).⁴³

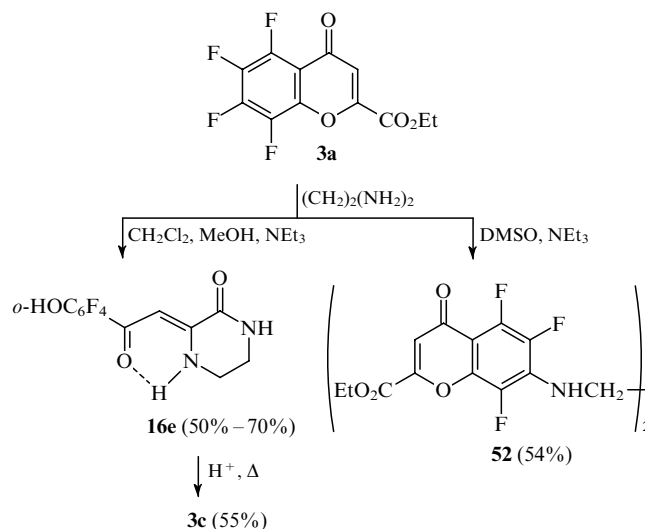


The reaction of 2-ethoxycarbonylchromone **3a** with hydrazine yields a mixture of products, which are difficult to identify. 2-Carboxychromone **3c**, like nonfluorinated analogues, reacts with hydrazine and phenylhydrazine more selectively to form the corresponding 1-R-5-(tetrafluoro-2-hydroxyphenyl)pyrazole-3-carboxylic acids **51a,b**.⁷⁹

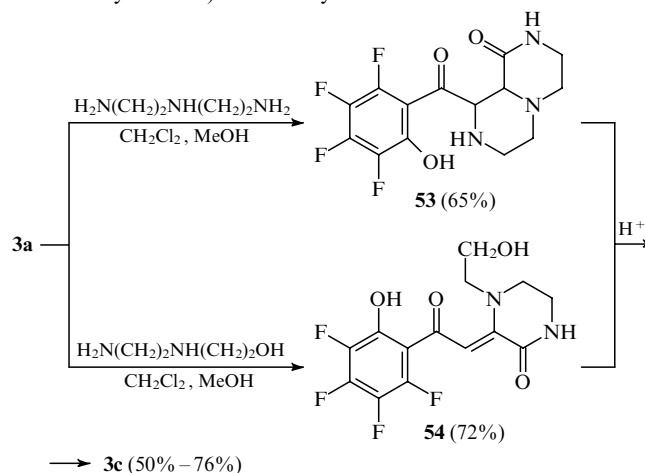


The reaction of 2-ethoxycarbonylchromone **3a** with ethylenediamine yields either piperazin-2-one **16e** as a result of the reaction at the C(2) atom and the ester group or a product of nucleophilic aromatic replacement of the fluorine atom at position 7, *viz.*, *N,N'*-ethylenebis(7-amino-2-ethoxycarbonyl-5,6,8-trifluorophenylchromone) (**52**), depending on the solvent (Scheme 8).⁴³ The formation of these compounds is attributable to an increase in the electron-withdrawing ability of the polyfluoroaryl ring (and consequently, the ability to undergo nucleophilic replacement of the fluorine atom) in going from protic solvents (alcohols) to a bipolar aprotic solvent (DMSO).⁸⁰ However, the reaction of chromone **3a** with ethylenediamine in acetonitrile also affords piperazin-2-one **16e**.⁴³ Apparently, acetonitrile, unlike DMSO, does not hinder the formation of an ionic pair of ethylenediamine with chromone at the electrophilic carbon atom of the ester group or at the C(2) atom.

Scheme 8



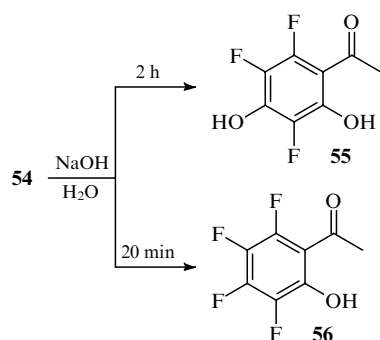
2-Ethoxycarbonylchromone **3a** reacts with diethylenetriamine with the involvement of all three nucleophilic centres to form a binuclear triazaheterocyclic derivative, *viz.*, 9-(3,4,5,6-tetrafluoro-2-hydroxybenzoyl)perhydropyrazino[1,2-*a*]pyrazin-1-one (**53**).⁸¹ An analogous bicyclic system is obtained by the reaction of 2-amino-4-iminoperfluoropent-2-ene (an aza analogue of heptafluoroacetylacetone) with diethylenetriamine.^{82, 83}



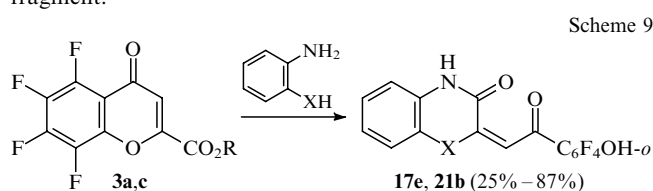
The reaction of chromone **3a** with *N*-(2-hydroxyethyl)-ethylenediamine under analogous conditions is completed in the stage of formation of a mononuclear heterocyclic compound, *viz.*, 3-(3,4,5,6-tetrafluoro-2-hydroxybenzoylmethylidene)-4-(2-hydroxyethyl)piperazin-2-one (**54**).⁸¹

Attempts to perform further intramolecular heterocyclisation of compound **54** with the use of acid or base catalysis, which favours nucleophilic addition of the hydroxy group at the C = C bond, failed. Under conditions of acid catalysis in the presence of water, compound **54** is readily hydrolysed to form carboxychromone **3c**. When boiled in toluene with *p*-toluenesulfonic acid, the initial piperazinone **54** remains unchanged. Heating of compound **54** in an alkaline medium results in its decomposition to 3,5,6-trifluoro-2,4-dihydroxyacetophenone **55** or, in the case of the shorter reaction time, to tetrafluoro-2-hydroxyacetophenone **56**.⁸¹

Analogous hydrolytic cleavage to form dihydroxy(hydroxy)-polyfluoroacetophenones was also observed in the cases of piperazinone **16e** and aminoacrylic acid **7**.⁸⁴

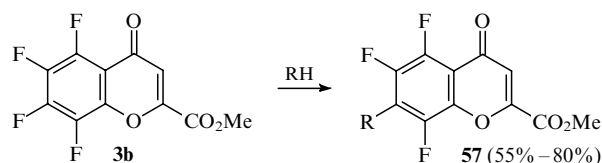


2-Ethoxycarbonylchromone **3a** and 2-carboxychromone **3c** react with *o*-phenylenediamine to form quinoxaline derivative **17e** (the yields were 70% and 30%, respectively) (Scheme 9).⁷⁹ The reactions of compounds **3a** and **3c** with *o*-aminophenol afford benzooxazinone **21b** containing the tetrafluorohydroxyphenyl fragment.^{53, 66}



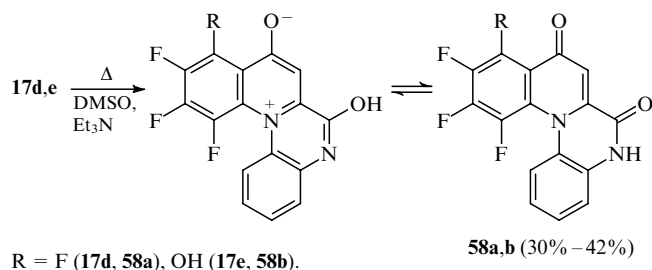
R = Et (**3a**), H (**3c**); X = NH (**17e**), O (**21b**).

The reaction of 2-methoxycarbonylchromone **3b** with *o*-aminothiophenol yields only a product of nucleophilic replacement of the fluorine atom, *viz.*, 7-(2-aminophenylthio)-5,6,8-trifluoro-2-methoxycarbonylchromone (**57**).³⁹



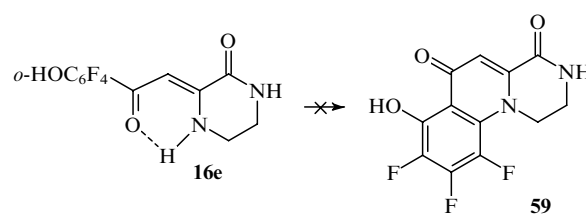
R = *o*-H₂NC₆H₄S.

When heated in DMSO in the presence of triethylamine, both quinoxalones containing the hydroxy group in the fluoroaromatic fragment (**17e**) and hydroxy-free quinoxalones (**17d**) undergo heterocyclisation to form 1,2,3-trifluoro-4-R-(5*H*)-5-oxoquinolino[1,2-*a*]-8*H*-quinoxalin-7-ones **58a,b** due apparently to the completely aromatic character of the possible zwitterion.⁷⁹

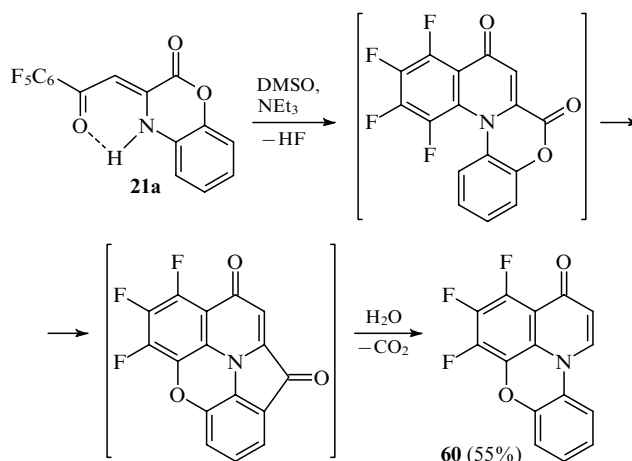


R = F (**17d**, **58a**), OH (**17e**, **58b**).

In this connection it should be noted that piperazinone **16e** whose nitrogen atoms should be more nucleophilic than those in quinoxalones does not give the corresponding heterocyclic system **59** either under analogous conditions or under more drastic conditions (K₂CO₃ or LiH). Apparently, this is associated with the fact that none of its possible tautomeric forms is completely aromatic.⁷⁹



It is remarkable that the benzooxazinone derivative **21a** also undergoes intramolecular cyclisation upon heating in DMSO. This reaction, unlike the above-mentioned transformation of quinoxalones **17d,e** into quinolinoquinoxalones **58a,b**, affords 4,5,6-trifluoro-3*H*-pyrido[3,2,1-*k*]phenoxazin-3-one (**60**). Apparently, the formation of compound **60** proceeds *via* intermediates shown in the following scheme:⁸⁵



Summarising the data on the reactions of 2-alkoxycarbonyl- (**3a,b**) and 2-carboxy-5,6,7,8-tetrafluorochromones (**3c**) with binucleophiles, it can be suggested that the mechanisms of the first stages of the reactions of chromones **3a,b** and **3c** are different, although the reactions can afford identical products (for example, in the reactions with *o*-phenylenediamine and *o*-aminophenol).

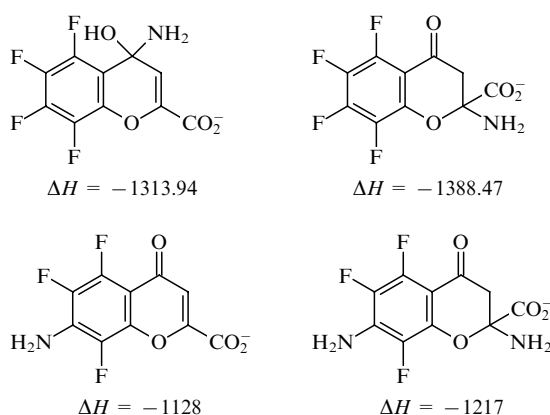
Apparently, the initial stage of the reactions of chromones **3a,b** with N-dinucleophiles involves the charge-controlled attack of one amino group of the reagent on the electrophilic C(9) centre. It counts in favour of this suggestion that the reaction of chromone **3a** with methylamine affords *N*-methylamide **41** (see Scheme 5). However, the reaction with an excess of methylamine involves also the orbital-controlled attack of the nucleophile on the C(7) centre. In this connection it should be noted that the orbital control may become predominant, *e.g.*, in the reactions of chromone **3a** with primary and secondary amines in dioxane yielding 7-substituted products **42** and **6** (see Scheme 5) or in the reaction of chromone **3a** with ethylenediamine in DMSO to form product **52** (see Scheme 8). This regioselectivity is apparently determined by the effect of specific solvation of the initial reagents by the solvent, much as in the reactions of 5-aryl-2,3-dihydrofuran-2,3-diones with aromatic amines in dioxane.⁸⁶

The second amino group of the N-dinucleophile (ethylenediamine, *o*-phenylenediamine or *o*-aminophenol) attacks the nearest C(2) atom of chromone **3a**. In this case, the pyran ring is opened to form new heterocyclic compounds, *viz.*, piperazinones **16e**, quinoxalones **17e** or oxazines **21b**, respectively (see Schemes 8 and 9). Evidently, this process is governed by thermodynamic factors.

Unlike 2-alkoxycarbonylchromones **3a,b**, 2-carboxychromone **3c** reacts with an equimolar amount of primary amines to form stable salts **45** (see Scheme 6). The reactions of these salts with an excess of amine follow different routes. Thus heating in dioxane results in resinification of the reaction mixture. In an aqueous medium, the reversible interaction of the amino group of primary amine with the electrophilic C(4) and C(2) centres occurs. In the latter case [the reaction at the C(2) atom], either products of

addition at the double C(2) = C(3) bond (products **49** and **50**) can be formed (see Scheme 7) or derivatives of aminoacrylic acid, viz., compounds **46** and **47**, can be obtained due to the opening of the heterocycle of the chromone, as in the case of the reaction with cyclohexylamine (see Scheme 6). However, when heated in dioxane, the products of addition of cyclohexylamine undergo identical conversions to form apparently the more stable initial salts.

It is remarkable that under kinetically controlled conditions the reaction at the C(4) atom can occur as a charge-controlled process because the charge on this atom is the second largest, exceeded in value only by the C(9) atom. However, the reaction of amine at the C(2) atom of the carboxylate anion, as in the case of 2-ethoxycarbonylchromone, is not apparently kinetically controlled. Actually, calculations of model compounds demonstrated that the attack of a nucleophile on the C(2) atom of the fluorinated carboxylate anion affords a thermodynamically more stable reaction product than the attacks on the C(4) and C(7) nucleophilic centres. This is evident from the comparison of the enthalpies of formation of the following compounds (ΔH /kJ mol⁻¹):⁷⁹



In our opinion, the formation of the corresponding carboxylate anion followed by the attack of a nucleophile (an excess of amine in the case of hydrazines and the second amino group in the case of *o*-phenylenediamine and *o*-aminophenol) on the C(2) atom is also typical of the reactions of 2-carboxychromone **3c** with hydrazines, *o*-phenylenediamine and *o*-aminophenol. The subsequent reaction path is determined by the thermodynamic stability of the final products, as in the case of nonfluorinated aroylpyruvic acids.

VIII. Conclusion

Analysis of the above-considered published data demonstrated that the reactions of fluorinated acyl(aroyl)pyruvates are analogous to the reactions of nonfluorinated α - and β -DCC. Thus fluoroacyl(aroyl)pyruvates react at the β -dicarbonyl fragment (for example, with hydrazines) and enter into the reactions at the active methylene group as β -DCC (for example, with orthoformate and aryldiazonium salts) and at the α -oxo-ester fragment as α -DCC (for example, with diamines).

However, the introduction of fluorine atoms into aroylpyruvate molecules can radically change their reactivity. Thus the heterocyclisation of fluoroaroylpyruvates, which is untypical of their nonfluorinated analogues, affords 2-ethoxycarbonyl(carboxy)-5,6,7,8-tetrafluorochromones. The latter, in turn, can react with HO-, HN- and HS-nucleophiles to form various fluorinated heterocyclic compounds.

In summary the above-considered data substantially extend the knowledge of synthetic potentialities of fluorinated 2,4-dioxo acids and their derivatives for constructing various classes of heterocyclic systems.

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Phosphine in the synthesis of organophosphorus compounds

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Abstract. Published data on the synthesis of organophosphorus compounds based on phosphine are fully surveyed, described systematically and analysed for the first time. The bibliography includes 211 references.

I. Introduction

Phosphine is used in the chemistry of organic compounds of phosphorus for the formation of C–P bonds and for the synthesis of organic and heteroorganic phosphines including functionally substituted ones, which are important auxiliary reagents, building blocks, intermediate products, ligands for metal-complex catalysts, extractants and fire-proofing agents.^{1–11}

Phosphine, possessing versatile reactivity, reacts with various classes of organic compounds (oxidants, organyl halides, alkenes, alkynes, aldehydes, ketones, oxiranes, thiiranes, amines, alcohols, esters, organyl isocyanates, *etc.*) both with transition into the tetracoordinated state and according to the substitution–addition patterns under conditions of base and acid catalysis and radical initiation.

The interest in the chemistry of phosphine does not attenuate; in our opinion, phosphine deserves even more attention. Known methods for the synthesis of organic compounds of phosphorus based on phosphine are being developed and improved; simultaneously, new phosphine-based methods for the synthesis of organophosphorus compounds appear (for example, the method based on the use of superbasic suspensions such as ‘alkali metal hydroxide–high-polarity non-hydroxylic solvent’ systems^{6, 7, 12} or phase transfer catalysis^{6, 7, 12}).

In recent years, considerable attention has been paid to nucleophilic reactions of phosphine with organyl halides^{12, 13} and reactions with electrophilic aryl(hetaryl)alkenes^{14–20} and -alkynes^{21–23} in superbasic systems, which permit selective and efficient syntheses of primary, secondary and tertiary phosphines. Most of these reactions occur under mild conditions at an atmospheric pressure of phosphine. The use of these methods was greatly facilitated by the development of a convenient

procedure for the generation of phosphine from red phosphorus and an alkali metal hydroxide in a water-organic medium.¹⁴

Although the chemistry of organic phosphines has been the subject of numerous reviews^{10, 11, 24, 25} and even monographs,^{1, 9, 25} the reactions of phosphine with organic compounds have not been considered systematically and are represented by few examples. Several reactions of phosphine are described in monographs^{1, 2, 9} and handbooks (see, for example, Ref. 25). The data on the use of phosphine in the synthesis of organophosphorus compounds published before 1961 were discussed most fully (but not exhaustively) in a short (13 pages) review,³ the bibliography of which includes 70 references. In another review,¹¹ which is devoted to α -hydroxyalkylphosphines and -phosphine oxides, reactions of PH_3 and organic phosphines with carbonyl compounds have been considered in detail.

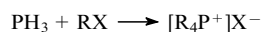
The purpose of the present review, in which data on the phosphine-based methods of the synthesis of organophosphorus compounds are described fully and systematically for the first time, is to provide the reader with not only general information but also data concerning particular reactions of phosphine and its organic derivatives.

II. Phosphine in substitution reactions

1. Alkylation of phosphine

a. Alkylation with organic halides

According to patents,^{26–29} the vapour-phase (210–280 °C) catalytic alkylation of phosphine with alkyl halides yields alkylphosphonium halides, their structures being dependent on the ratio of the reactants. Activated carbon or Pt, Pd and Au supported on Al_2O_3 or SiO_2 are used as catalysts. When excess alkyl halide with respect to phosphine is used, the reaction (210–280 °C, 11 atm, 85 h, activated carbon) gives tetraalkylphosphonium halides (in up to 83% yields).^{26, 27}



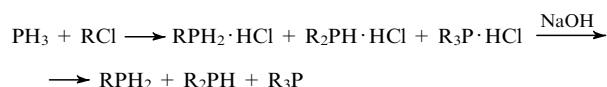
R = Alk(C_1 – C_4); X = Cl, Br.

The reactions of phosphine with alkyl chlorides (equimolar ratio, 280 °C, 5 days, activated carbon) afford mixtures of mono-, di- and trialkylphosphonium chlorides, monoalkylphosphonium chloride being the major product, which are converted into the corresponding phosphines on treatment with aqueous NaOH.²⁸

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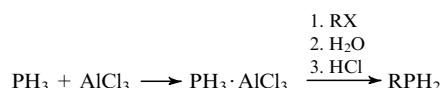
Received 11 June 1998

Uspekhi Khimii 68 (3) 240–250 (1999); translated by Z P Bobkova



R = Alk, cyclo-Alk, PhCH₂.

Having been bound in a complex on heating (70–80 °C) with an equimolar amount of AlCl₃, phosphine reacts with alkyl halides,^{30–31} cycloalkyl halides³⁰ and adamantyl bromide³² to give, after the subsequent treatment of the reaction mixture with ice water and HCl, primary phosphines in 15%–83% yields. When alkyl iodides are used, phosphorylation is complicated by side processes. Aryl halides do not enter into this reaction.³⁰

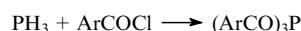


R = Alk(C₄–C₆) (37%–64%), Alk(C₈–C₁₈) (62%–83%), cyclo-Alk (15%–28%); X = Cl, Br.

It should be noted that even when the complex PH₃·AlCl₃ reacts with excess alkyl halide, the reaction occurs as monoalkylation; the formation of minor amounts of secondary phosphines was detected only for lower alkyl halides.³⁰

The reactions of phosphine with alkyl halides under the Friedel–Crafts conditions occur most likely by a carbocationic mechanism. This is indicated, in particular, by the fact that the reaction of dodecyl bromide with the complex PH₃·AlCl₃ yields a mixture of primary phosphines, presumably,³¹ structural isomers of dodecylphosphine.

The reaction of phosphine with chlorides of aromatic carboxylic acids in dry pyridine gives rise to tris(aryl)phosphines.^{33–35}



Ar = Ph,³³ 3-MeC₆H₄, 4-MeC₆H₄, α-C₁₀H₇, β-C₁₀H₇.^{33–35}

b. Alkylation with alcohols, ethers and amines

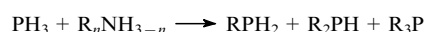
The synthesis of alkylphosphines by high-temperature catalytic alkylation of phosphine with alcohols,³⁶ ethers³⁶ and amines^{37,38} has been described in patents.^{36–38}

Thus aliphatic and cycloaliphatic primary and secondary phosphines are formed in good yields when phosphine reacts (200–300 °C, atmospheric pressure) with alcohols and ethers in the presence of dehydrated natural and synthetic metal aluminosilicates or zeolites of various brands, the pores of which are permeable for mono- and diorganylphosphines but impermeable for triorganylphosphines.³⁶



R = Alk, cyclo-Alk; R' = H, Alk.

A method for the preparation of primary, secondary and tertiary alkylphosphines by heating phosphine (150–400 °C, pressure up to 2 atm) with amines in the presence of a catalyst (activated carbon, copper chromite, Group IB and VIIIB metals) has been proposed.³⁷



R = Me, Et, Pr; n = 1–3.

Under the same conditions, phosphine can also be alkylated by mixtures of amines with hydrogen halides and/or alkyl halides, *i.e.* by the corresponding ammonium salts.³⁸

2. Reactions of phosphide ions with organic halides

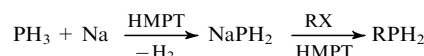
In the presence of strong bases, phosphine is converted into phosphide ions, which react with organyl halides by nucleophilic substitution to give primary and secondary phosphines. The role of bases in these reactions is played by the systems 'alkali (or alkaline earth) metal–organic solvent (or liquid ammonia),'

organometallic compounds (triphenylmethylsodium, phenyllithium, butyllithium) or strong bases generated from alkali metal hydroxides in polar non-hydroxylic solvents or under conditions of phase transfer catalysis.

a. Reactions of metal phosphides

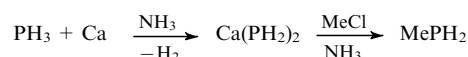
Phosphorylation of organyl halides by the 'phosphine–alkali (or alkaline earth) metal' systems yields predominantly primary phosphines.^{1,2,39–45} This reaction can be carried out for alkyl halides,^{39–41} aryl halides,^{1,42} aminoalkyl halides,⁴³ sodium halocarboxylates^{44,45} and dihaloalkanes.^{41,46–49} The process is carried out in an organic solvent or in liquid ammonia using stoichiometric amounts of reactants.

Thus alkylphosphines and allylphosphines have been obtained in good yields (55%–78%) by a one-pot procedure which includes the reaction of sodium, dispersed preliminarily in hexamethylphosphotriamide (HMPA), with phosphine and the addition of alkyl halides to the resulting solution of sodium dihydrophosphide.⁴⁰

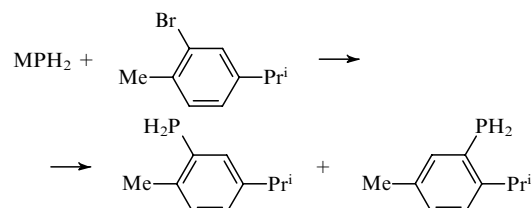


R = Me, Et, CH₂=CHCH₂; X = Cl, Br.

When calcium metal is used in this process instead of sodium and liquid ammonia is used instead of HMPA, phosphorylation becomes more efficient; for example, the reaction between chloromethane and phosphine gives methylphosphine in 87% yield.⁴¹

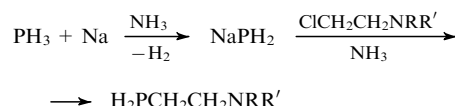


It has been reported that aryl halides can be involved in the reaction with alkali metal phosphides.^{1,42} Thus potassium phosphide prepared from phosphine and potassium in liquid ammonia slowly reacts with bromo- and iodobenzene to give phenylphosphine.¹ A mixture of (5-isopropyl-2-methylphenyl)phosphine and 2-isopropyl-5-methylphenyl)phosphine is formed when 2-bromo-4-isopropyl-1-methylbenzene reacts with sodium phosphide or lithium phosphide in boiling ether.⁴²



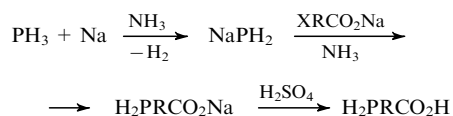
M = Li, Na.

The 'phosphine–sodium–liquid ammonia' system has been used successfully in phosphorylation of aminoalkyl halides⁴³ and halocarboxylic acids^{44,45} aimed at synthesising the corresponding functionalised primary phosphines. Thus (2-R,R'-aminoethyl)phosphines have been obtained in 54%–70% yields from 2-R,R'-aminoethyl chloride and phosphine.⁴³



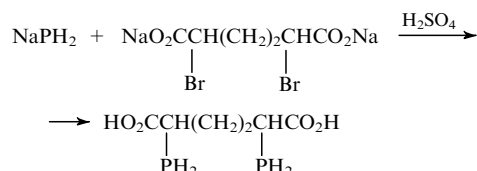
R, R' = H, Et.

When sodium halocarboxylates are treated with phosphine in the 'sodium–liquid ammonia' system and then the reaction mixture is treated with dilute sulfuric acid, 1- and 2-carboxyalkylphosphines are formed in 70%–85% yields.^{44,45}

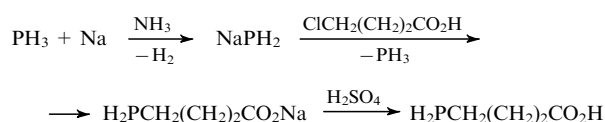


R = CH₂, CHMe, CHEt, CMe₂, CH₂CH₂; X = Cl, Br.

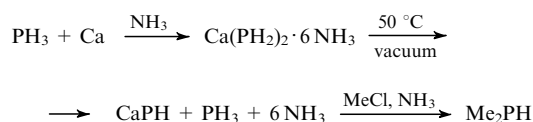
Under the same conditions, sodium 2,5-dibromoadipate was converted into 2,5-diphosphinoadipic acid formed as a mixture of racemic and meso forms in 45 : 55 ratio.⁴⁴



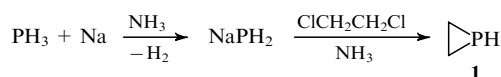
The synthesis of 3-carboxypropylphosphine from 4-chlorobutyric acid demonstrated that not only salts but also acids themselves can efficiently react with phosphine and excess sodium in liquid ammonia.⁴⁴



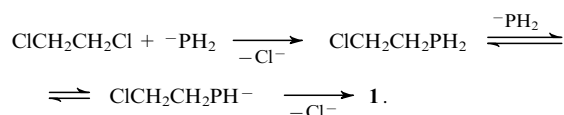
Thus, metallation of phosphine with an alkali or alkaline earth metal followed by treatment of the phosphide with an organyl halide results in the formation of primary phosphines of various structures in high yields.^{40, 41, 43–45} However, this approach has scarcely been used for the synthesis of diorganylphosphines, apparently, due to the difficulty of formation of disubstituted metal derivatives upon metallation of phosphine.¹ Only preparation of dimethylphosphine in a relatively low yield (33%) by treatment of calcium hydrophosphide with chloromethane in liquid ammonia has been reported.⁴¹



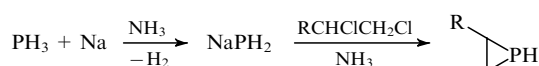
Dihaloalkanes can be phosphorylated by the 'PH₃–alkali metal–liquid ammonia' system to give, depending on the length of the alkylene chain, either cyclic phosphines or their mixtures with primary alkylendiphosphines. The reaction of 1,2-dichloroethane with sodium dihydrophosphide in liquid ammonia yields phosphirane **1** as the main product (yield 74%).^{47–49}



The cyclisation was suggested⁴⁷ to occur as follows:

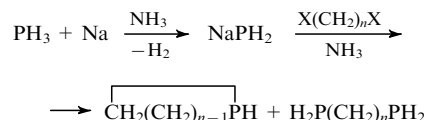


Methyl- and ethylphosphiranes have been prepared from the corresponding 1,2-dichloroalkanes under the same conditions (yields 30% and 25%, respectively).⁴⁰



R = Me, Et.

α,ω-Dihaloalkanes with a number of methylene units $n \geq 3$ are phosphorylated by phosphine in the 'sodium–liquid ammonia' system yielding simultaneously cyclic secondary phosphines and alkylendiphosphines.^{48, 49}



X = Cl, Br; $n = 3–7$.

The transformation of 1,4-dichlorobutane under these conditions gave a mixture of phospholane and 1,4-diphosphinobutane (each in 47% yield).⁴⁸

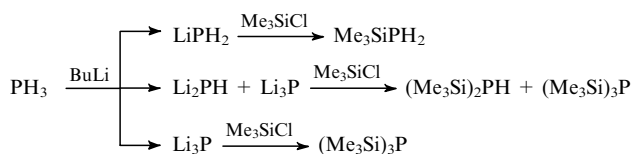
Phosphine can be metallated with equal success by some organometallic compounds, for example, triphenylmethylsodium,¹ phenyllithium^{1, 50, 51} and butyllithium.⁵²

For example, when a fast stream of phosphine is passed through diethyl ether to which phenyllithium is being simultaneously added, lithium dihydrophosphide is formed; its subsequent treatment with organyl halide affords primary phosphines in 65%–75% yields.⁵⁰



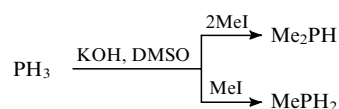
R = Et, Prⁿ, Bu^t, PhCH₂; X = Cl, Br.

Depending on the reactant ratio, the reaction of butyllithium with phosphine gives rise to lithium phosphide, trilithium phosphide or its mixture with dilithium phosphide. The reactions of these phosphides with chlorotrimethylsilane at 0–10 °C resulted in the formation of trimethylsilylphosphine (yield 30%), a mixture of bis- and tris(trimethylsilyl)phosphines (yields 35% and 24%, respectively) or tris(trimethylsilyl)phosphine (yield 45%).⁵²



b. Reactions of phosphine in the presence of a strong base

Methylation was the first example of alkylation of phosphine with an organyl halide in the presence of a strong base.^{53, 54} When methyl iodide is added to a DMSO suspension of KOH preliminarily saturated with phosphine, methylphosphine or dimethylphosphine is formed, depending on the initial ratio of reactants (yields 75%⁵³ and 65%,⁵⁴ respectively).

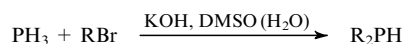


Later, other organyl halides have also been involved in this reaction; this gave monoorganylphosphines in 70%–94% yields.¹² The reaction was carried out in a mixture of a 56%–64% aqueous solution of KOH with DMSO (depending on the nature of the halide used, the temperature and pressure varied in the ranges 0–60 °C and 4–7.5 atm).



R = Me, Et, CH₂=CHCH₂, Buⁿ, Bu^t, PhCH₂; X = Br, Cl.

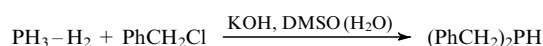
Diallyl- and dibutylphosphines were obtained in this reaction (yields 53% and 23%, respectively) by using a two- or four-fold excess of potassium hydroxide with respect to the corresponding organyl bromide.¹²



R = Bu, CH₂=CHCH₂.

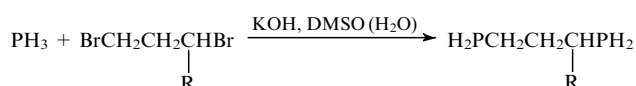
No products of the possible prototropic rearrangement — propen-1-yl- or di(propen-1-yl)phosphines — have been obtained under these conditions, although this rearrangement does occur during phosphorylation of allyl halides with red phosphorus in a highly basic aqueous-organic emulsion.^{5, 55, 56}

Recently dibenzylphosphine has been prepared in 50% yield from phosphine and benzyl chloride.^{13, 57} The reaction occurs under mild conditions (atmospheric pressure, 40 °C). Benzyl chloride is slowly added to a suspension of KOH in DMSO in the presence of a slight amount of water and simultaneously, a phosphine–hydrogen mixture, generated from red phosphorus and an alkali metal hydroxide, is vigorously passed through the suspension.



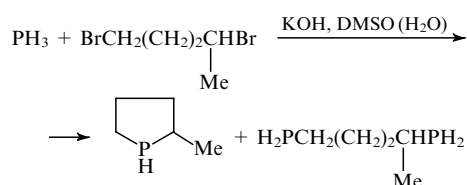
This reaction gives as well a noticeable amount of dibenzyl ether (up to 20%) resulting from solvolytic transformations of benzyl chloride.¹³

Unlike reactions of metal phosphides with dihalopropane, which afford phosphorus-containing heterocycles^{48, 49} (Section II.2.a), the reactions of phosphine with 1,3-dihalopropane or -butane in the KOH–DMSO(H₂O) system give only acyclic products, 1,3-diphosphinopropane or -butane (yields 59% and 75%, respectively).¹²

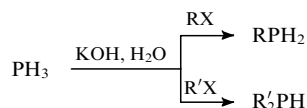


R = H, Me.

Phosphorylation of 1,4-dibromopentane under similar conditions gives rise to 2-methylphospholane (yield 80%), only minor amounts of the corresponding acyclic product, 1,4-diphosphinopentane, being formed.¹²



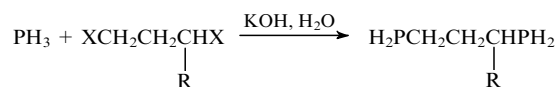
Alkylation of phosphine with organyl halides has also been carried out in the presence of bases generated under conditions of phase transfer catalysis, *i.e.* in the systems ‘aqueous potassium hydroxide–organic solvent (toluene, pentane)–tetraalkylammonium or tetraalkylphosphonium salt.’^{12, 58, 59} Depending on the reactant ratio and the reaction conditions (temperature, pressure), primary or secondary phosphines are formed in the 55%–92% yields.



R = Alk(C₁–C₂₄), CH₂=CHCH₂,^{12, 58} PhCH₂,⁵⁸

-CH₂CH₂,¹² Ph₂PCH₂,⁵⁹ R' = Me,¹² Ph₂PCH₂,⁵⁹ X = Cl, Br.

1,3-Dihaloalkanes react with phosphine under the conditions of phase transfer catalysis to give, as in the KOH–DMSO system,¹² 1,3-diphosphinoalkanes in yields of up to 89%.^{12, 58}



R = H, Alk; X = Cl, Br.

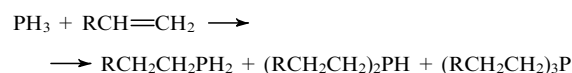
III. Phosphine in addition reactions

1. Addition to C = C bonds

The reaction of phosphine with alkenes is a convenient method for the synthesis of organic phosphines. Phosphine can add to C = C bonds by both ionic and radical mechanisms. The reaction pathway is determined by its conditions and the nature of the alkene used.

a. Nucleophilic addition

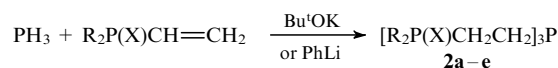
Nucleophilic addition of phosphine to the C = C bond was first described by Rauhut *et al.*^{60, 61} for alkenes containing strong electron-withdrawing substituents at the *sp*² carbon atom. In the presence of bases (a 10 M aqueous solution of KOH, heptamethylbiguanide, a concentrated solution of ammonia, solid sodium hydroxide), phosphine reacts with acrylonitrile,^{60, 62} acrylamide, nitroethylene, mesityl oxide and lauryl acrylate⁶¹ to give a mixture of primary, secondary and tertiary phosphines.



R = CN, CONH₂, NO₂, *etc.*

The process selectivity can be increased by varying its conditions (the molar ratio and the rate of mixing of the reactants, temperature, heating duration or pressure).^{60, 61} For example, when a flow of phosphine is passed through the system ‘aqueous KOH–acetonitrile’ heated to 30–35 °C and acrylonitrile is simultaneously added to it, the addition rate being adjusted in such a way as to maintain a slight excess of acrylonitrile relative to phosphine, tris(2-cyanoethyl)phosphine is obtained in 80% yield. A decrease in the concentration and the rate of addition of acrylonitrile under the same conditions results in bis(2-cyanoethyl)phosphine being formed predominantly (yield 63%). The primary phosphine is formed in 52% yield in the phosphorylation of acrylonitrile in an autoclave under an elevated pressure of phosphine (28–32 atm).⁶⁰

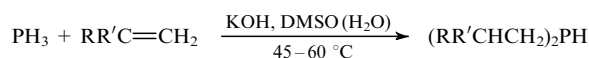
In the 1970s, a series of studies was published on the nucleophilic addition of phosphine to dialkyl vinylphosphonates,^{63, 64} vinylalkylphosphine sulfides,^{65, 66} and even to relatively weak electrophiles — vinylphenylphosphine^{67–70} and vinylphosphonous diamides.⁷¹ The reactions occur in boiling THF in the presence of Bu^tOK,^{63–66, 70} or in benzene in the presence of PhLi at 100 °C (autoclave),^{67–69} or in the ‘metallic potassium–liquid ammonia’ system⁷¹ and result in the formation of functionalised tertiary phosphines **2a–e**, their yields ranging from 24% (**2a**) to 95% (**2e**).



R = Ph (**a**), Me₂N (**b**), X is absent; R = Me₂CHO (**c**), X = O;
R = Me (**d**), Me₃CCH₂ (**e**), X = S.

Recently^{14–21} it has been found that phosphine is capable of adding to weakly electrophilic C = C bonds in aryl and hetaryl-ethenes in the KOH–DMSO system, and preparative methods for the synthesis of bis- and tris(2-arylethyl)- and -(2-hetaryl-ethyl)phosphines have been developed. In the absence of KOH, all other factors being the same, phosphorylation does not occur, which confirms the nucleophilic mechanism of the reaction. Phosphine is generated as a mixture with hydrogen by the addition of an aqueous solution of KOH (or NaOH) to a suspension of red phosphorus in dioxane.¹⁴

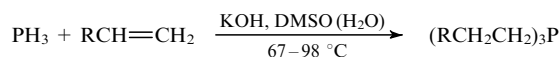
Bis(2-arylethyl)- and bis(2-hetarylethyl)phosphines have been selectively synthesised in 60%–80% yields by slow addition of an alkene to a suspension of KOH in DMSO heated to 45–60 °C with simultaneous vigorous passing of a phosphine stream through the suspension.^{14–20}



R = H, R' = Ph, 4-FC₆H₄, , , , Me-;
R = Me, R' = Ph.

1-Methyl-2-vinylpyrrole could not be involved in the reaction with phosphine, apparently, because of the low electrophilicity of the double bond in this alkene (due to the electron-donating mesomeric effect of the 1-methyl-2-pyrrolyl group).¹⁴

Exhaustive and selective aryl(hetaryl)ethylation of phosphine by styrene and vinylpyridines occurs at 95–98 °C and 65–67 °C, respectively, in the KOH–DMSO system, giving rise to tris(2-phenylethyl)-, tris[2-(4-pyridyl)ethyl]- and tris[2-(2-methyl-5-pyridyl)ethyl]phosphines (yields 65%–76%).^{18, 19}



R = Ph, , Me-.

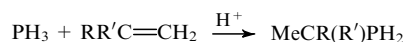
When this reaction is conducted at a lower temperature (30–40 °C), the corresponding primary phosphines can also be obtained in 20%–24% yields. However, bis(2-phenylethyl)- and bis(2-pyridylethyl)phosphines are the main reaction products under these conditions.^{19, 20}

It has been noted that a base generated under the conditions of phase transfer catalysis (a 60% aqueous solution of KOH–dioxane–benzyltrimethylammonium chloride) is not sufficiently strong to enable phosphorylation of arylalkenes and vinylpyridines with phosphine.¹⁹

An unsuccessful attempt to carry out the reaction of phosphine with diphenylethene and fumaronitrile in the presence of a base has been reported.⁷²

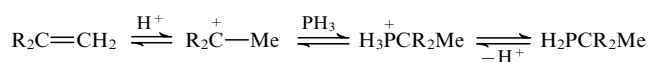
b. Electrophilic addition

The acid-catalysed addition of phosphine to unsaturated compounds is relatively little studied. It has been reported^{73, 74} that alkenes of various structures (linear and branched alkenes, cycloalkenes, polypropenes, polybutenes, styrene, limonene, *etc.*) react with phosphine under relatively rigorous conditions (60–90 °C, 30–47 atm, acid catalysis) according to the Markovnikov rule to give mostly primary phosphines.



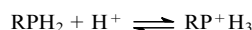
R, R' = H, Alk(C₁–C₆₃), Ph, *etc.*

Best results in this reaction are obtained when 1,1-disubstituted alkenes are used, because they form the most stable intermediate tertiary carbocations and in addition, they are the least susceptible to cationic polymerisation.



Thus the highest yield (90%) of the primary phosphine was observed when phosphine was made to react with C₁₂-polypropene.⁷³ The reaction of phosphine with 2-methylprop-1-ene, 2-ethylhex-1-ene and 1-methylcyclopentene is less efficient (the yield of the corresponding primary phosphines is 41%–75%), which is apparently due to the fact that these alkenes are more prone to undergo polymerisation than C₁₂-polypropene. Phosphorylation of linear alkenes, ethene, propene and dodec-1-ene, results in even lower yields (14%–20%) of primary phosphines.

Among the catalysts tested in the reaction of phosphine with alkenes (mineral and organic acids, sulfonic acids, Lewis acids), methanesulfonic acid is the most active.⁷³ It should be noted that for this reaction to go to completion, almost stoichiometric amounts of acid catalysts are needed, because the monoalkylphosphines, which are formed in the process, are stronger bases than phosphine; therefore, they react reversibly with the acid to give phosphonium ions.



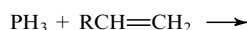
The reactions of phosphine with some alkenes (styrene, limonene) in an acid medium are accompanied by polymerisation giving rise to telomeric phosphines.⁷⁴

Since the electrophilic addition of phosphine to alkenes is a carbocationic process, the reactions of linear alkenes with phosphine under these conditions may be accompanied by isomerisation of the hydrocarbon chain (as has been shown in relation to the interaction of phosphine with alkyl halides in the presence of AlCl₃).³¹ However, in the study cited,⁷³ this aspect is not considered.

c. Radical addition

The addition of phosphine to alkenes under conditions of radical initiation [organic peroxides, azobisisobutyronitrile (AIBN), UV irradiation] has been studied fairly comprehensively. This method is used to prepare organic phosphines of various structures, because this reaction has been performed for a broad range of unsaturated organic compounds including functionally substituted ones: linear unsubstituted alkenes with a terminal^{74–88} or (more rarely) internal^{80, 81, 93, 94} double bond, cycloalkenes,^{75, 76, 78, 80, 81, 85, 90} arylalkenes,^{75, 78, 80, 81, 90} dienes,^{78, 79, 90, 113–118} trienes,¹¹⁹ fluorinated alkenes,^{103–109} vinyl^{75, 80, 81} and divinyl^{111, 112} ethers and thioethers,^{80, 81} alcohols,^{76, 80, 81, 85, 95} amines,^{76, 80, 81} ketones,^{80, 81} acrylic acid derivatives,^{75, 80, 81, 96–98} and allyl^{80, 81} and vinyl^{99, 100} carboxylates and phosphonates.^{80, 81, 85}

Radical addition of phosphine to alkenes normally results in the formation of mixtures of primary, secondary and tertiary phosphines, their ratio being dependent most of all on the ratio of the initial reactants.^{75, 77}



R = Alk, Ph, H₂NCH₂, HOCH₂, MeO, BuO, MeS, MeO₂C, EtO₂C, Me(CH₂)₃CH(Et)CH₂O₂C, *etc.*

Primary phosphines are formed as the major products when a substantial excess of phosphine in relation to alkene is used.^{75, 78, 79} Octylphosphine is formed in 65% yield when a mixture of phosphine with oct-1-ene (molar ratio 3.6 : 1) is heated (78–89 °C, AIBN) at a pressure of ~33 atm. The yields of dioctyl- and trioctylphosphines under these conditions are 18% and 4%, respectively.⁷⁵ An even higher yield (80%) of octylphosphine was attained when the reaction was carried out at a phosphine pressure of 120–180 atm,⁷⁸ because at higher phosphine pressures, its solubility in the liquid phase increases and, hence, the yield of primary phosphine also increases.⁷⁵

A similar influence of high pressures of phosphine on the yield of the reaction product was observed⁷⁵ for 2-methylprop-1-ene.

Tertiary phosphines are prepared in high yields (70%–96%) by using excess alkene with respect to phosphine.^{75, 76, 80–85} For instance, phosphorylation of oct-1-ene by phosphine at a molar ratio of 3 : 1 (80–100 °C, pressure 3.3 atm, AIBN) afforded trioctylphosphine in 83% yield.⁷⁵ The synthesis of tributylphosphine in a nearly quantitative yield (96%) from phosphine and but-1-ene under conditions of radical initiation is described in a patent.⁸³

However, the yield of secondary phosphines in the radical addition of phosphine to alkenes is, as a rule, relatively low (20%–30%).⁷⁵

Naturally, the structure of the alkene used also has an influence on the ratio of primary, secondary and tertiary phosphines formed in the alkylation of phosphine with alkenes. Sterically hindered alkenes (2-methylpropene, but-2-ene,^{80, 81, 93, 94} cyclohexene^{75, 76, 78, 80, 81, 85, 90}) react less vigorously than, for example, oct-1-ene to give mostly primary and secondary phosphines even when an excess of alkene with respect to PH_3 is used.

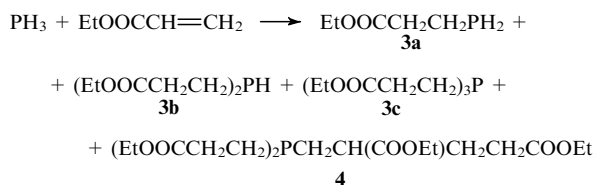
UV irradiation of an equimolar mixture of phosphine and styrene gives rise to phenethylphosphine.⁸¹ The same product is formed, together with bis(phenethyl)phosphine (yields 36% and 29%, respectively), when styrene is phosphorylated with a 1.5-fold molar excess of phosphine in the presence of AIBN (80 °C, ~28 atm).⁷⁵

Phosphorylation of fluorine-substituted alkenes with phosphine is activated by heating (150–160 °C)^{103–105} or UV radiation.^{106–109} This reaction gives mostly primary phosphines, the yields of which are higher (up to 74%–91%) in the case of UV activation.

The reactions of phosphine with alkyl vinyl ethers,^{75, 80, 81} alkyl vinyl sulfides,^{80, 81} allylamines^{76, 80, 81} and allyl alcohol^{76, 80, 81} (a two-fold molar excess of the corresponding alkene was normally used) occurring on exposure to UV radiation^{76, 80, 81} or in the presence of AIBN (80 °C, 31 atm)⁷⁵ afford mostly primary and secondary phosphines (total yield 50%–75%); the yields of tertiary phosphines do not exceed 10%.

On exposure of an equimolar mixture of phosphine and vinyl methyl ketone to UV radiation, (2-acetyethyl)phosphine was formed as the major product.^{80, 81}

A complex mixture of phosphines is formed when ethyl acrylate is made to react with phosphine (70–100 °C, AIBN, 28 atm).⁷⁵ The reaction products contain not only the expected primary, secondary and tertiary phosphines **3a–c** (yields 21%, 20% and 23%, respectively) but also bis(2-ethoxycarbonyl)ethyl-2,4-diethoxycarbonylbutylphosphine **4** (yield 19%).

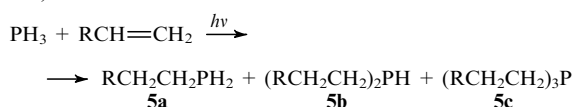


The phosphine **4** is formed apparently upon the addition of bisphosphine **3b** to diethyl α -methyleneglutarate resulting from dimerisation of the initial ethyl acrylate.



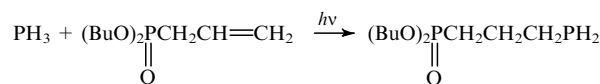
The radical addition of phosphine (AIBN, 90–120 °C, 15 atm) to acrylonitrile at a molar ratio of the reactants of 2.9–3.2 : 1 occurs selectively to give tris(2-cyanoethyl)phosphine in 93% yield.^{97, 98} Nevertheless, the synthesis of this tertiary phosphine from acrylonitrile and phosphine under the conditions of base catalysis (Section III.1.a) is undoubtedly more convenient and practically feasible, because it readily occurs on moderate heating (25–30 °C) under atmospheric pressure.⁶⁰

A mixture of primary, secondary and tertiary phosphines **5a–c** is produced upon photochemical addition of phosphine to allyl^{80, 81} and vinyl^{99, 100} carboxylates (most often, to vinyl acetate).

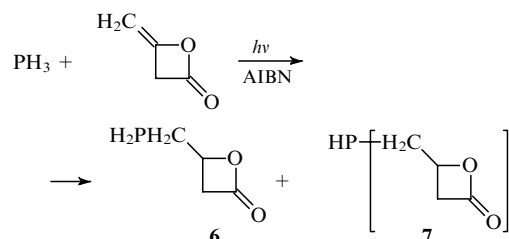


R = MeCO_2 , MeCO_2CH_2 .

Photoinitiated addition of phosphine to vinyl-^{80, 85} and allylphosphonates⁸¹ has been described. Thus UV irradiation of an equimolar mixture of phosphine and dibutyl allylphosphonate gave 3-(dibutoxyphosphoryl)propylphosphine.⁸¹

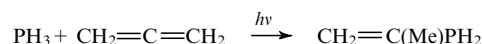


NMR analysis of the reaction mixture obtained upon UV irradiation of phosphine and diketene in the presence of AIBN showed the presence of 2-oxo-4-oxetanylmethyl- (**6**) and bis(2-oxo-4-oxetanylmethyl)phosphines **7**; these products were not isolated because of their low stability.¹⁰¹

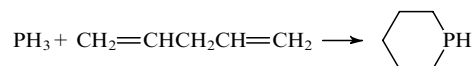


The addition of phosphine to terpenes and their derivatives in the presence of AIBN has been patented.¹⁰²

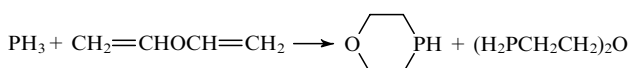
On exposure of a mixture of allene and phosphine to UV radiation, the first representative of primary vinylphosphines, propen-2-ylphosphine, was obtained in 3% yield.¹¹⁰



Under conditions of radical initiation (AIBN, 50–70 °C, 10–20 atm), phosphine reacts with penta-1,4-diene to give phosphorinane.⁷⁹

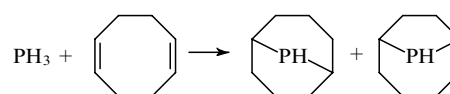


The radical addition of phosphine to divinyl ether (AIBN or UV irradiation, 75–80 °C, 10 atm) results in the formation of both a cyclic phosphine (4-oxaphosphorinane) and a linear primary diphosphine (the yield of each product is 7%–10%).^{111, 112}

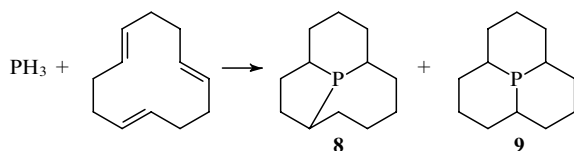


According to patent data,¹¹³ the reaction between phosphine and dicyclopentadiene under conditions of radical initiation (AIBN or organic peroxides, 90 °C, 3–20 atm) gives rise to a mixture of isomeric secondary phosphines with the composition $\text{C}_{20}\text{H}_{27}\text{P}$. It was proposed to use this mixture as a ligand for the preparation of metal-complex catalysts and also as a flotation reagent.¹¹³

Bicyclic secondary phosphines are formed upon homolytic addition of phosphine to 4-vinylcyclohex-1-ene¹¹⁴ and to cyclic dienes.^{78, 90, 115–118} Thus heating (70–180 °C) cycloocta-1,5-diene with phosphine under a pressure of 30–40 atm in the presence of AIBN or organic peroxides affords a mixture of 9-phosphabicyclo[3.3.1]nonane and 9-phosphabicyclo[4.2.1]nonane (in a total yield of up to 96%, ratio 1 : 0.8).¹¹⁵



Prolonged (79 h) γ -irradiation (⁶⁰Co) of a mixture of phosphine and cyclododeca-1,5,9-triene has given rise to isomeric tricyclic phosphines **8** and **9** (overall yield 20%).¹¹⁹



d. Addition in the presence of heterogeneous and metal-complex catalysts

Data on the interaction of phosphine with branched and cyclic alkenes and with dienes in the presence of heterogeneous solid catalysts (zeolites, phosphates and metal oxides) at an elevated pressure (8–190 atm) and at temperatures of 100–200 °C have been reported.¹²⁰ Thus heating of phosphine and 2-methylpropene in an autoclave (200 °C, 190 atm) in the presence of a borosilicate zeolite gave *tert*-butylphosphine in 70% yield.¹²⁰

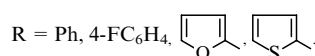
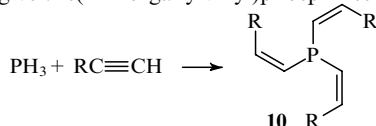


As noted above (Section III.1.b), this reaction can be carried out under milder conditions (60 °C, 33 atm) in the presence of methanesulfonic acid, *tert*-butylphosphine being formed in a comparable yield (61%).⁷³

The addition of phosphine to acrylonitrile has been accomplished in the presence of metal-complex catalysts [a mixture of $\text{P}(\text{CHR}(\text{OH}))_3$, where $\text{R} = \text{H}$ ^{121,122} or Alk ($\text{C}_1\text{--C}_6$),¹²² with reduced iron¹²¹ or chloroplatinic acid¹²²]. The reaction occurs in the medium of a lower aliphatic alcohol at room temperature to give tris(2-cyanoethyl)phosphine.^{121,122} However, this compound can be easily prepared without expensive metal-complex catalysts by cyanoethylation of phosphine with excess acrylonitrile in the presence of an aqueous solution of KOH⁶⁰ (Section III.1.a).

2. Addition to $\text{C}\equiv\text{C}$ bonds

Known examples of the addition of phosphine to triple carbon–carbon bonds are limited to phosphorylation of aryl- and heteroalkynes.^{21–23} The reaction proceeds under mild conditions (55–60 °C, atmospheric pressure) upon passing a phosphine–hydrogen mixture, generated from red phosphorus and potassium hydroxide in aqueous dioxane, through an alkyne–KOH–HMPA (H_2O) suspension. The reaction occurs stereoselectively to give tris(*Z*-2-organylviny)lphosphines **10** in 60%–80% yields.



The kinetic control of this reaction was confirmed by the thermal transformation (160–165 °C, 7 h) of tris[(*Z*)-styryl]-phosphine into the complete *E*-isomer *via* the intermediate formation of the corresponding mixed *E,Z,Z*- and *E,E,Z*-isomers.¹²³ In the absence of KOH, all other factors being the same, phosphine does not react with alkynes, pointing to a nucleophilic mechanism of this process.

Unlike the reactions of phosphine with aryl- and heteroalkynes (Section III.1.a), the addition of phosphine to alkynes in highly basic suspensions (KOH–HMPA) cannot be terminated at the stage of formation of mono- or diadducts;²² this has been explained⁷ by the fact that vinylphosphines are more acidic than alkylphosphines.

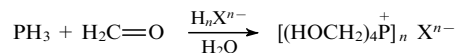
3. Addition to $\text{C}=\text{O}$ bonds

a. Reactions of phosphine with aldehydes

Although the first data concerning the reactions of phosphine with aliphatic aldehydes in the presence of hydrogen halides to give tetrakis(1-hydroxyalkyl)phosphonium halides were reported back

in 1888¹²⁴ and in 1921,¹²⁵ this reaction has not attracted attention of researchers for a long period.

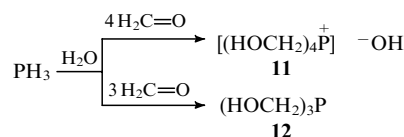
Only 35 years later, did a series of studies appear^{126–134} in which tetrakis(hydroxymethyl)phosphonium salts were prepared in quantitative yields by passing a flow of phosphine through an aqueous or aqueous-organic solution of formaldehyde (–10 to 40 °C, atmospheric pressure) in the presence of acids.



$\text{X} = \text{Cl}^-, \text{F}^-, \text{SO}_4^{2-}, \text{MeCOO}^-, -\text{OOC}-\text{COO}^-; n = 1, 2.$

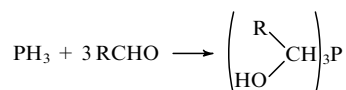
This reaction, which occurs presumably² *via* the intermediate formation of the $\text{H}_2\text{C}^+\text{OH}$ cation, has also been carried out for non-branched aliphatic aldehydes.^{128,135,136}

In the presence of heavy metals (Fe, Pt, Pd, Hg, Ag) or their salts (PtCl_4 , HgCl_2 , *etc.*), phosphine reacts with an aqueous solution of formaldehyde to give, depending on the ratio of the reactants^{137–139} and the nature¹⁴⁰ and the amount¹³⁰ of the catalyst, either tetrakis(hydroxymethyl)phosphonium hydroxide **11**^{128,130,134,137,138,140} or tris(hydroxymethyl)phosphine **12**.^{130,139–142} In the acid-catalysed reaction the latter product was not detected.^{126–134}



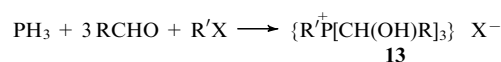
Since the phosphine **12** has also been obtained by treatment of the phosphonium hydroxide **11** with PH_3 in the presence of heavy metals or heavy metal salts,^{11,139} it can be suggested that the compound **12** is formed *via* the compound **11**.

Hydroxyalkylation of phosphine is a general reaction, which has been described for a broad range of aliphatic, unsaturated, aromatic and heteroaromatic aldehydes including acrolein, glyoxal, cinnamaldehyde and furfural. Tris(1-hydroxyalkyl)phosphines can be readily prepared by this reaction in high yields (up to 92%).¹⁴³



$\text{R} = \text{Me}, \text{Et}, \text{CH}=\text{CH}_2, \text{Ph}, 2\text{-FC}_6\text{H}_4, \text{Cl}_3\text{C}, \text{etc.}$

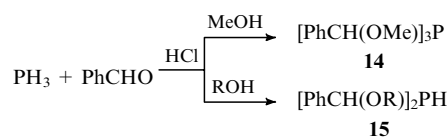
If phosphorylation of aldehydes with phosphine is carried out in the presence of a co-reagent, for example, an organyl halide or an alcohol, and a heavy metal or a heavy metal salt, non-symmetrical phosphonium compounds **13** can be obtained.^{144–146}



$\text{R} = \text{H}, \text{Alk}, \text{Ar}; \text{R}' = \text{Alk}, \text{CH}_2=\text{CHCH}_2, \text{PhCH}_2, \text{HOCH}_2\text{CH}_2,$

$\text{CH}_2\text{I}, \text{O} \diagup \text{CH}_2, \text{O} \diagdown \text{CH}_2; \text{X} = \text{Hal}, \text{OH}.$

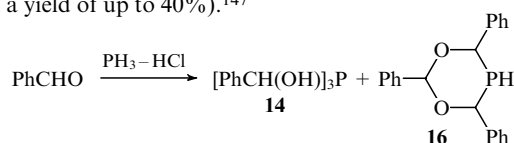
Benzaldehyde reacts with phosphine in methanol saturated with HCl^{131,147} to give tris[methoxy(phenyl)methyl]phosphine **14** in 85% yield. Phosphorylation of benzaldehyde with phosphine in the medium of $\text{C}_2\text{--C}_4$ alcohols gives the corresponding secondary phosphines **15** as the main products (yield 80%–90%).¹⁴⁷



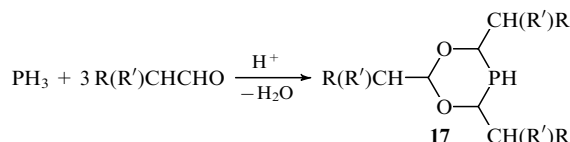
$\text{R} = \text{Et}, \text{Pr}^n, \text{Pr}^i, \text{Bu}^n.$

In the absence of alcohol, benzaldehyde reacts with the $\text{PH}_3\text{--HCl}$ system to give, in addition to the tris[hydroxy(phenyl)-

meth]phosphine, 2,4,6-triphenyl-1,3,5-dioxaphosphorinane **16** (in a yield of up to 40%).¹⁴⁷



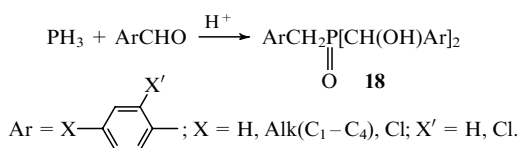
1,3,5-Dioxaphosphorinanes **17** are the main products of the reaction of phosphine with aliphatic aldehydes substituted at the α -carbon atom carried out in an acid medium.^{135, 148–151}



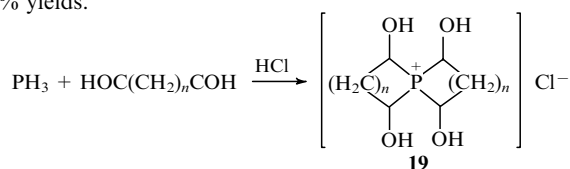
R = R' = Me (78%); R = Et, R' = Bu (90%).

Apparently, the addition of the secondary phosphines $[\text{R}(\text{R}')\text{CHCH}(\text{OH})_2\text{PH}]$, formed initially in this reaction, to a third aldehyde molecule involves the hydroxy group rather than the PH group and thus gives an acetal fragment.¹⁵¹

Unlike the hydroxyalkylation of phosphine with aldehydes in dilute acids, which gives phosphines,^{3, 131, 147} the reaction of PH_3 with aromatic aldehydes in concentrated aqueous solutions of HCl, HBr and H_2SO_4 affords tertiary phosphine oxides **18** (yield 35%–65%),^{152, 153} apparently as a result of transfer of the aldehyde oxygen atom to phosphorus (the mechanism of this process is described in Section III.3.b).

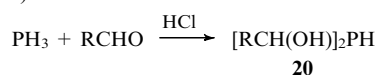


Dialdehydes (glutaric, succinic,^{135, 151, 154} phthalic,¹⁵⁴ etc.) are usually phosphorylated with phosphine in the presence of concentrated aqueous HCl to give spiroposphonium salts **19** in up to 65% yields.



$n = 2, 3$.

α -Halo-containing aldehydes, for example, chloral,^{135, 155, 156} dichloroacetic,^{135, 156} trifluoroacetic, 2,2-dichlorobutyric and 2,2,3-trichlorobutyric¹⁵⁶ aldehydes react with phosphine in the presence of acids^{135, 155, 156} or without acids in an organic solvent (ether)¹⁵⁵ to give secondary phosphines **20** in high yields (80%–90%).



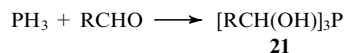
R = CCl_3 , CHCl_2 , CF_3 , EtCCl_2 , MeCHClCCl_2 .

It has been reported¹⁵⁷ that tris(2,2,2-trichloro-1-hydroxyethyl)phosphine is formed in 75% yield from chloral and PH_3 in the presence of aqueous HCl. However, later it has been shown¹⁵⁸ that passing phosphine through the chloral hydrate–HCl– H_2O system yields initially tris(2,2,2-trichloro-1-hydroxyethyl)phosphine, which then undergoes disproportionation with PH_3 to give a secondary phosphine, bis(2,2,2-trichloro-1-hydroxyethyl)phosphine.



The reaction of phosphine with chloral in the presence of concentrated HCl gave only tris(2,2,2-trichloro-1-hydroxyethyl)phosphine in 92% yield.¹⁵⁸

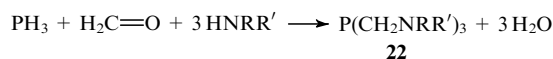
Phosphorylation of fluorinated aldehydes with phosphine occurs under mild conditions (for example, in the case of trifluoroacetic aldehyde, on cooling to -70°C), requires no catalyst and affords tertiary phosphines **21** in 50%–94% yields.¹⁵⁹



R = F_3C , CF_2CHF_2 , $(\text{CF}_2)_4\text{H}$.

It should be noted that in the absence of a catalyst, phosphine reacts with formaldehyde only at elevated temperatures (80 – 150°C) and pressures (4 – 40 atm)^{160–168} to give, depending on the ratio of the reactants, tris(hydroxymethyl)phosphine^{160–164} or tetrakis(hydroxymethyl)phosphonium hydroxide.^{165, 166}

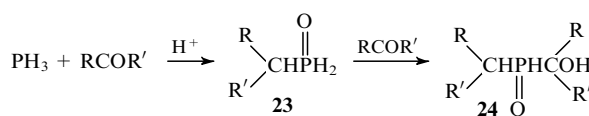
Phosphorylation of formaldehyde with phosphine in the presence of secondary amines follows the Mannich reaction pattern giving rise to tertiary aminomethylphosphines **22**.^{169–171}



R = Alk, cyclo-Alk, Ar; R' = H, Alk.

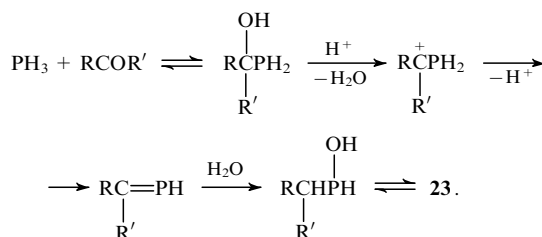
b. Reactions with ketones

Being weaker electrophiles than aldehydes, unsubstituted aliphatic ketones do not react with phosphine in the absence of acids or catalysts even under relatively rigorous conditions (100°C , elevated pressure);¹⁷² in the presence of hydrogen halides in anhydrous solvents^{2, 11, 124} or in dilute aqueous solutions of acids^{173–175} the reaction does not occur either. However, in the presence of concentrated mineral acids, phosphine adds to ketones at 60°C and 2–3 atm to give a mixture of primary alkylphosphine oxides **23** and secondary alkyl(1-hydroxyalkyl)-phosphine oxides **24**.^{173–175}



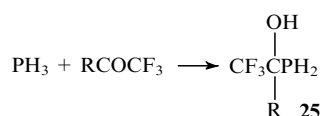
R = R' = Me, Et; R = Me: R' = Pr, Ph; R–R' = $(\text{CH}_2)_4$, $(\text{CH}_2)_5$.

The primary phosphine oxides **23**, which were first synthesised by this method, are formed, in the opinion of the researchers cited,¹⁷³ upon the transfer of the oxygen atom from carbon to phosphorus according to the following scheme:



The second stage of the process, which gives rise to the phosphine oxides **24**, occurs as the normal addition of the P–H bond to the carbonyl group.¹⁷³ The **23**:**24** ratio depends on the structure of the initial ketone and increases in the sequence cyclohexanones < cyclopentanone < acetone < pentan-2-one < heptan-2-one < pentan-3-one < acetophenone < heptan-4-one from 1:9 (for cyclohexanone) to 9:1 (for heptan-4-one).^{173, 174}

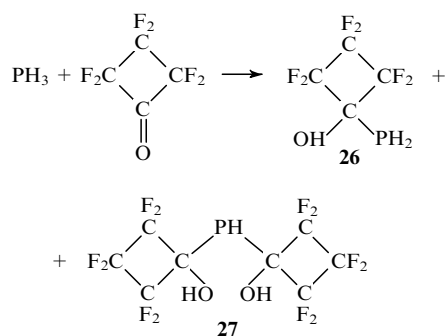
Trifluoro-^{176, 177} and hexafluoroacetone^{172, 177} react with phosphine without a catalyst at an elevated temperature (60 – 100°C) and pressure (10 – 30 atm) to give primary phosphines **25** in 85% and 62% yields, respectively.



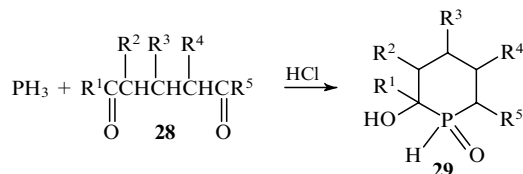
R = Me, CF₃.

It is believed^{172, 176, 177} that the reaction stops at the stage of formation of the primary phosphines **25** because these products are less nucleophilic than PH₃. However, recently the synthesis of a secondary phosphine, bis[(1-hydroxy-1-trifluoromethyl)-ethyl]-phosphine, from phosphine and trifluoroacetone has been reported.¹⁷⁸

Phosphine and hexafluorocyclobutanone readily react at room temperature to give primary (**26**) and secondary (**27**) phosphines. When excess ketone is used, the yield of the phosphine **27** amounts to 91%.¹⁷⁹

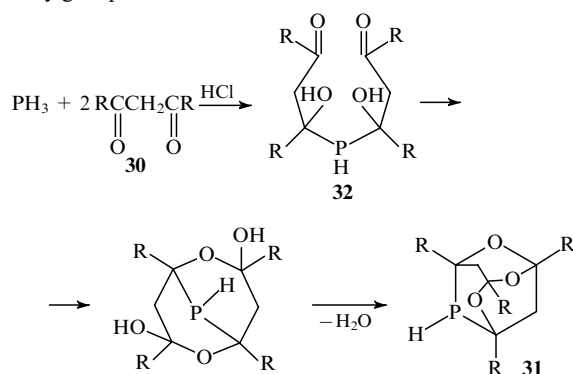


The reaction of 1,5-diketones **28** with phosphine occurs in the presence of HCl as addition–cyclisation with simultaneous transfer of oxygen on the phosphorus atom and results in the formation of 2-hydroxyphosphorinane 1-oxides **29** (yield 30%–80%).^{180–182}



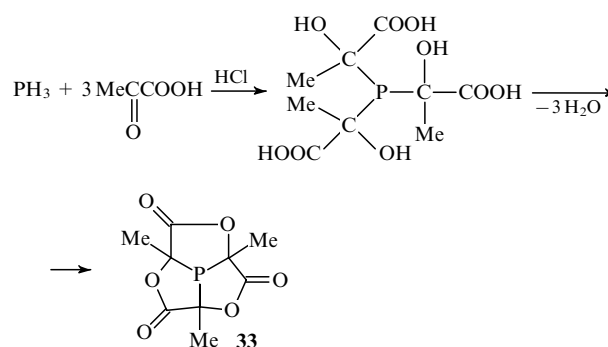
R¹ = R⁵ = Ph, R² = R³ = R⁴ = H; R¹–R² = (CH₂)₄, R³ = R⁴ = H, R⁵ = Ph; R¹–R² = R⁴–R⁵ = (CH₂)₄, R³ = Ph; R¹–R² = (CH₂)₄, R³ = R⁵ = Ph, R⁴ = H; R¹–R² = CH₂CM₂OCH₂, R³ = R⁵ = Ph, R⁴ = H.

Unlike 1,5-diketones, 1,3-diketones **30** react with phosphine in the presence of concentrated HCl to give tricyclic phosphines **31**.^{183–185} The reaction occurs apparently *via* the intermediate secondary phosphine **32**, which forms from two 1,3-diketone molecules; this intermediate undergoes intramolecular cyclisation involving the cross attack on the carbonyl carbon atoms by the hydroxy groups and elimination of water.



R = Me, CF₃.

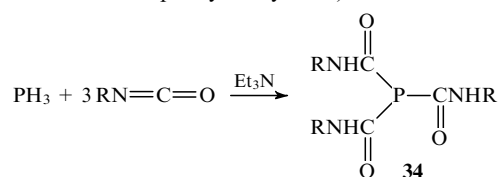
Tricyclic phosphine **33** with three lactone rings has been obtained from phosphine and pyruvic acid.^{153, 186}



The general character of this reaction was confirmed by involvement of some other oxo acids into the interaction with phosphine.¹⁸⁶

4. Addition to C=N bonds

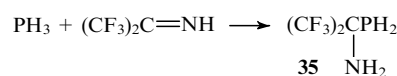
The addition of phosphine to organyl isocyanates occurs in the presence of triethylamine (room temperature, 2–3 atm, anhydrous benzene), involves the C=N bond and gives rise to tricarbamoylphosphine derivatives **34**, their yields being dependent on the nature of the substituent in the isocyanate and ranging from 13% (phosphorylation of phenyl isocyanate) to 100% (the reaction with nitrophenyl isocyanate).^{187–189}



R = Et, C₈H₁₇, Ph, 4-MeC₆H₄, 4-ClC₆H₄, 4-NO₂C₆H₄.

The fact that mono- or diadducts have not been detected during this reaction (even when the reactants were taken in equimolar amounts) suggests that the intermediate organic carbamoylphosphines are more active nucleophilic addends in this process than PH₃.¹⁸⁷

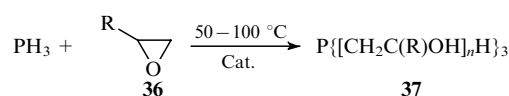
The addition of equimolar amounts of phosphine to the C=N bond in hexafluoroisopropylideneimine stops when primary phosphine **35** has been produced (yield 96%).¹⁹⁰



5. Reactions of phosphine with oxiranes and thiiranes

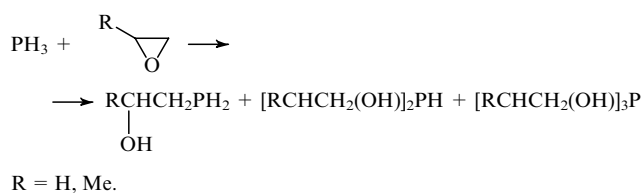
Cleavage of an oxirane or thiirane ring by phosphine occurs in the presence of various catalysts.

Heating (50–100 °C) phosphine with oxiranes **36** in the presence of inorganic or organic bases or acids has resulted in the synthesis of tertiary phosphines **37** with oligooxyalkylene oxide radicals.¹⁹¹ Complexes of tris(hydroxymethyl)phosphine with nickel(II) chloride¹⁹² or with chloroplatinic acid¹⁹³ can also be used successfully as the catalysts in this reaction.

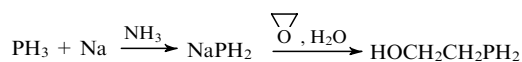


R = H, Me, CH₂Cl, Ph; n = 3–10.

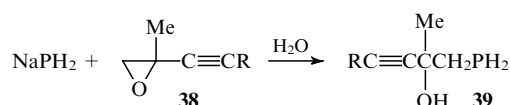
In the absence of a catalyst (heating a mixture of phosphine with an oxirane in an autoclave), the total yield of mono-, bis- and tris(2-hydroxyalkyl)phosphines does not exceed 17%.¹⁹⁴



A convenient and efficient method for the synthesis of 2-hydroxyethylphosphine (yield 70%) based on phosphorylation of oxirane by the 'phosphine–sodium metal–liquid ammonia' system has been reported.¹⁹⁴



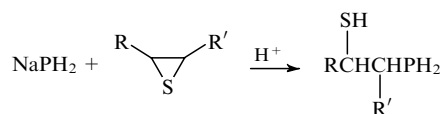
Later, organylethynloxiranes **38** have also been involved in this reaction to give the corresponding primary hydroxyorganylphosphines **39** in yields of up to 73%.¹⁹⁵



R = Me, Bu, CH₂ = CH.

The attempt to carry out phosphorylation of 1-methyl-1-propyloxirane by the 'phosphine–sodium–liquid ammonia' system failed.¹⁹⁵

Thiirane and its alkyl- and dialkyl-substituted derivatives react with alkali metal dihydrophosphides to give primary 2-sulfanylalkylphosphines.^{196–198}

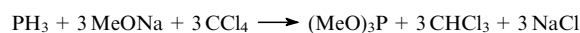


R = R' = H, Me; R = Me, R' = H.

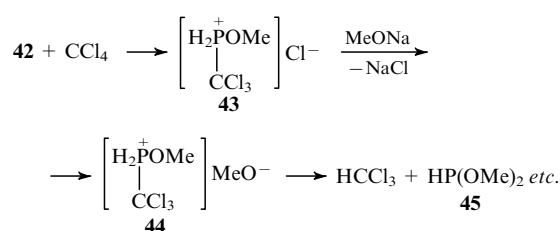
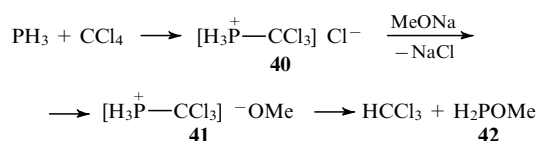
IV. Other reactions of phosphine with organic compounds

1. Synthesis of esters and amides of phosphorous and phosphoric acids

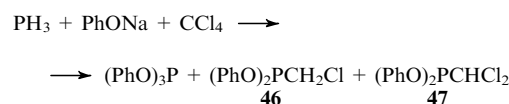
According to patents,^{199–201} phosphine reacts with sodium alkoxides^{199, 200} or with the alcohol–alkali metal hydroxide systems²⁰¹ in a halogenated hydrocarbon solvent to give triorganyl phosphites. Thus trimethyl phosphite was prepared in a quantitative yield from phosphine and sodium methoxide in CCl₄ at 0–20 °C.¹⁹⁹



Apparently, the reaction starts with the formation of phosphonium salt **40**; the chloride ion in this salt is replaced by the methoxy ion to give the phosphonium salt **41**. This is followed by elimination of chloroform, and the resulting methoxyphosphine **42** reacts again with CCl₄ to give phosphonium salt **43**. The latter is converted into salt **44** upon exchange with sodium methoxide and then into dimethoxyphosphine **45** upon elimination of a CHCl₃ molecule. The last hydrogen atom in the compound **45** is substituted in a similar way.



Heating (80 °C) a mixture of phosphine, sodium phenoxide and CCl₄ in a propylene carbonate medium gives not only triphenyl phosphite but also chloromethylphosphonite **46** and dichloromethylphosphonite **47**, the total yield of the products being 90% (30% of each compound).²⁰⁰



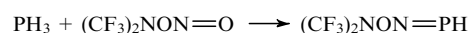
Phosphine reacts with trifluoromethanesulfonyl chloride at –95 °C to give, depending on the ratio of the reactants, *S,S,S*-tris(trifluoromethyl) trithiophosphite or *S,S*-bis(trifluoromethyl) phosphonodithioite in 96% and 72% yields, respectively.^{3, 202}

In recent years, studies have been published dealing with oxidative dehydrocondensation of phosphine with alcohols,^{140, 203, 204} primary²⁰⁵ and secondary¹⁴⁰ amines and pyridine;²⁰⁶ these reactions occur in the presence of copper and platinum compounds and give trialkyl phosphites,¹⁴⁰ trialkyl phosphates,^{140, 203, 204} phosphorous triamides,²⁰⁵ alkylimidophosphoric triamides¹⁴⁰ and tris(2-pyridyl)phosphine,²⁰⁶ respectively. Unfortunately, these publications^{140, 203–206} barely give any experimental details and, what is more important, they present no data confirming the structures of the compounds synthesised.

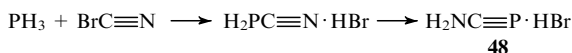
2. Synthesis of organophosphorus compounds with a mono- or dicoordinated phosphorus atom

Synthesis of organophosphorus compounds with mono- or dicoordinated phosphorus atoms based on phosphine is a topical line of research in modern organic chemistry. However, to the best of our knowledge, the data on these reactions are limited to a few publications.^{207–210}

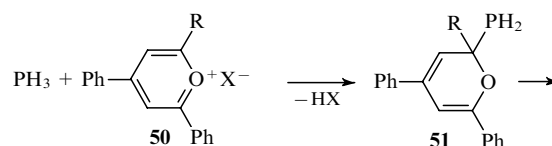
Thus the reaction of phosphine with *O*-nitrosobis(trifluoromethyl)hydroxylamine at room temperature gave *N*-bis(trifluoromethyl)nitroxyiminophosphine (yield 60%).²⁰⁷

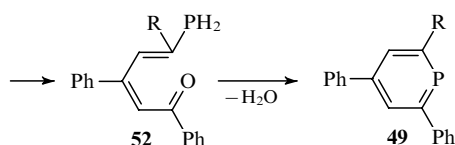


The reaction of phosphine with cyanogen bromide affords aminocarbophosphyl hydrobromide **48**.²⁰⁸ The reaction occurs *via* the initial formation of cyanophosphine hydrobromide, which rearranges into the hydrobromide **48**.



Phosphorus analogues of pyridine, phosphorines **49**, have been prepared by treatment of the pyrylium salts **50** with phosphine in butanol in the presence of mineral acids at 120–130 °C (yields up to 61%).^{209, 210} Apparently, the reaction passes through the intermediate formation of primary phosphines **51** and **52**.





R = Me, Ph; X = BF₄.

V. Conclusion

The data considered in this review demonstrate that phosphine, which is the simplest available phosphorus compound, is a convenient reagent for the formation of a C–P bond in the synthesis of various organic, organoelement and functionally substituted phosphines, which are finding ever increasing use as ligands for the preparation of metal-complex catalysts.

The ease and practical feasibility of the preparation of phosphine by direct hydrolysis of elemental phosphorus, which had been noted long ago by D I Mendeleev and V N Ipat'ev,²¹¹ and its high, although not adequately studied, reactivity are the objective prerequisites for more extensive involvement of phosphine in organophosphorus synthesis.

However, it should be noted that unlike its nitrogen analogue — ammonia — which has become the synthetic base for the whole chemistry of the organic compounds of nitrogen, phosphine has not found equally wide use in organophosphorus chemistry despite the numerous obvious advantages of phosphine over, for example, phosphorus chlorides.

The authors hope that this review would be favourable for further development of the chemistry of phosphine and, first of all, development of new convenient methods for the synthesis of various organophosphorus compounds based on phosphine. The exceptionally simple method for the generation of a phosphine–hydrogen mixture by alkaline hydrolysis of red phosphorus that we developed previously may stimulate further studies along this line.^{6, 7, 14, 22}

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^a — *Russ. J. Org. Chem. (Engl. Transl.)*

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Synthesis of tritium-labelled biologically important diazines

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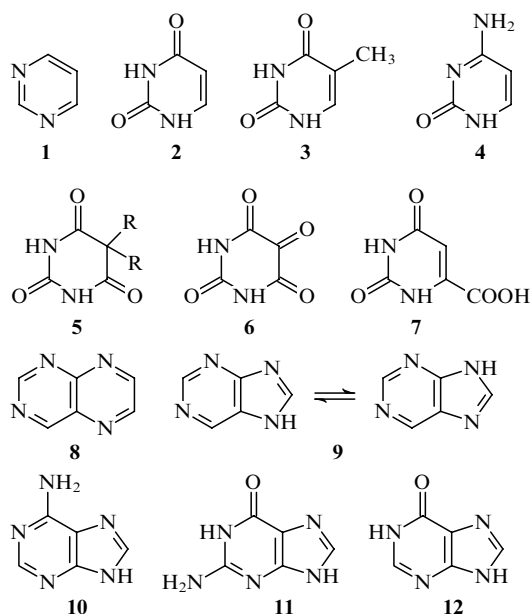
Abstract. The methods for the introduction of tritium (by chemical synthesis and isotope exchange in both solution and solid state) into biologically active diazines, *viz.*, nucleic acid components (heterocyclic bases, nucleosides, nucleotides), DNA synthesis terminators and cytokinins are considered. The bibliography includes 178 references.

I. Introduction

Recent progress in molecular biology, biochemistry, molecular genetics and experimental medicine are largely determined by the possibility of wide use of various radioactively labelled compounds. The application of such compounds has allowed direct studies of the mechanisms of chemical and biochemical reactions, as well as metabolic pathways in living organisms (*in vivo*) and in open systems (*in vitro*). Determination of quantitative characteristics of biochemical processes with the aid of labelled compounds is important for understanding of the essential features of processes occurring in living organisms and elucidation of the regulatory mechanisms underlying metabolism.

For over three decades now, researchers have been showing unremitting interest in tritium-labelled compounds. This is due to the valuable physical properties of tritium: its half-life period is sufficiently long for conducting experiments of virtually any duration; the low energy of tritium β -particles ($E_{\max} = 18.6$ keV) determines low radiotoxicity of tritium-labelled compounds, which makes it possible to handle relatively large quantities of this isotope without special protective measures. Substitution of one tritium atom for hydrogen yields a compound with a molar radioactivity (A_{mol}) of 29.12 Ci mmol⁻¹. The use of such preparations and modern scintillation counters allows detection of $< 10^{-14}$ mol of a labelled compound.

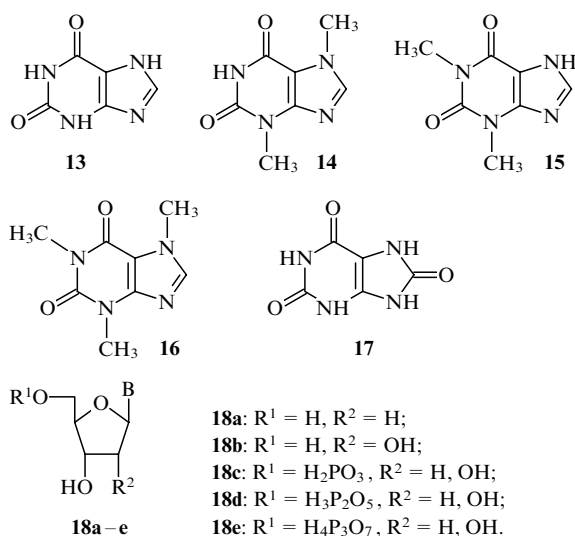
Pyrimidine (1) is the most important compound among the diazines, since its derivatives, *viz.*, uracil (2), thymine (3), and cytosine (4), form part of nucleic acids. Barbiturates (5), alloxan (6) and orotic acid (7) are also pyrimidine derivatives and contain no condensed rings. Among the polycyclic derivatives of pyrimidine, like pteridine (8), purine (9) deserves to be mentioned. Its derivatives, adenine (10) and guanine (11), also form part of ribo- and deoxyribo-nucleic acids. Other purine derivatives, such as hypoxanthine (12), xanthine (13), theobromine (14), theophylline (15), caffeine (16), and uric acid (17) are important natural compounds, which show biological activity. 2'-Deoxyribose (18) and ribose are linked to nitrogen bases through the N-glycosidic bond. These compounds have been called deoxyribonucleosides (18a) and ribonucleosides (18b), respectively, and the phosphorus esters of nucleosides have been termed nucleotides (18c–18e). We have thus grouped the natural diazines under the common name of 'components of nucleic acids'. The number of such compounds for the main bases (2–4, 10, 11) of nucleic acids is more than 40.



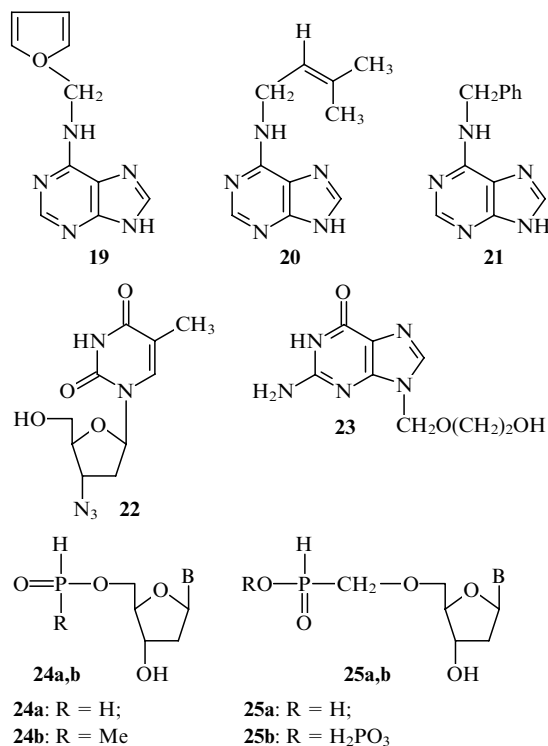
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In recent years, considerable attention is being devoted to the so-called cytokinins, which are derivatives of 6-aminopurine, discovered in the 1950s. The cytokinins are natural substances that promote germination and blossoming of plants and retard their wilting. When used at concentrations 10^{-3} – 10^{-5} mol litre⁻¹, they stimulate cell division. The principal cytokinins are kinetin (**19**), zeatin (**20**), benzylaminopurine (**21**) and a number of other compounds.



Analogues of nucleosides with the modified glycoside ring often appear to be DNA synthesis terminators. Azidothymidine (**22**), acyclovir (**23**), nucleoside phosphinates **24a** and nucleoside methylphosphinates **24b**, 5'-O-hydroxyphosphoryl-2'-deoxynucleosides **25a** and the corresponding nucleotides **25b** may be cited as examples. They are potential inhibitors of retroviruses, including the HIV virus.^{1,2}

This review considers methods used for the preparation of the above-mentioned compounds labelled with tritium. The main attention is centred on the general methods allowing synthesis of the widest set of compounds with maximum molar radioactivity.

II. Dehalogenation in solution

The reaction of catalytic hydrogen-for-halogen replacement (hydrogenolysis) has been known for a long time;³ however, its use for the synthesis of tritiated compounds has come into practice relatively recently.^{4,5} Catalytic dehalogenation is usually carried out in air-tight vessels with vigorous stirring of a suspension of a catalyst in solution of a halogenated compound under gaseous tritium. In this type of reaction, both polar and nonpolar solvents are employed. The tritium halide formed in this reaction must be neutralised since it poisons the catalyst, which leads to deceleration of the reaction.⁶ The mechanism of tritium incorporation into the solvent under conditions of catalytic dehalogenation (catalysts PdO, Pd/BaSO₄, Raney nickel) has been considered.⁷

Catalysts of hydrogenation (mainly, supported Pd) are used for dehalogenation. The conditions for catalytic dehalogenation for the synthesis of tritium-labelled compounds have been published.^{8,9} Examples of precursors and target compounds obtained by dehalogenation are given in Table 1.

Table 1. Results of halogen – tritium replacement in purines and pyrimidines.

Precursor	Target compound	<i>A</i> _{mol} (sec ^a)	Ref.
5-Iodocytidine	[5- ³ H]cytidine	17.4	10
8-Bromoadenine	[8- ³ H]adenine	15–20	11
2-Chloroadenine	[2- ³ H]adenine	20–25	12
2,8-Dichloroadenine	[2,8- ³ H ₂]adenine	25–50	13
5-Iodoorotic acid	[5- ³ H]orotic acid	15.6	13
5-Iododeoxyuridine	[5- ³ H]deoxyuridine	26.4	13
5-Iodouracil	[5- ³ H]uracil	15–20	14
5-Iodouridine	[5- ³ H]uridine	15–20	14
5-Iodo-6-azauracil	[5- ³ H]6-azauracil	15–20	15
5-Iodo-6-azauridine	[5- ³ H]6-azauridine	15–20	15
8-Bromoadenosine	[8- ³ H]adenosine	11.6–19	16, 17
8-Bromoguanosine	[8- ³ H]guanosine	5.4–8	16, 17
8-Bromoinosine	[8- ³ H]inosine	15	17
8-Bromo-AMP	[8- ³ H]AMP	10	18, 19
8-Bromo-GMP	[8- ³ H]GMP	15	20
5-Bromo-UMP	[5- ³ H]UMP	10	21
8-Bromo-cAMP	[5- ³ H]cAMP	17	22
5,6-Dibromouracil	[5,6- ³ H ₂]uracil	45–50	23, 24
5-Bromouracil	[5- ³ H]uracil	20–30	25
6-Chlorouracil	[6- ³ H]uracil	20–30	25
5-Bromocytosine	[5- ³ H]cytosine	20–30	25
8-Bromo-substituted purine nucleotides	[8- ³ H]purine nucleotides	20–30	25
5-Bromo-substituted pyrimidine nucleotides	[5- ³ H]pyrimidine nucleotides	20–30	25

Notes. Abbreviations: AMP, adenosine 5'-monophosphate; GMP, guanosine 5'-monophosphate; UMP, uridine 5'-monophosphate; cAMP, adenosine 3',5'-cyclicmonophosphate.

^a Dimension/ Ci mmol⁻¹.

Synthesis of a tritium-labelled compound **10** has revealed¹¹ that dehalogenation in aprotic solvents (dimethylformamide, dimethyl sulfoxide, dioxane) in the presence of catalysts (Pd black, Pd on carbon and on BaSO₄) has no advantages over the reaction in a protic solvent (aqueous – ethanolic solution): in both cases the maximum radioactivity is not attained. In the introduction of a tritium label into adenosine and guanosine, the rate of dehalogenation of the corresponding 8-bromo-compounds in 1 M KOH and 0.1 M HCl was higher than that in water; however, the

yields of labelled compounds and their molar radioactivity were larger in alkaline solution.¹⁶ Table 1 presents data that characterise the synthesis of specific compounds. This reaction was not investigated as a method for the synthesis of tritiated diazines. In particular, the isotope effects of hydrogen, the ratio of reactants, the nature of reagents and the activity of catalysts have not been found to influence the yield and the molar radioactivity of the target compounds. Hydrogenolysis has been investigated as a method for the incorporation of a tritium label into diazines.^{26–31} Hydrogenolysis of various compounds was conducted in the same solvents and with the same parameters such as tritium pressure, solvent, temperature, concentration of halogenated compound and reaction time. The basic characteristics of hydrogenolysis with tritium of bromo-substituted purines²⁶ and pyrimidines²⁷ are presented in Table 2.

Table 2. Basic characteristics of catalytic dehalogenation with tritium of 8-bromosubstituted purines and 5-bromo-substituted pyrimidines on supported Pd as the catalyst.^{26,27}

Labelled compound	Tritium concentration (%)	Yield (%)	A_{mol} / Ci mmol^{-1}
[8- ³ H]Adenosine	85	19.5	9.8
[8- ³ H]AMP	85	49.0	6.2
[8- ³ H]AMP – TOA ^a	98	28.0	16.7
[8- ³ H]cAMP	95	26.7	21.6
[8- ³ H]dAMP	75	61.0	7.3
[8- ³ H]Guanosine	98	45.4	12.7
[8- ³ H]GMP	80	46.2	11.0
[8- ³ H]GMP – TOA ^a	98	4.1	0.8
[8- ³ H]cGMP	70	55.0	5.5
[8- ³ H]dGMP	98	29.0	14.0
[5- ³ H]Uracil	80	79.0	18.0
[5- ³ H]Uridine	90	21.0	21.0
[5- ³ H]Uridine	70	65.0	13.0
[5- ³ H]UMP	90	96.0	3.7
[5- ³ H]UMP – TOA ^a	98	80.0	19.0
[5- ³ H]2'-Deoxyuridine	85	92.0	21.2
[5- ³ H]dUMP	75	43.0	8.6
[5- ³ H]cUMP	95	61.0	12.2
[5- ³ H]CMP	70	34.0	1.1
[5- ³ H]CMP – TOA ^a	70	89.0	9.3
[5- ³ H]CMP – TOA ^a	98	74.0	25.1
[5- ³ H]dCMP	95	74.0	18.0
[5- ³ H]cCMP	95	54.0	18.1

Notes. Abbreviations: dAMP, 2'-deoxyadenosine 5'-monophosphate; cGMP, guanosine 3',5'-cyclomonophosphate; dGMP, 2'-deoxyguanosine 5'-monophosphate; dUMP, 2'-deoxyuridine 5'-monophosphate; cUMP, uridine 3',5'-cyclomonophosphate; CMP, cytidine-5'-monophosphate; dCMP, 2'-deoxycytidine-5'-monophosphate; cCMP, cytidine 3',5'-cyclomonophosphate.

^a Trioctylammonium salt (TOA).

The processes occurring in the hydrogen–palladium–water system with participation of hydrogen isotopes (protium and tritium) and their influence on the molar radioactivity (A_{mol}) of hydrogenolysis products have been investigated.²⁷ It was pointed out that one of the major reasons for the decrease in A_{mol} of the target compounds is the dilution of tritium with protium due to isotope exchange with the solvent protons and high values of protium–tritium partition coefficients ($\alpha_{\text{H-T}}$ reaches 12). The processes with different kinetics are analysed below.

1. The rate of the main reaction (dehalogenation, hydrogenation, isotope exchange) is much higher than that of tritium isotope exchange with the solvent (tritium is virtually undiluted with protium). Here, two extreme cases are possible: (a) if the contribution from the reaction of homomolecular isotope

exchange may be disregarded, the molar radioactivity of the reaction product is equal to the A_{mol} of the initial tritium with consideration of the isotope effects of hydrogen on dissolution and adsorption on palladium (for this process $\alpha_{\text{H-T}} = 2.5$); (b) if an isotope equilibrium is established on palladium, it is necessary to take into account the reaction of monomolecular isotope exchange ($\alpha_{\text{H-T}} = 4.7$ or 3.6 for 50% tritium).

2. The rate of the main reaction is comparable or lower than the rate of isotope exchange of tritium with the solvent, *i.e.*, continuous dilution of tritium with protium takes place. Examination of this process requires consideration of the isotope equilibrium in the hydrogen–palladium–water system ($\alpha_{\text{H-T}} = 12$). Table 3 presents data that illustrate the effect of tritium concentration on the molar radioactivity of labelled products obtained by the reaction in an aqueous solution for different protium–tritium partition coefficients. The extreme values of A_{mol} (2.2 and 28.3 Ci mmol^{-1}) were calculated for the extreme cases. Hence, the increase in the molar radioactivity of purine and pyrimidine compounds is related to minimisation of the effect of hydrogen isotope partition on palladium in the course of catalytic dehalogenation in solution.

Table 3. Effect of isotopy on the molar radioactivity of labelled products of hydrogenolysis in aqueous solution.

[³ H] (%)	A_{mol} (Ci mmol^{-1}) for different $\alpha_{\text{H-T}}$ values			
	2.5	3.6	4.7	12
99	28.3	—	27.8	26.0
95	25.4	—	23.3	17.8
90	22.2	—	19.1	12.5
85	19.5	—	15.9	9.3
80	17.1	—	13.4	7.3
75	15.1	13.2	—	5.8
70	13.3	11.5	—	4.7
60	10.2	8.6	—	3.2
50	7.7	6.3	—	2.2

One of the ways of minimisation is enhancement of the rate of the main dehalogenation reaction, which can be achieved using more active palladium catalysts. The A_{mol} can increase with the greater palladium/bromo-substituted compound ratio. This is characteristic mostly of purine compounds.

Yet another method for the increase in molar radioactivity is the use of catalysts with a low (0.01%–0.05%) percentage of supported palladium.³¹ In such catalysts, virtually no dissolution of the hydrogen isotopes occurs, and the hydride form is absent. If the protium–tritium partition coefficient is assumed to be equal to 2.5, the molar radioactivity of the dehalogenation product with 95% tritium must reach 25.4 Ci mmol^{-1} , which is consistent with the experimental data.³¹ In practice, low-percentage supported palladium catalysts are rarely employed, since satisfactory yields of the target products are obtained at definite precursor/catalyst ratios in the reaction mixture (approximately 1 g of a catalyst per 1 mg of a precursor). This requires a larger volume of the solvent and, consequently, leads to a greater volume of the reaction tube, increased uptake of gaseous tritium, more difficult stirring of the reaction mixture, *etc.*

Gordeeva *et al.*³² have described the synthesis of nucleoside 5'-triphosphates labelled with tritium in position 5 of the pyrimidine ring and in position 8 of the purine ring by catalytic dehalogenation of the corresponding bromo-substituted precursors.³² The A_{mol} values of the compounds obtained are presented in Table 4. As a rule, the tritium-labelled nucleoside 5'-triphosphates have higher molar radioactivities than the nucleoside 5'-monophosphates prepared under similar conditions. These results correlate with the suggested³⁰ interrelation of such parameters as the sorption degree of the initial compounds on the catalyst and

Table 4. Results of catalytic dehalogenation of bromo-substituted nucleoside 5'-triphosphates with gaseous tritium.³²

Initial compound	Catalyst	$A_{\text{mol}} / \text{Ci mmol}^{-1}$
8-Bromo-ATP	5% Pd/BaSO ₄	17
8-Bromo-dATP	5% Pd/BaSO ₄	15
	α -Pd	18
8-Bromo-GTP	5% Pd/BaSO ₄	11
	α -Pd	19
8-Bromo-dGTP	5% Pd/BaSO ₄	5
	α -Pd	18
5-Bromo-UTP	5% Pd/BaSO ₄	17
	α -Pd	23
5-Bromo-dUTP	5% Pd/BaSO ₄	12
	α -Pd	14
5-Bromo-CTP	5% Pd/BaSO ₄	21
5-Bromo-dCTP	5% Pd/BaSO ₄	18

Notes. Abbreviations: ATP, adenosine 5'-triphosphate; dATP, 2'-deoxyadenosine 5'-triphosphate; GTP, guanosine 5'-triphosphate; dGTP, 2'-deoxyguanosine 5'-triphosphate; UTP, uridine 5'-triphosphate; dUTP, 2'-deoxyuridine 5'-triphosphate; CTP, cytidine 5'-triphosphate; dCTP, 2'-deoxycytidine 5'-triphosphate.

the molar radioactivity, as well as the dependence of the latter on the ratio of the rates of dehalogenation and heterogeneous isotopic exchange of gaseous tritium with water.

Catalytic dehalogenation of respective bromo-substituted precursors has been employed for the synthesis of the following compounds:^{33–40}

Compound	$A_{\text{mol}} / \text{Ci mmol}^{-1}$
[5- ³ H]2',3'-Dideoxycytidine	—
[8- ³ H]ATP	—
[2- ³ H]ATP	26.2
[5- ³ H]dCTP	15.0
[6- ³ H]Thymine	—
[2- ³ H]Adenine	12.7
[2- ³ H]Adenosine	—
[8- ³ H]9-[(2-Hydroxyethoxy)methyl]guanine	25.0
[5- ³ H]1- β -D-Arabinofuranosylcytosine	20.0
1-[(3- ³ H]Tetrahydrofuryl-2)-5-fluorouracil	29.7
[8- ³ H]9- β -D-Arabinofuranosyladenine	20.0
5-Amino-7-(2[2',3',5'- ³ H ₂]phenylethyl)-2-(2-furyl)pyrazolo[4,3- <i>e</i>]-1,2,4-triazolo[1,5- <i>c</i>]pyrimidine	68.6

Tritium-labelled purine and pyrimidine nucleoside phosphates have been prepared by catalytic dehalogenation of respective bromo-substituted precursors with gaseous tritium.⁴¹

Baraldi *et al.*⁴² have synthesised three tritiated inhibitors of reverse transcriptase by hydrogenolysis of bromobenzoazole precursors. The molar radioactivity of the compounds obtained was 3–10 Ci mmol^{−1}.

In the process of dehalogenation, tritium can be incorporated not only into the heterocyclic base but also into the carbohydrate moiety of the molecule. Thus dehalogenation of the corresponding precursor has yielded [2',3'-³H]2',3'-dideoxythymidine 5'-phosphate.⁴³

The experimental procedure for the catalytic dehalogenation in solution is relatively simple and the products have rather high molar radioactivity. In these products, the tritium label is as a rule in a definite position determined by the replacement of the halogen atom by tritium. With a set of halogenated precursors at disposal, this reaction can be used for the synthesis of a series of the required tritium-labelled compounds. A disadvantage of this method is the necessity to synthesise special halogenated precur-

sors. For example, in order to prepare [2-³H]ATP it was necessary to carry out a six-stage synthesis of 2-bromo-ATP from guanosine.³⁵

III. Catalytic dehalogenation without a solvent

The solvent-free method of catalytic dehalogenation has been proposed for the synthesis of ³H-labelled uracil.⁴⁴ For this purpose, 5-iodouracil applied onto a Pd catalyst was treated with gaseous tritium under the conditions of a high-voltage and high-frequency discharge. This resulted in the formation of [5-³H]uracil ($A_{\text{mol}} = 16.1 \text{ Ci mmol}^{-1}$). Tritium-labelled thymine was prepared by the dehalogenation of 5-halogenomethyluracil with gaseous tritium over a Pd catalyst at 100 °C.⁴⁵ This method has been studied in detail in the synthesis of tritium-labelled components of nucleic acids and was called solid-state catalytic reductive dehalogenation (SCRD).⁴⁶ The SCR D reaction can be initiated in two ways, *viz.*, by a high-voltage and high-frequency electric discharge⁴⁷ and heating from 50 to 150 °C.⁴⁸ The kinetics of SCR D has been investigated and its mathematical model has been proposed in which the catalyst was regarded as a consumable component of the reaction. The proposed model explains well the dependence of the yield and A_{mol} of the target compounds on the percentage of palladium on the support. Some kinetic characteristics of SCR D are presented in Table 5. The SCR D method was employed for the preparation of the following ³H-labelled compounds:⁴⁶

Compound	$A_{\text{mol}} / \text{Ci mmol}^{-1}$	Compound	$A_{\text{mol}} / \text{Ci mmol}^{-1}$
[5- ³ H]Uracil	16.1	[8- ³ H]2'-deoxyadenosine	16.4
[Methyl- ³ H]thymine	3.1	[8- ³ H]AMP	4.9
[8- ³ H]Guanine	12.4	[8- ³ H]GMP	5.2
[5- ³ H]Cytidine ^a	16.3	[5- ³ H]UMP	2.8
[8- ³ H]Guanosine	6.7	[5- ³ H]CMP	5.9
[8- ³ H]Adenosine ^a	10.6	[8- ³ H]dAMP	2.1
[5- ³ H]Uridine ^a	11.5	[8- ³ H]dGMP	1.6
[5- ³ H]2'Deoxyuridine ^a	18.5	[8- ³ H]dCMP	1.7
[5- ³ H]Deoxycytidine ^a	33.0		

^a Degradation products of the corresponding nucleotides.

If SCR D is carried out at elevated temperatures, some by-products are produced along with the target compounds due to the cleavage of the phosphoester and N-glycosidic bonds. The molar radioactivity of degradation products is higher than that of the target compound, which seems to be related to molecular excitation upon cleavage of these bonds. The results obtained indicate that the A_{mol} of the compounds does not reach its theoretical value on substitution of one halogen atom by tritium (29.12 Ci mmol^{−1}). This is explained⁴⁶ by dilution of the initial gaseous tritium by the mobile hydrogen present in the substance–catalyst system (hydrogen is capable of rapid isotope

Table 5. Kinetic parameters of SCR D of bromo-substituted components of RNA.⁴⁶

Initial compound	Reaction rate constant (min ^{−1} mmol ^{−2}) at different temperatures (°C)					$E / \text{cal mol}^{-1}$
	100	78	56	35	23	
8-Bromo-AMP	30.45	20.62	14.03	10.42	8.06	3380
8-Bromoguanosine	30.43	25.20	15.18	11.25	9.09	3670
5-Bromo-UMP	24.00	17.15	10.80	6.55	4.74	4760
5-Bromo-CMP	33.25	16.15	10.29	4.89	1.76	6470

exchange). In the solid-state process, some labile hydrogen is present in the compound to be labelled and in the catalyst itself.⁴⁶ It was found experimentally that 100 mg of 5% Pd/C catalyst contains 0.21 mmol of hydrogen capable of isotope exchange with tritium.

The SCRD process has not found wide practical usage for the synthesis of tritium-labelled diazines, since the reactions in solution are experimentally simpler and make it possible to obtain comparable, and often higher, A_{mol} values of the products. Nonetheless, the appearance of the SCRD method may be regarded as an important stage in the development of solid-state reactions involving gaseous tritium.

IV. Reactions of isotope exchange

There is a certain distinction between reactions of isotope exchange with tritium-containing solvents (including tritiated water) and catalytic reactions involving gaseous tritium. The reactions of catalytic isotope exchange are most often carried out using heterogeneous palladium catalysts,⁴⁹ homogeneous catalysts, such as trifluoromethanesulfonic acid,⁵⁰ rhodium trichloride and ruthenium acetylacetonate,⁵¹ as well as catalysts composed of polymers^{52,53} and metals (Pt, Ni, Rh) applied to hydrophobic supports (Teflon, polyethylene, polystyrene).⁵⁴ The isotope exchange of activated aromatic protons in the $\text{AcO}^3\text{H}-3\text{HCl}$ solution has been investigated.⁵⁵ The catalytic role of metals and hydrogen ions has been discussed in Ref. 56.

1. Reactions with tritium-containing solvents

Reactions with a tritium-containing solvent, which is most often represented by tritiated water, are usually carried out in a strongly alkaline aqueous solution.⁵⁷ Werstiuk and Ju⁵⁸ have proposed a preparative method for the specific introduction of hydrogen isotopes into fused benzoheterocycles. This method is based on the isotope exchange with deuterated or tritiated water at a temperature above 145 °C. The methods for the preparation of heterocyclic and heteroaromatic compounds containing hydrogen isotopes have been reviewed.^{59,60}

The nucleic acid components exchange most readily the proton bound to the C(8) atom of the purine bases. The hydrogen bound to the C(2) atom is exchanged with a much greater difficulty. For example, by employing ^1H NMR spectroscopy (pD 6–7, 100 °C), Wong and Keck⁶¹ have shown that the rate of isotope exchange of hydrogen at the C(8) atom of adenine is ~ 1000 times as high as that at the C(2) atom.

Eidinhoff and Knoll⁶² observed the exchange of the proton bound to the C(8) atom of adenine in the presence of a reduced platinum catalyst. The hydrogen isotope exchange has also been reported to occur on heating (> 90 °C) of purine and adenosine in D_2O .^{63,64} Such an exchange leads to the disappearance of the peak corresponding to signals for the protons at the C(8) atom in the ^1H NMR spectra of these compounds. IR spectroscopy of the isotope exchange in the purine base residues in the DNA macromolecule has also pointed to the preferential exchange of the C(8) hydrogen.⁶⁵

Shelton and Clark⁶⁶ have used the reaction of isotope exchange for the incorporation of tritium into purine compounds. This reaction was conducted in an alkaline medium with tritiated water on heating to 100 °C. It was established that the guanine compounds were labelled more rapidly than the adenine ones. The exchange rate is increased in both bases as the pH is increased from 2 to 11. The conditions for tritium labelling are rather mild. This allowed one to apply them for the preparation of tritium-labelled nucleosides (adenosine, deoxyadenosine, and nucleotides), adenosine 3',5'-cyclomonophosphate⁶⁷ and ATP.⁶⁸

The kinetics of isotope exchange with water and the dependence of the rate constant of isotope exchange in ATP and GTP on pH have been investigated.⁶⁹ The kinetics of the incorporation of the tritium bound to the C(8) atom of purines of poly(A), poly(A)-poly(U) duplex, RNA, tRNA and DNA was studied by Gamble *et*

*al.*⁷⁰ The reaction of tritium–hydrogen exchange has been used for the introduction of tritium into oligonucleotides,⁷¹ oligodeoxyribonucleotides,⁷² polyribonucleotides,⁷³ DNA,^{74–77} tRNA^{Ileu} and tRNA^{Tyr} from yeast.⁷⁸ Drutsa⁷⁹ has proposed optimal conditions for the introduction of tritium into oligodeoxyribonucleotides: 2–4 h at 60 °C in tritiated water in an 0.3 M NaOH solution. Isotope exchange with tritiated water has been used for the preparation of an inhibitor of 5-lipoxygenation of arachidonic acid, which is an antiprosthetic agent ($A_{\text{mol}} = 19.8 \text{ Ci mmol}^{-1}$).⁸⁰ Mackenzie *et al.*⁸¹ have investigated the isotope exchange of the hydrogen bound to the C(2) atom in ethyl 5-amino-1-(2,3-*O*-isopropylidene- β -D-ribofuranosyl)imidazole-4-carboxylate (pH 1.77–12.0, 65 °C).

The analysis of changes in the isotope exchange rate of protons at the C(8) atom of purine residues provided information about conformational changes in natural biopolymers such as polynucleotides^{82–85} and RNA.^{70,86,87} It has been established that the rate of hydrogen exchange at the C(8) atom in adenine, guanine and hypoxanthine in nucleic acids is comparable with the respective rates in nucleoside monophosphates.⁸⁸ In DNA, the protium–tritium exchange is approximately 2.4–2.8 times as slow as that in deoxynucleoside monophosphates.⁸⁹

The study of the mechanism of isotope exchange with water in the C(8)H groups of purines has shown^{87,90,91} that the exchange proceeds by the so-called ylide mechanism, *viz.*, not in neutral molecules, but in the protonated [at the N(7) atom] forms of purine derivatives and in zwitter-ions with a positive charge on the N(7) atom. Agranovich *et al.*⁹² have studied the kinetics of protium–tritium exchange between water and the C(8)H group of purine bases, mono- and polynucleotides for different specific radioactivities of the medium over a wide temperature range (from 4 to 80 °C) and for different pH. It was shown that at high specific radioactivity of the medium, two non-competitive parallel exchange reactions occur simultaneously in the temperature interval studied: one follows the ylide mechanism and the other proceeds with participation of highly reactive radicals resulting from radiolysis of water under the action of β -radiation from tritium. The relative contribution from the radical exchange to the observed reaction rate decreases with higher temperature and lower specific radioactivity of the medium. In the case of polynucleotides and DNA, the isotope exchange follows basically the ylide mechanism at temperatures above 25 °C and in the case of nucleotide **18c** — above 37 °C (at a specific radioactivity of the medium of 1 Ci ml^{-1}). The increase in the medium acidity to pH 1 accelerates appreciably the radical exchange reaction, while the presence of β -mercaptoethanol decelerates it sharply. Changes in the observed hydrogen exchange rate in the C(8)H group of purine allow the estimation of variation of the pK_a of polynucleotides and nucleic acids caused by changes in the macromolecular conformation.⁹³

The protons bound to the C(5) atom of pyrimidines are readily exchanged for tritium from the tritium-containing water in uracil photohydrates. The isotope exchange between 5,6-dihydro-6-hydroxyuridine 5'-phosphate and tritiated water with heating yields 5-tritium-substituted uridine 5'-phosphate.⁹⁴ Boer and Johns⁹⁵ have reported a method for the preparation of tritium-labelled 5,6-dihydro-6-hydroxyuridine 5'-phosphate on heating with tritiated water. Similar exchange was observed in the photohydrates of cytosine derivatives.⁹⁵ The reaction of hydrogen isotope exchange between uracil and tritiated and deuterated water proceeds only in the presence of Pt and Pd catalysts.^{96,97} In the absence of a catalyst, this reaction takes place only under very drastic conditions.^{98–100} The exchange of C(5) hydrogen is markedly easier than that of the C(6) hydrogen. Wechter¹⁰¹ has proposed conditions for isotope exchange allowing the selective deuteration of C(6) in pyrimidine nucleosides. This method consists in the synthesis of 5,6-dideuterio compounds and the reexchange of deuterium from position 6 under special conditions. An analogous method has been proposed by Rabi and Fox.¹⁰² Isotope exchange of the hydrogen bound to the C(5) in pyrimi-

dines is accelerated in the presence of citrate buffer¹⁰³ and such compounds as 2-mercaptoethylamine, ethylamine, ethanolamine, sodium hydroxide,¹⁰⁴ hydrogensulfite anion,^{105, 106} methyl-, dimethyl- and trimethyl-amine hydrogensulfites, ethyl- and diethyl-amine, and imidazole,¹⁰⁷ cysteine and other sulfur-containing compounds, *e.g.*, 2-mercaptoethanol.^{108, 109} Under specific conditions, the reaction of nucleic acids with hydrogensulfite in the presence of tritiated water results in the transformation of the cytidine fragments into uridine fragments.¹⁰⁶ In all cases, the isotope exchange proceeds under mild conditions. Tritium is incorporated into uracil and cytosine derivatives in alkaline and acidic medium, respectively. These reactions can be used for the synthesis of tritium-labelled pyrimidine derivatives.

Hesk *et al.*⁵¹ have described a method for homogeneous hydrogen isotope exchange under the action of RhCl₃ in dimethylformamide at 110 °C, which allows high regioselective introduction of tritium in the *ortho*-position of various aromatic acids, amides, amines and heterocyclic compounds. This study has also shown that in addition to RhCl₃, ruthenium acetylacetonate is another efficient catalyst of isotope exchange in the *ortho*-position of benzoic acids.

The reaction with tritium-containing solvents is a versatile method for the preparation of tritium-labelled compounds, diazines in particular. This method does not require synthesis of special precursors, and the conditions of tritium labelling are sufficiently mild to allow its use for the incorporation of this label into compounds of rather complex structure, *e.g.*, nucleic acids. When employing this reaction, the main attention should be paid to the choice of efficient homogenous or heterogeneous catalysts and solvents (tritium sources). A disadvantage of this method is a relatively low level of molar radioactivity of the target products. This is mainly determined by the specific radioactivity of the tritiated water used, which usually does not exceed 100–200 Ci ml^{−1} (3%–6% of its theoretical level). Tritiated water with higher specific radioactivity is unstable because of its autoradiolysis. Reactions of isotope exchange may be carried out with the tritiated water with very high specific radioactivity if it is mixed with an inert anhydrous organic solvent.¹¹⁰ The isotope exchange with steroids has demonstrated¹¹⁰ that the maximum A_{mol} is reached when a solution of ³H₂O (2%–3%) in an inert solvent is used. This corresponds to a volume radioactivity of a solution of 65–100 Ci ml^{−1}. Solutions of highly active tritiated water were prepared by the oxidation of gaseous tritium over palladium oxide in an anhydrous organic solvent. Tritium-labelled benzylaminopurine has been obtained using highly active ³H₂O ($A_{\text{mol}} = 24$ Ci mmol^{−1}).¹¹¹ The proposed method is laborious, while disadvantages such as relatively low levels of molar radioactivity (a few tens of Ci mmol^{−1}) and the necessity to use large volumes of tritiated water prevent its wide application for the synthesis of tritium-labelled components of nucleic acids. However, this method proves to be virtually the only one possible for compounds containing groups that can be readily reduced and/or hydrogenated (*e.g.*, steroids and pharmaceutical preparations¹¹²).

2. Catalytic liquid-phase heterogeneous isotope exchange with gaseous tritium

In 1974, two reports^{113, 114} were published simultaneously on the method of tritium labelling of organic compounds based on isotope exchange of gaseous tritium with hydrogen in the compound subject to labelling dissolved in an appropriate solvent in the presence of heterogeneous catalysts. Buchman *et al.*¹¹³ have proposed a method of non-specific labelling with gaseous tritium in the presence of an activated platinum catalyst. The catalyst PtO₂ was more active than PdO in the isotope exchange reaction.¹¹⁵ Evans *et al.*¹¹⁴ conducted the isotope exchange reaction in a phosphate buffer in the presence of a PdO/BaSO₄ catalyst. Tritium was incorporated into carbohydrates, aliphatic and aromatic amino acids and nucleic acid components. Table 6 shows the conditions of isotope exchange reactions for the introduction of tritium into purine and pyrimidine compounds

Table 6. Purine and pyrimidine compounds prepared by catalytic heterogeneous isotope exchange with gaseous tritium.¹¹⁴

Compound	Reaction conditions		$A_{\text{mol}} / \text{Ci mmol}^{-1}$
	pH	<i>t</i> / min	
Arabinosyladenosine	8.2	240	5.6
Adenosine	8.2	120	12.0
cAMP	10.0	60	25.0
AMP	10.0	960	11.0
ATP	8.2	60	20.0
2'-Deoxyadenosine	8.2	210	17.0
2'-dATP	10.0	60	18.1
<i>N</i> ⁶ , <i>O</i> ^{2'} -Dibutyl- <i>c</i> AMP	10.0	60	19.5
Guanosine	8.0	120	0.42
cGMP	8.0	20	0.88
GTP	8.2	30	1.5
IMP	8.0	5	1.2
	8.0	20	3.9
	8.0	60	2.7
	8.0	20	2.7
Nicotinamide	8.0	120	—
NAD	8.0	120	—
Puromycin	8.2	120	3.7
Puromycin aminonucleoside	8.2	120	13.7
Thymidine	8.0	60	5.0
	8.0	60	7.0
Uracil	8.0	60	9.0
	8.0	60	2.5

Notes. Abbreviations: IMP, inosine 5'-monophosphate; NAD, nicotinamide adenine dinucleotide.

with this method. This is of a high practical value for the synthesis of tritium-labelled components of nucleic acids. Presumably, the isotope exchange proceeds by the free-radical mechanism and is facilitated for mobile hydrogen atoms, such as aromatic protons and hydrogen bound to the C(8) atom of purines. One could hardly expect high levels of molar radioactivity for the compounds with aliphatic protons, and it seems for protons combined with C(5) and C(6) of pyrimidines. Hanus *et al.*¹¹⁶ have employed heterogeneous catalysts (PdO, PtO₂ and Pd/BaSO₄) in order to investigate the process of tritium incorporation into such compounds as dioxane, tetrahydrofuran, ethyl acetate, dimethylformamide, dimethylacetamide and acetic anhydride. It was shown that the proportion of tritium incorporated by the direct interaction with the solvent is negligibly small compared with that introduced in the presence of catalysts. The degree of tritium incorporation depends on the solvent purity. In extremely pure solvents, the tritium is present in the form of heavy water.

The method of catalytic heterogeneous exchange with gaseous tritium has allowed synthesis of [³H]acyclovir³⁹ and the following tritium-labelled compounds:^{117–120}

Compound	$A_{\text{mol}} / \text{Ci mmol}^{-1}$
5-Azacytidine	17.4
5-Aza-2'-deoxycytidine	19.5
<i>N</i> ⁴ -(5-Aminopentyl)cytidine	3.0
5-Methylcytidine	1.9
5-Methylcytosine	4.2
Arabinosyl-5-azacytosine	12.5
5-Hydroxy[6- ³ H]uracil	0.35
5-Amino[6- ³ H]uracil	2.4
1-β-D-Arabinofuranosyl[5,6- ³ H]cytosine	12.0
9-[(2-Hydroxyethoxy)methyl][8- ³ H]guanine	8.8
9-β-D-Arabinofuranosyl[8- ³ H]adenine	1.0

Kaminskii *et al.*³⁸ have demonstrated that the use of AMP 1-*N*-oxide as the precursor facilitates significantly the tritium exchange

at the C(2) atom of the adenine ring. Introduction of tritium into adenine dinucleoside phosphates¹²¹ and the P–H group of 2'-deoxyadenosine 5'-H-phosphonate has been described.¹²²

The rate constants for liquid-phase catalytic heterogeneous protium–tritium exchange of [8-³H] nucleotides of the adenine series with hydrogen¹²³ have been measured (the experimental procedure is given in Ref. 124). It has been established¹²⁵ that the exchange rate decreases in the following sequence: cAMP > ATP > ADP > AMP. An equation of the dependence of the rate constant for isotope exchange on pH has been deduced. At low concentrations of nucleotides, the reaction order with regard to nucleotide is 1, whereas at higher nucleotide levels it is close to 0.

Lacey *et al.*¹²⁶ have described a general method for specific introduction of tritium label into benzoimidazole carbamates (BIC), which includes catalytic isotope exchange in dioxane at 60 °C under gaseous tritium. The yield of labelled BIC was found to range from 8% to 70% with the molar radioactivity varying from 0.44 to 13.4 Ci mmol⁻¹. The use of gaseous tritium in the presence of a catalyst based on iridium complexes has made it possible to obtain high levels of molar radioactivity for benzophenones, quinolines, 2-aminopyridines, 2-aminobenzoxazole derivatives, benzoazepinone amides and complex benzamides.¹²⁷

It is noteworthy that the reactions of catalytic dehalogenation and catalytic heterogeneous isotope exchange proceed under similar conditions. This fact should be taken into account in conducting catalytic reactions of hydrogenation, dehalogenation, *etc.* The tritium label can be introduced by both a chemical reaction and isotope exchange. For example, dehalogenation of monobromopapaverine on a palladium catalyst yielded a product with $A_{\text{mol}} = 43 \text{ Ci mmol}^{-1}$ (see Ref. 128). In this case, the percentages of the label due to the tritium substitution for bromine and the exchange of the methylene group proton with tritium were 49% and 46%, respectively, with 5% of the tritium introduced in other positions. A similar process takes place on dehalogenation of 2-halogeno-purines: tritium substitutes hydrogen at the C(2) atom owing to dehalogenation reaction and at the C(8) atom owing to isotope exchange.³⁸

This reaction underlies the most versatile method used for the preparation of tritium-labelled compounds. As regards its general character, the method described is comparable to the isotope exchange with a tritium-containing solvent. The main advantage of this method consists in high levels of molar radioactivity of the compounds obtained. This is due to the fact that the isotope source is a high-percentage (> 95%) gaseous tritium whose molar radioactivity is higher than that of any tritium-containing solvent. A disadvantage of this method is that processes of dehalogenation, hydrogenation and reduction of various functional groups can take place under given reaction conditions.

V. Reduction and hydrogenation

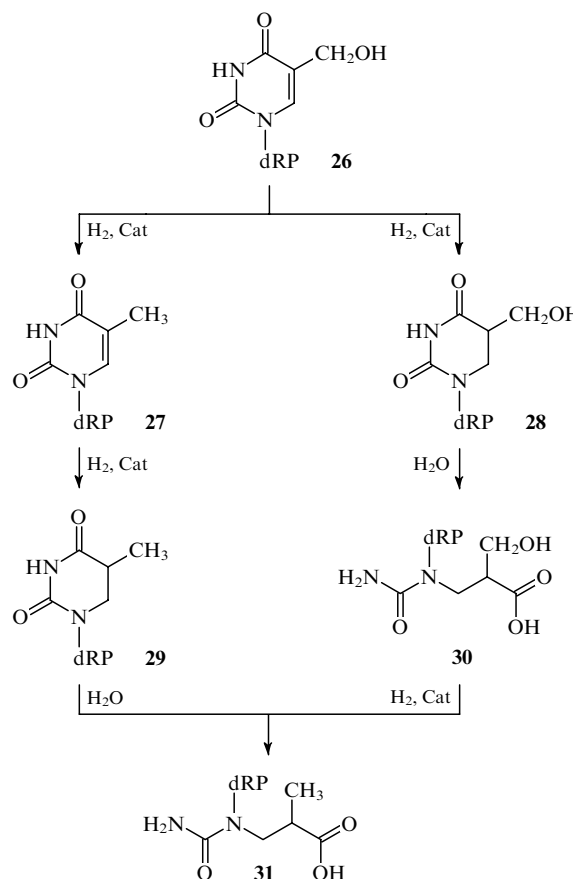
Processes of reduction and hydrogenation are used mostly for the introduction of tritium into the methyl group of thymine and its derivatives, and also into the carbohydrate moiety of nucleosides. Reduction is usually performed by means of catalytic reactions using gaseous tritium and tritium-labelled NaBH₄ and LiAlH₄. Coates *et al.*¹²⁹ have proposed to use lithium triethylborotritide (super-tritide) obtained by the reaction of LiT with Et₃B for the incorporation of tritium into various compounds by the reduction of certain functional groups.

Tritium-labelled thymidine ($A_{\text{mol}} = 27.5 \text{ Ci mmol}^{-1}$) was prepared by the reduction of 5-hydroxymethyl-2'-deoxyuridine in the presence of rhodium on alumina as a catalyst.¹³⁰ Tritium-labelled 5-hydroxymethyl-2'-deoxyuridine was synthesised by the reduction of 5-formyl-2'-deoxyuridine in a phosphate buffer.¹³¹

Hydrogenation of 5-hydroxymethyl- and 5-formyluracil in the presence of a palladium catalyst yielded^{132, 133} thymine with up to 2 tritium atoms in the methyl group. Successful application of Raney nickel for the reduction of 5-formyluracil to 5-hydroxymethyluracil has been reported.¹³⁴ Hydrogenation of 5-formyluracil

in water with gaseous tritium over 1.5% Pd/BaSO₄ produced 5-hydroxymethyl[hydroxymethyl-³H]uracil ($A_{\text{mol}} = 64.8 \text{ Ci mmol}^{-1}$).¹³⁵ Further reduction of the latter with tritium over palladium in dry dioxane yielded [methyl-³H]thymine.¹³⁶ In order to prepare thymine with the complete substitution of hydrogen by tritium in its methyl group, Yakovleva *et al.*¹³⁷ carried out catalytic reduction of 5-cyanouracil to aldimine followed by its hydrolysis to 5-formyluracil with subsequent catalytic reduction with gaseous tritium. Reduction of 5-formyluracil ethylene dithioacetal with tritium in dioxane over Raney nickel also led to the formation¹³⁸ of [methyl-³H]thymine ($A_{\text{mol}} = 11.6 \text{ Ci mmol}^{-1}$). Catalytic reduction of 5-formyluracil with gaseous tritium is described in Ref. 139.

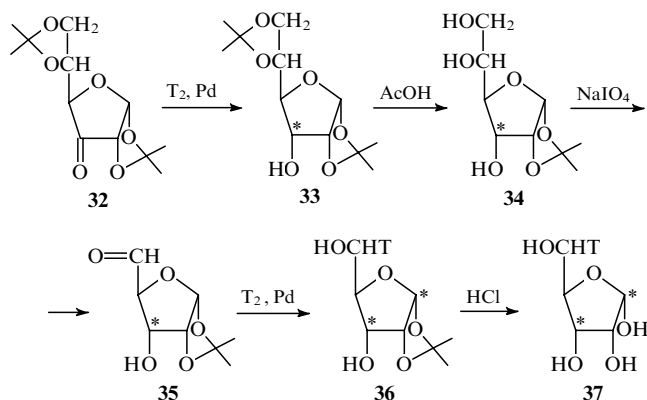
One-stage methods for the preparation of tritium-labelled thymidine 5'-monophosphate (TMP, **27**) have been reviewed.¹⁴⁰ The precursors of TMP were 5-hydroxymethyl-dUMP (**26**) and 5-formyl-dUMP. It was established that under specific conditions (depending on the nature of catalyst employed and the reaction medium) hydrogenation can affect the 5,6-double bond of the pyrimidine ring and lead to the formation of 5-hydroxymethyl-5,6-dihydro-dUMP (**28**), 5,6-dihydroTMP (**29**), 2'-hydroxy-3-(N¹-2'-deoxy-5'-phospho-β-D-ribofuranosyl)ureidoisobutyric acid (**30**), and 3-(N¹-2'-deoxy-5'-phospho-β-D-ribofuranosyl)ureidoisobutyric acid (**31**).



The general method used for the synthesis of nucleosides labelled with tritium at the 5'-atom of the carbohydrate residue is based on the reduction of β-D-ribofuranosyl-1,4-furanosides of respective nucleic bases with gaseous tritium or sodium boro[³H]hydride. This method was used for the preparation of compounds labelled at the 5'-position, such as 9-β-arabino-furanosyladenine,¹⁴¹ thymidine,¹³⁸ 2',3'-O-isopropylideneadenosine.¹⁴² In order to prepare adenosine, guanosine and uridine labelled with tritium at C(5'), Akulov *et al.*¹⁴³ conducted the reduction reaction using gaseous tritium in the presence of a catalyst as well as sodium boro[³H]hydride. Synthesis of [5'-³H]3'-azido-3'-deoxythymidine ($A_{\text{mol}} = 14 \text{ Ci mmol}^{-1}$) was carried out

by the oxidation of its precursor to 5'-aldehyde and subsequent reduction with NaB^3H_4 .¹⁴⁴ Introduction of deuterium and tritium in the positions 5' and 4' of 2'-deoxynucleosides is described in Ref. 145. For this purpose, the corresponding 5'-aldehydes were prepared from deoxyguanosine, deoxycytidine and thymidine by the Moffatt method and then reduced with NaBD_4 to form 5'-deuteronucleosides. Heating of 5'-aldehydes in a D_2O –Py mixture (1:1) with subsequent reduction yielded 4'-deuteronucleosides. It is pointed out that the use of a similar procedure for the tritiation yields labelled compounds with low molar radioactivity. A recent US patent¹⁴⁶ describes a method of tritium introduction into oligodeoxyribonucleotides in which an immobilised oligonucleotide with a free 5'-hydroxy group is oxidised with an appropriate agent to aldehyde and then reduced, e.g., with NaB^3H_4 , to give a tritium-labelled 5'-hydroxymethyl group. Riboflavin (vitamin B_2) selectively labelled with tritium in the position 5' was prepared¹⁴⁷ by the reduction of the 5'-aldehyde group with sodium borotr[^3H]hydride. Synthesis of [ribose-2,3- ^3H]2',3'-dideoxycytidine phosphonate,⁴³ [ribose-2,3- ^3H]2',3'-dideoxyadenosine and [ribose-2,3- ^3H]2',3'-dideoxyinosine³³ was carried out by catalytic hydrogenation of the corresponding unsaturated analogues with gaseous tritium.

The key compound in the synthesis of tritium-labelled nucleotides and nucleosides is D-ribose. The use of tritium-labelled D-ribose and heterocyclic bases in enzymic reactions^{12, 24, 148, 149} allows synthesis of nucleosides and nucleotides containing tritium in the ribose and heterocyclic moieties of the nucleoside and nucleotide molecules. We have proposed the following scheme for the synthesis of tritium-labelled D-ribose: reduction of 1,2:5,6-di-*O*-isopropylidene- α -D-ribohexofuranos-3-ulose (**32**) by tritium to 1,2:5,6-di-*O*-isopropylidene- α -D-allofuranose (**33**), oxidation of 1,2-*O*-isopropylidene- α -D-allofuranose (**34**) to 1,2-*O*-isopropylidene- α -D-ribose-5-phosphonate (**35**) and reduction of the latter to 1,2-*O*-isopropylidene- α -D-ribofuranose (**36**) combined with the hydrogen isotope exchange at the C(1) atom.



(The asterisks indicate the sites of tritium incorporation).

These consecutive reactions make it possible to synthesise the tritium-labelled D-ribose (**37**) with up to 3 tritium atoms.

VI. Solid-state catalytic hydrogenation

The method of solid-state catalytic hydrogenation (SCH) was proposed in 1967. Dehalogenation of 5-iodouracil may be regarded as an example of SCH reaction. Subsequent studies have shown that hydrogenation¹⁵⁰ and isotope exchange¹⁵¹ occur under similar conditions. This method consists in the treatment of a solid mixture of the initial compound and catalyst with gaseous tritium. In order to intensify the process, an external supply of energy was provided. The optimum version of the initiation of this reaction proved to be heating of the reaction system. The solid-state reactions of isotope exchange have been further developed in the studies of Meshi and Takahashi.¹⁵² The use of catalysts increases appreciably the extent of tritium incorporation and its

selectivity. Zolotarev *et al.*,^{150, 151} who investigated SCH in the reactions of hydrogenation, reduction and isotope exchange, have concluded that a new process took place in all cases. It has been demonstrated^{153, 154} that the SCH is based on the spillover of hydrogen activated on the catalyst and its diffusion into the layer of organic compound. A diffusion model of this process has been proposed.¹⁵⁵ The applicability of this model was exemplified with solid-state isotope exchange in thymine accompanied by the hydrogenation of the 5,6-double bond.¹⁵⁶ The extent of isotopic substitution in the SCH reaction depends on the nature of the metal used as the catalyst (Pd, Pt, Rh, Ru) and support (BaSO_4 , CaCO_3 , Al_2O_3 , SiO_2 , C), the catalyst–compound ratio and the reaction temperature.

The application of the SCH method for the synthesis of biologically important diazines labelled with tritium gave good results. Solid-state catalytic hydrogenation of 5-formyluracil afforded thymine with the molar activity corresponding to the incorporation of three tritium atoms into the methyl group.^{132, 133} Investigation of the hydrogenation kinetics of 5-formyluracil has shown¹⁵⁷ that starting from a definite temperature, the incorporation of tritium into thymine exceeds the stoichiometry corresponding to the reduction of the formyl group. This is explained by the fact that under given conditions, the reduction is accompanied by a parallel reaction of isotope exchange of the formyl group hydrogen with tritium. This leads to thymine with a virtually complete substitution of hydrogen by tritium in its methyl group ($A_{\text{mol}} \approx 87 \text{ Ci mmol}^{-1}$). The use of another precursor, *viz.*, 5-hydroxymethyluracil, a specially selected catalyst and more drastic reaction conditions have permitted synthesis of thymine¹⁵⁷ in which all tritium was substituted for hydrogen over all the C–H bonds ($A_{\text{mol}} > 100 \text{ Ci mmol}^{-1}$), and the use of 5-hydroxymethyldeoxyuridine as the precursor has yielded tritium-labelled thymidine ($A_{\text{mol}} = 76 \text{ Ci mmol}^{-1}$).¹⁵⁸

Let us consider the basic regularities of the introduction of tritium label by the SCH method with synthesis of specific compounds as an example. It has been shown¹⁵⁷ that in the SCH reaction of tritium with purine bases the rate of isotope exchange is sharply increased in the temperature range 150–170 °C. This leads to a virtually complete substitution of hydrogen by tritium.

The results of synthesis of 11 alkylxanthines labelled with tritium using the SCH reaction are presented in Ref. 159. Analysis of the labelled compounds by ^3H NMR spectroscopy has revealed that the tritium label was incorporated not only in the C(8) position but also in the alkyl groups. The dependences of the yield of compound **22** prepared by SCH with tritium and of its molar radioactivity on temperature and the catalyst/compound ratio have been investigated.¹⁶⁰ The same dependences for compounds **19** and **21** were studied by Lushkina *et al.*¹⁶¹ It has been found that for virtually all the compounds studied the higher temperature and the greater catalyst/compound ratio the lower the yield of specific products but the higher its molar radioactivity. Thus, the variation of reaction conditions [temperature, catalyst, catalyst/compound mass ratio and reaction time] opens wide possibilities for the synthesis of labelled compounds.

The main side reaction of SCH is degradation (thermolysis) of the initial compound. The products of the synthesis of tritium-labelled 2',5'-oligoadenylate were found to include an isomerisation product, *viz.*, 3',5'-isomer, which was separated by chromatography.¹⁶² In the case of SCH of pyrimidines, hydrogenation of the 5,6-double bond of the heterocyclic ring may occur in parallel leading to the formation of compounds **28–31**.

The SCH method was employed for the introduction of a tritium label into compounds of a more complex structure such as polynucleotides and natural polymers,¹⁶² e.g., 15S RNA. The liquid- and solid-state catalytic isotope exchange with gaseous tritium in thymidine 5'-H-phosphonates, 2'-deoxyadenosine, and 2'-deoxy-5-hydroxymethyluridine has been investigated.¹⁶³ Analysis by ^3H NMR spectroscopy has revealed that tritium is incorporated into the P–H group. The solid-state method for the preparation of tritium-labelled DNA synthesis terminators

(**22**, **23**, azidothymidine phosphonate, acyclovir phosphonate, 3'-deoxythymidine) is described in Ref. 43. The tritium-labelled 5'-*O*-phosphorylmethylthymidine ($A_{\text{mol}} = 71 \text{ Ci mmol}^{-1}$) was obtained by the solid-state reaction of isotope exchange at 150 °C.¹⁶⁴

Table 7 lists the A_{mol} values of tritium-labelled purine and pyrimidine compounds prepared by the SCH method. The values presented are higher than those for these and analogous compounds labelled by other methods. For compounds of relatively simple structure, such as **2**, **3**, **10**–**13**, a virtually complete isotope substitution of hydrogen by tritium has been attained. Variation of the solid phase composition and temperature permits the directed modification of the yield and the molar radioactivity of specific compounds. The SCH method does not require synthesis of special precursors and offers the possibility of a greater degree of hydrogen substitution by tritium than do other methods. Degradation of thermally labile compounds, the occurrence of parallel reactions of hydrogenation, dehalogenation and reduction of various functional groups may be regarded as disadvantages of the SCH method. However, in many cases these disadvantages are not critical since a careful choice of reaction conditions makes it possible to minimise (as far as possible) the influence of side reactions and to synthesise compounds containing the groups (the 5,6-double bond of pyrimidines) susceptible to hydrogenation and even some thermally unstable compounds (oligo- and poly-nucleotides, RNAs).

Thus, the SCH method may be regarded as one of the most promising methods for the synthesis of tritium-labelled natural diazines, in particular, of the components of biologically important substances.

Table 7. Molar radioactivities of diazines obtained by SCH reactions.

Compound	$T/^\circ\text{C}$	$A_{\text{mol}}/\text{Ci mmol}^{-1}$
Adenine	170	54.2
Guanine	210	24.9
Xanthine	180	25.1
Hypoxanthine	200	51.1
Thymine ^a	140	85.0
Thymine ^b	170	110.0
Thymine ^c	170	115.0
Alkylxanthines (11 compounds)	170	17–203
Uracil	170	49.0
Benzyladenine	190	180.0
Theophylline	160	24.8
Furfuryl-adenine	160	160.0
Adenosine	210	120.0
2'-Deoxyadenosine	190	84.0
Guanosine	210	69.0
2'-Deoxyguanosine	200	35.0
Thymidine ^d	160	76.0
3'-Azidothymidine	120	30.0
Acyclovir	210	125.0
2',3'-Dideoxythymidine	120	66.0
3'-Azidothymidine phosphonate	120	63.0
Acyclovir phosphonate	120	56.0
2',5'-ApApAp	200	58.0
3',5'-ApA	110	9.2
3',5'-ApApA	110	50.0
3',5'-pApApAp	110	27.0
Poly-A (7–8 S)	180	10.2 ^e
Poly-U (12 S)	180	12.0 ^e
15 S RNA	180	12.1 ^e

^a From 5-formyluracil; ^b from 5-hydroxymethyluracil; ^c from thymine;

^d from 5-hydroxymethyl-2'-deoxyuridine. ^e Specific radioactivity/ Ci g^{-1} .

Table 8. Characteristics of different methods used for the synthesis of biologically active diazines labelled with tritium.

Reaction	Reaction condition	$A_{\text{mol}}/\text{Ci mmol}^{-1}$
Tritium incorporation by chemical synthesis		
Dehalogenation	in solution	15–45
	in solid state	5–20
Hydrogenation, reduction	in solution	15–40
	in solid state	40–90
Tritium incorporation by isotope synthesis		
Isotope exchange with:		
³ H-solvent	in solution	5–10
highly radioactive water	"	up to 25
gaseous tritium	"	5–25
	in solid state	20–120, up to 250

Comparative characteristics of different methods used for the synthesis of tritium-labelled biologically important diazines are presented in Table 8.

VII. Other methods of tritium labelling

A number of methods exist that did not find wide application for the synthesis of tritium-labelled natural diazines. Some pyrimidine derivatives labelled with tritium in the position 5 were prepared by heating (to 160 °C) the respective iodo-substituted compounds in DMSO with tritiated water.¹⁶⁵ The molar radioactivity of uracil, uridine, cytosine, cytidine and orotic acid thus obtained made up 30% of the A_{mol} level of [³H]H₂O.¹⁶⁶ Electrolytic reduction of 5-bromouracil in tritiated water (mercury cathode, platinum anode) yielded [5-³H]uracil.¹⁶⁷

Decarboxylation of 5-substituted derivatives of orotic acid labelled with tritium in the carboxyl group produced [6-³H]thymine¹⁶⁸ from 5-methylorotic acid, 5-fluoro[6-³H]uracil¹⁶⁹ and 5-bromouracil¹⁷⁰ from the corresponding 5-halogeno-derivatives of orotic acid. The molar radioactivity of these products did not exceed 1 Ci mmol^{−1}. Heating of orotic acid supported on a Cu/BaSO₄ catalyst, which was partially oxidised in air, in the tritium atmosphere yielded [6-³H]uracil (23 Ci mmol^{−1}).¹⁷¹ β-D-Arabinofuranosyladenosine ($A_{\text{mol}} = 0.43 \text{ Ci mmol}^{-1}$) was prepared by isotope exchange with UV-activated gaseous tritium.¹⁷² Alkylation of [2,8-³H₂]adenosine with 4-bromo-2-methylbut-2-ene in dimethylformamide gave *N*⁶-(2-isopentyl)[2,8-³H]adenosine, which was transformed into *trans*-[2,8-³H]zeatin riboside ($A_{\text{mol}} = 22 \text{ Ci mmol}^{-1}$) by allylic oxidation.¹⁷³ Heating (60 °C, 2 h) of *N*⁶-(3-iodobenzyl)-*N*⁹-[methyl(2,3-di-*O*-acetyl-β-D-ribofuranosyl)uronate]-2-chloroadenosine with tritium-labelled methylamine in methanol provided *N*⁶-(3-iodobenzyl)-*N*⁹-[*N*-methyl-(β-D-ribofuranosyl)uronamide] ($A_{\text{mol}} = 29 \text{ Ci mmol}^{-1}$).¹⁷⁴ Azidothymidine was synthesised using tritium-labelled thymidine.¹⁷⁵ Deamination of [5-³H]1-β-D-arabinofuranosylcytosine led to the formation of [5-³H]1-β-D-arabinofuranosyluracil ($A_{\text{mol}} = 20 \text{ Ci mmol}^{-1}$).³⁹ [8-³H]9-β-D-Arabinofuranosyladenine ($A_{\text{mol}} = 10 \text{ Ci mmol}^{-1}$),³⁹ [2-³H]adenine and [2-³H]adenosine³⁸ are the products of catalytic reductive desulfurisation of the corresponding SH-derivatives with gaseous tritium. The processes of tritium incorporation from the gas phase into thymidine and deoxyuridine in an aqueous solution have been considered.¹⁷⁶ Incorporation of tritium into these compounds resulted mainly from the attack by the ³HeT⁺ species rather than the radiolysis induced by β-particles.

VIII. Conclusion

Nowadays, synthesis of tritium-labelled physiologically significant compounds may be regarded as an independent field of applied radiochemistry that makes use of the approaches and methods of bioorganic chemistry, biochemistry and enzymology. This is characterised by both the development of efficient techniques for tritium incorporation and organisation of the production of labelled substances. The above considerations suggest a number of inferences on the state-of-the-art of the synthesis of tritium-labelled diazines.

In the 1970s, rapid progress of molecular biology and molecular genetics increased dramatically the demand for tritium-labelled components of nucleic acids. This has stimulated the development of new methods and the improvement of existing techniques of their synthesis. Tritium-labelled compounds have played an important role in the studies of the structure and functions of nucleic acids. Catalytic dehalogenation in solution may be regarded as the general method for the synthesis of the tritium-labelled components of nucleic acids. The development of this method has allowed synthesis of compounds with a definite position of the tritium label and relatively high molar radioactivities ($20\text{--}30\text{ Ci mmol}^{-1}$). The need for the components of nucleic acids possessing high and superhigh molar radioactivity has stimulated the development of techniques for the preparation of purine and pyrimidine bases multiply labelled with tritium. These include reactions of catalytic dehalogenation (e.g., of 2,8-dichloroadenine, 5-bromouracil and 6-chlorouracil) and solid-state catalytic hydrogenation (e.g., synthesis of [2,8- ^3H]adenine and [methyl-6- ^3H]thymine from the respective unlabelled precursors). The use of the enzymes of purine and pyrimidine metabolism has opened a simple and reliable pathway for the preparation of a virtually complete set of nucleic acid components multiply labelled with tritium.

The recent years witness an ever-increasing interest in the tritium-labelled pharmaceutical preparations of rather complex structures. As regards diazines, these are mainly various DNA synthesis terminators, medicinal drugs in the stage of pharmaceutical assays and coenzymes. These and similar tritium-labelled compounds are most often synthesised by catalytic reactions of isotope exchange, in particular the isotope exchange with gaseous tritium in solution and in solid state. Such reactions may be considered as express-methods that do not require synthesis of special precursors. For example, tritium-labelled nicotinamide adenine dinucleotide (111 Ci mmol^{-1}) and coenzyme A (3.9 Ci mmol^{-1}) were prepared by the solid-state reactions of isotope exchange with gaseous tritium.¹⁷⁷ The application of the reactions of isotope exchange involving gaseous tritium is limited by the requirement that the initial compounds contain groups capable of easy reduction or hydrogenation and are thus susceptible to modification or substitution by tritium. In this case, the reaction of isotope exchange with highly active tritiated water is a promising method. The possibilities of the application of this method for the synthesis of tritium-labelled biologically active substances, including diazines, have been discussed.¹⁷⁸

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^e — *Russ. J. Mol. Biol. (Engl. Transl.)*

^f — *Russ. J. Gen. Chem. (Engl. Transl.)*

Dialdehyde-containing nucleic acids and their components: synthesis, properties and affinity modification of proteins

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Abstract. Synthesis, structure and chemical properties of nucleoside dialdehyde derivatives are described. The introduction of aldehyde groups into oligonucleotides is discussed. The methods of affinity modification of proteins with periodate-oxidised nucleic acid derivatives are considered. The bibliography includes 48 references.

I. Introduction

The study of the nature of specific interactions of proteins with nucleic acids (NA) is an important problem of modern molecular biology. Relatively few methods allowing the identification of functional groups of proteins involved in protein–NA recognition are known. Covalent binding of proteins to NA is an efficient approach.¹ It consists in specific covalent attachment of a protein to NA by modification of one of the components of the protein – NA complex or by addition of a cross-linking reagent. The covalently bound protein is subjected to hydrolysis with proteases and then the amino acid composition of the peptide attached to NA, which is the region of the active site or a recognition domain of the protein, is determined. The method of covalent ‘cross-linking’ also makes it possible to study the topography of the protein–NA complexes and to establish their stoichiometry.

Elaboration of optimal conditions for protein–NA recognition is an essential feature required for this method. In this case, the modification must not induce significant distortions in the structure of the components of the complex and not interfere with the recognition of NA analogues by specific proteins. Affinity modification of non-modified proteins with NA upon UV irradiation is a way to perform covalent addition of proteins to NA.¹ Another approach consists in the introduction of chemically or photo-activated groups into a protein or NA followed by their activation. Reactive groups are introduced into heterocyclic bases of NA, into phosphate groups or into sugar residues. The first two types of NA activation and the formation of covalently bound products based on these derivatives have been described in several reviews.^{1–3} In the present work, we shall consider NA derivatives

containing two aldehyde groups in the sugar residue with regard to their synthesis, properties and affinity modification of proteins.

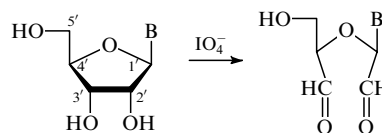
Earlier, dialdehyde derivatives of NA were extensively used for establishing the structure of monomeric components of nucleic acids and for the analysis and separation of oligonucleotide mixtures.⁴ The nucleotide sequences adjacent to the 3′-end of RNA were determined using oxidation of the 3′-terminal nucleotide unit of RNA with subsequent cleavage of the adjacent phosphodiester bond and identification of a heterocyclic base.⁴ At present, dialdehyde derivatives of NA are most often used for introduction of various functional groups into NA and affinity modification of proteins.

II. Introduction of aldehyde groups into the sugar residue of nucleic acids

The methods used for the introduction of two aldehyde groups into nucleosides and mononucleotides as well as into 3′- and 5′-terminal residues of oligonucleotides are well known. A procedure for introduction of aldehyde groups into any position of the oligonucleotide chain has been developed recently.

1. Synthesis and structure of dialdehyde derivatives of nucleosides and nucleotides

The synthesis of dialdehyde derivatives of nucleosides is based on periodate oxidation of ribonucleosides and their derivatives:⁴



Hereinafter B is a heterocyclic base.

The reaction of adenosine 5′-triphosphate (I) with sodium periodate is of the second order (the rate constant k_2 is equal to $1.06 \times 10^3 \text{ litre min}^{-1} \text{ mol}^{-1}$).⁵ The oxidation was carried out with an equimolar amount or a small excess of sodium periodate for 1 h at 4 °C.⁵ In another study,⁶ mono- and dinucleotides were oxidised with a 20-fold excess of sodium periodate for 1 h at 0 °C. The excess of sodium periodate was removed with ethylene glycol,⁶ a small excess of rhamnose⁶ or a 4-fold molar excess of NaAsO₂.⁷ The resulting solutions of oxidised nucleoside derivatives were used as such; the products could be purified by gel chromatography.

The aldehyde groups in various periodate-oxidised ribonucleotides are hydrated;^{8–10} thus the oxidation product of adeno-

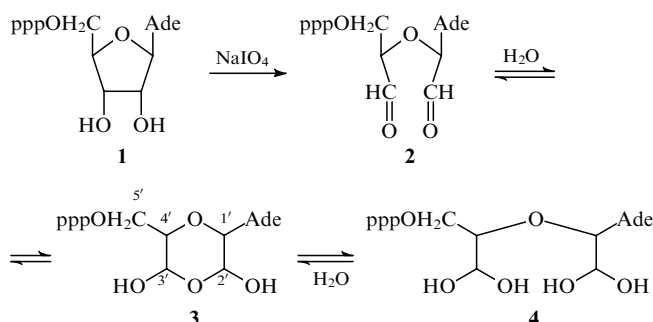
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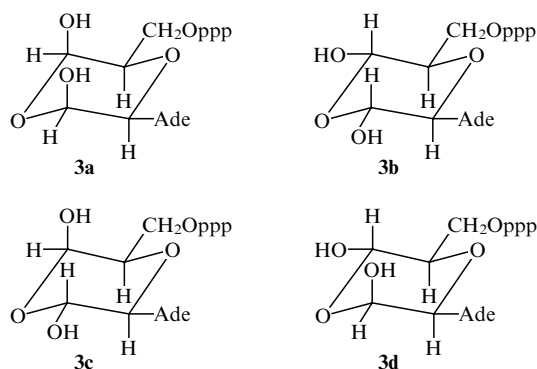
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sine 5'-triphosphate (oATP) exists as an equilibrium mixture of dialdehyde hydrates (structures **3** and **4**, Scheme 1).^{5,9}

Scheme 1



The ¹H and ¹³C NMR spectra of oATP do not contain resonance signals typical of free aldehyde groups; the polymeric form of oATP was not detected in solution. The cyclic hemiacetal **3** may exist as a mixture of four diastereomers **3a–d**.



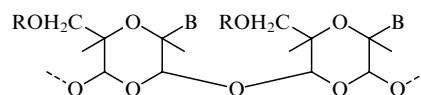
These conformers are preferred, since the adenine moieties and CH₂Oppp groups are equatorial.⁹ The coupling constants correspond to the structures **3b–d** (Table 1). Because of steric constraints due to the axial position of two hydroxy groups, the structure **3a** is probably not realised. The structures **3c** and **3d** are more preferable, since the hemiacetal hydroxy groups in 1,4-dioxanes and sugars tend to occupy the axial position (the so-called anomeric effect).¹¹ The ¹H and ¹³C NMR spectra also contained signals corresponding to the dialdehyde dihydrate **4**. Thus, oATP exists in solution as a mixture of four compounds, *viz.*, three diastereomers of the cyclic hemiacetal **3b–d** and the dihydrate **4**, which are in equilibrium with one another, and a small amount of the free dialdehyde **2**.

In aqueous solution at pH 7.0, the UV spectrum of oATP is similar to that of ATP.⁵

The circular dichroism (CD) spectra of dialdehyde derivatives of adenosine, uridine and cytidine revealed strongly reduced

Cotton effects in comparison with those observed for the corresponding nucleosides.¹² This points to enhanced free rotation of the heterocyclic base around the glycosidic bond. On the contrary, in the case of the dialdehyde derivative of guanosine the amplitude of the CD maximum increased, which was ascribed¹² to the self-assembly resulting in the formation of oligomers.

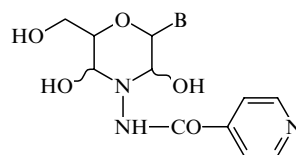
In the solid state, the dialdehyde derivatives of adenosine, guanosine, cytidine and uridine are totally polymerised.¹²



2. Some chemical properties of periodate-oxidised nucleoside derivatives

The chemical properties of periodate-oxidised nucleoside derivatives (*e.g.*, interaction with hydrazines and amines, degradation in alkaline media and reduction of aldehyde groups) are well known.^{4,13} Here, we consider only some model reactions which present interest from the standpoint of affinity modification of proteins.

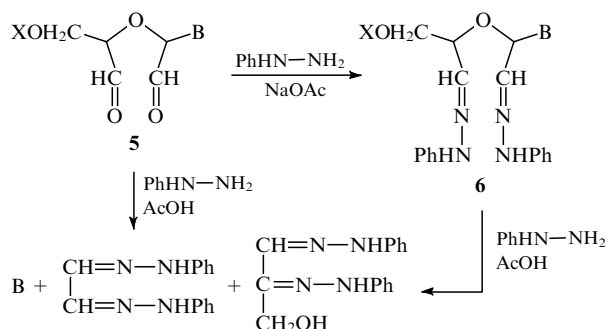
Dialdehyde derivatives of nucleosides and nucleotides readily react with hydrazides, the structure of the reaction products being dependent on the nature of the starting reagents and reaction conditions. The reaction of a nucleoside dialdehyde derivative with isonicotinohydrazide results in the addition of one hydrazide molecule to the nucleoside to give a morpholine derivative.⁴



An analogous product was obtained in the reaction of the above nucleoside derivatives with thiosemicarbazide.⁴

Dialdehyde derivatives of nucleosides and nucleotides **5** react with phenylhydrazine^{13,14} to give bisphenylhydrazones. Addition of an excess of phenylhydrazine results in the degradation of dialdehyde derivatives of ribonucleosides or ribonucleotides (Scheme 2).¹⁴

Scheme 2



X is the phosphate or H.

In the same way derivatives **5** react with semicarbazide.⁴

The products of periodate oxidation of ribonucleosides and ribonucleotides react readily with amines. The reaction of oxidised adenosine 5'-phosphate with methylamine yields a morpholine derivative of adenosine 5'-phosphate.⁴

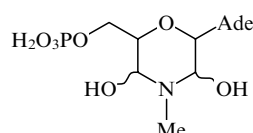
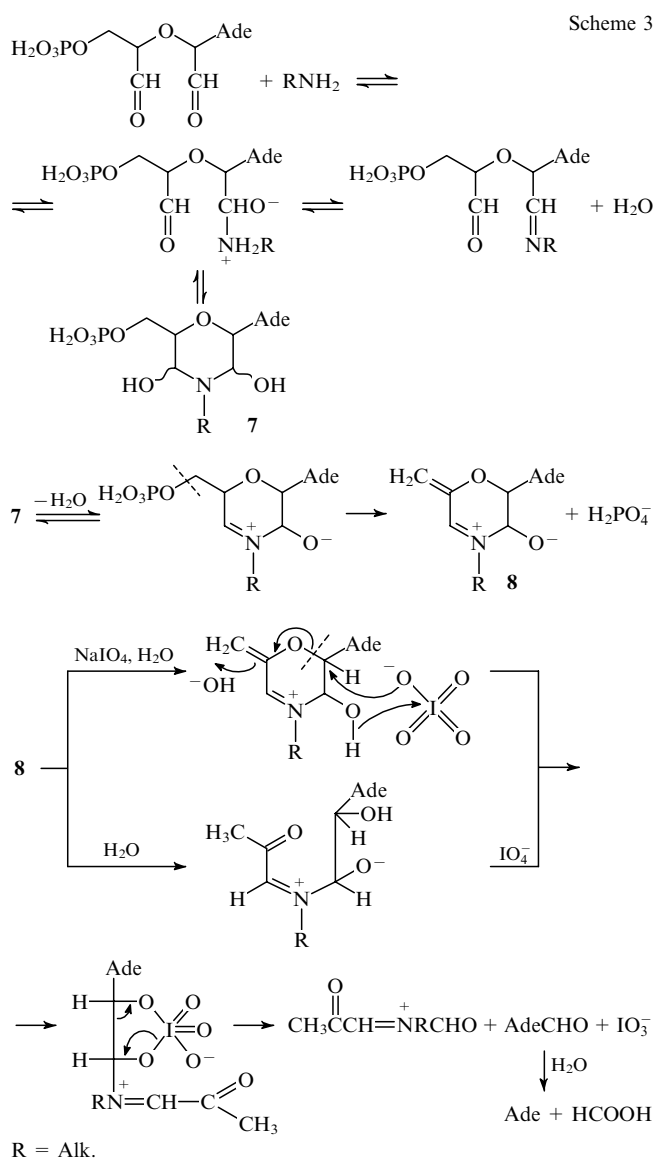


Table 1. Conformational analysis of hydrated forms of oATP (predicted and experimental values of coupling constants).⁹

Com- pound	Position of the OH-groups ^a		Predicted coupling constants (J/ Hz)		Experimental coupl- ing constants (J/ Hz)	
	2'-OH	3'-OH	J _{1',2'}	J _{3',4'}	J _{1',2'}	J _{3',4'}
3a	<i>a</i>	<i>a</i>	< 4	< 4	not detected	
3b	<i>e</i>	<i>e</i>	> 6	> 6	7.5	8.0
3c	<i>e</i>	<i>a</i>	> 6	< 4	8.0	1.7
3d	<i>a</i>	<i>e</i>	< 4	> 6	1.8	8.1
4	—	—	3–6	3–6	4.1	5.0

^a *a* — Axial, *e* — equatorial.

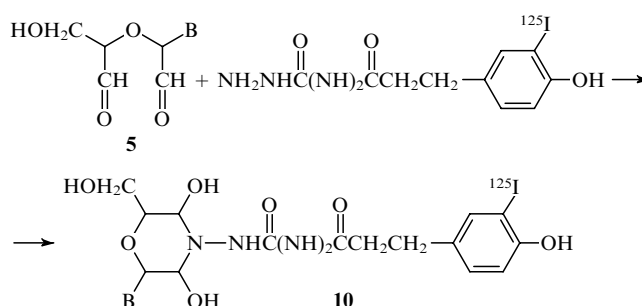


Combined treatment of ribonucleotide dialdehyde derivative with primary amines and an excess of sodium periodate results in its degradation with elimination of the free base (Scheme 3).¹⁵

The products of the reaction of periodate-oxidised adenosine with glycine in the presence and absence of sodium cyanoborohydride (NaBH_3CN) were identified by spectral methods.¹⁶ Putative condensation products are shown in Scheme 4. It was found that 2-adeninyl-4-carboxymethyl-6-hydroxymethylmorpholine (**9**) is the main reaction product.

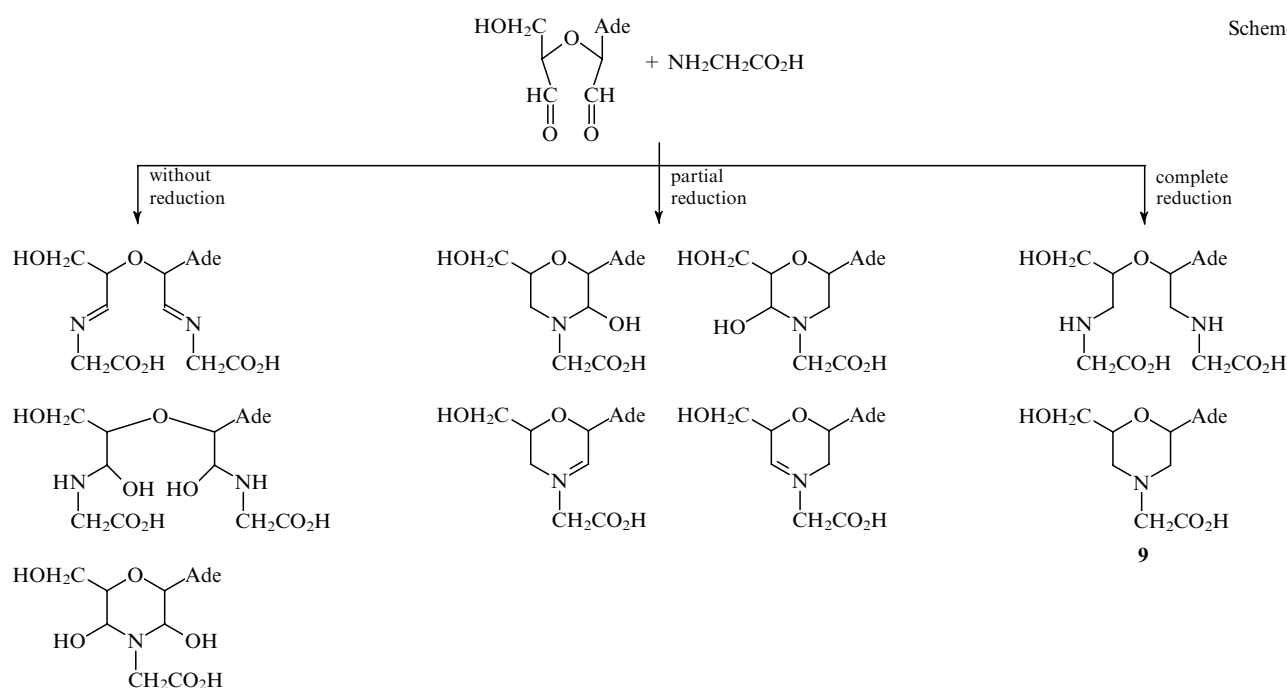
The hydrolytic stability of the condensation products of oxidised adenosine or oATP with diaminoethane following reduction with NaBH_3CN has been studied.¹⁶ It was found that stable reaction products are formed only after reduction with NaBH_3CN .

An ^{125}I -containing reagent, viz., 3-(3-iodo-4-hydroxyphenyl)-propionylcarbohydrazide, has been devised for identification and quantitative determination of periodate-oxidised ribonucleosides and RNA.⁷ Reaction of ribonucleoside-derived dialdehydes with this reagent gives the morpholine derivative **10**, which is stable in neutral and weakly acidic media, but is subjected to rapid degradation in alkaline media and in the presence of ammonia or primary amines.

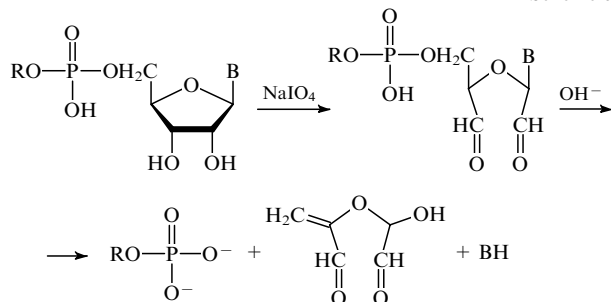


Dialdehydes from nucleoside 5'-phosphates and their derivatives are readily cleaved in alkaline media ($\text{pH} > 7$) with simultaneous scission of the glycosidic bond and β -elimination of the RPO_4^{2-} residue (Scheme 5).^{4,13} Primary amines also efficiently catalyse this reaction.

The aldehyde groups of nucleoside and nucleotide dialdehyde derivatives can be completely or partially reduced depending on

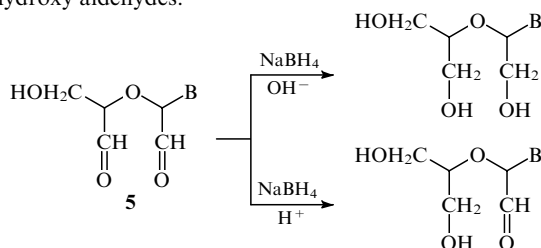


Scheme 5



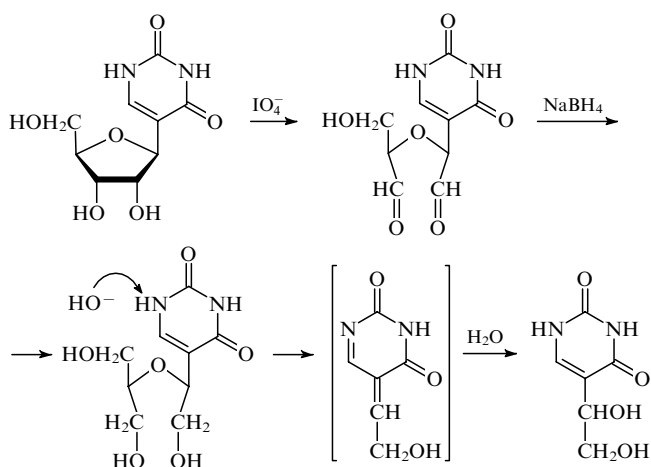
R = H or an oligoribonucleotide.

pH.¹⁴ This results in the formation of the corresponding triols or dihydroxy aldehydes.



Periodate oxidation of pseudouridine gives the corresponding dialdehyde and two unidentified products.⁴ Treatment of the dialdehyde with sodium borohydride and alkali results in 5-(α,β -dihydroxyethyl)uracil (Scheme 6).

Scheme 6



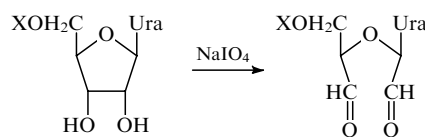
3. Introduction of the dialdehyde fragment into oligonucleotides

a. Introduction of the aldehyde groups into terminal nucleotide residues

The introduction of the dialdehyde fragment into 3'-terminus of RNA or oligoribonucleotides is effected by periodate oxidation. To introduce such a fragment into 3'-terminus of oligodeoxyribonucleotides or 5'-terminus of oligoribo- or oligodeoxyribo-nucleotides, one should first elongate them by attaching a ribonucleotide residue and then subject it to periodate oxidation. The conditions for oxidation of RNA do not practically differ from those for ribonucleosides and their derivatives.¹⁷

Thus the introduction of a dialdehyde fragment into the 3'-terminus of an oligodeoxyribonucleotide was preceded by attachment of a ribonucleotide.¹⁸ To this end, the oligodeoxyribonucleotide was incubated with ribonucleoside 5'-triphosphate in the presence of terminal deoxyribonucleotidyl transferase. In another study,¹⁹ cytidine 3',5'-diphosphate (pCp) was attached to

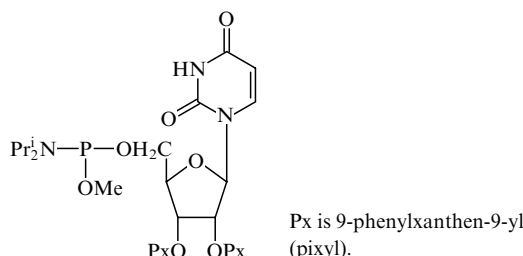
an oligodeoxyribonucleotide using T4 RNA-ligase. Then the 3'-terminal phosphate group of the resulting 5'-(oligodeoxyribonucleotide)-pCp3' was eliminated with alkaline phosphatase after which the 2',3'-*cis*-diol group was oxidised with periodate. The reaction was carried out with oligodeoxyribonucleotides having cytidine^{18–20} or uridine¹⁸ residues at the 3'-end.



X is 5'-(oligodeoxyribonucleotide)-3'.

An equimolar amount or a small excess of sodium periodate was used for the oxidation. The reaction was completed within 30 min at room temperature¹⁸ or within 2 h at 0–4 °C.¹⁹ The excess of sodium periodate was destroyed with ethylene glycol.¹⁸

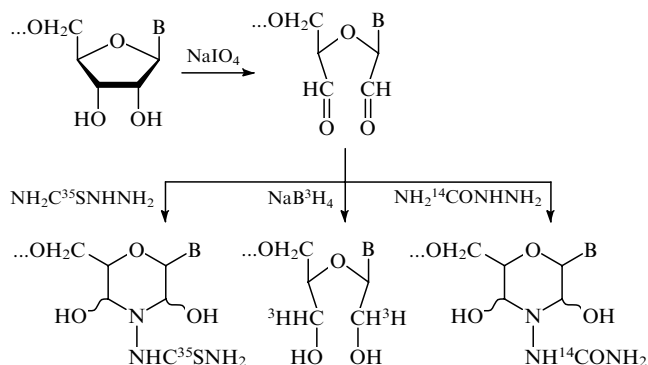
The dialdehyde fragment was also introduced into the 5'-end of an oligodeoxyribonucleotide.²¹ The uridine residue was attached to the oligodeoxyribonucleotide by automated solid-phase, phosphoramidite synthesis using a derivative with protected 2'-OH and 3'-OH groups.



Px is 9-phenylxanthen-9-yl (pixyl).

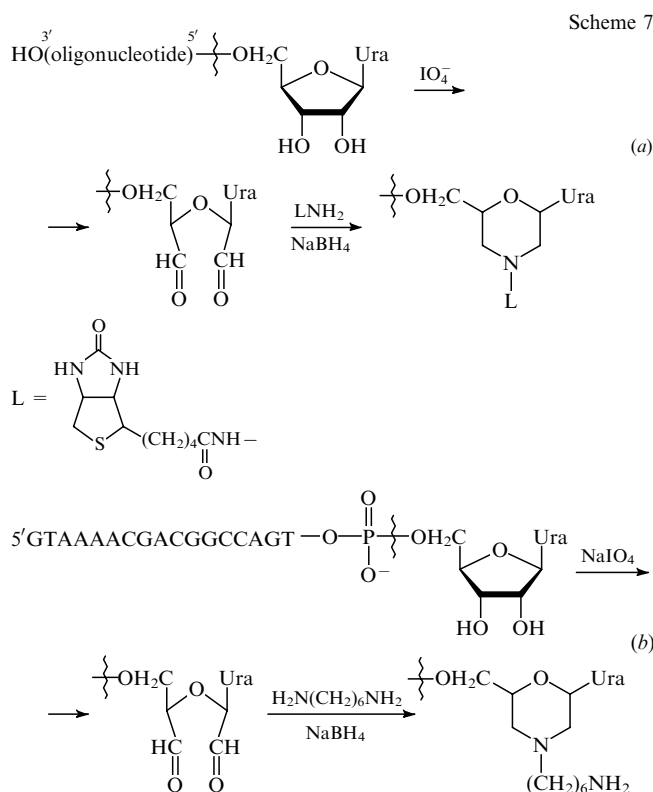
In this case, the 5'-end of the ribonucleoside was attached to the 5'-end of the oligodeoxyribonucleotide. After deprotection, the ribose residue was oxidised with periodate to give a dialdehyde derivative.

Oligodeoxy- and oligoribo-nucleotides containing oxidised ribose residues have found practical applications. Modified oligodeoxyribonucleotides with a 3'-terminal dialdehyde fragment were used for the introduction of the phosphate group into the 3'-end of the oligodeoxyribonucleotide. To this aim, the oligodeoxyribonucleotide with an oxidised 3'-terminal ribonucleoside residue was treated with a primary amine to give oligonucleotide 3'-phosphate, a dialdehyde derivative of ribose and a heterocyclic base.^{18,20} Radioactive labelling of the 3'-terminal nucleoside residue of RNA was based on the reaction of the aldehyde groups with [³⁵S]-thiosemicarbazide, [¹⁴C]-semicarbazide, [³H]-isonicotinohydrazide or [³H]-sodium borohydride.⁴



Dialdehyde derivatives of oligodeoxyribo- or oligoribo-nucleotides can be used for the introduction of a non-radioactive label by treating oligonucleotides with a compound containing an amino group and a non-radioactive label (*e.g.*, with biotin hydrazide, LNH₂) (Scheme 7a)²¹ or by preliminary introduction

of a primary amino group into the oligonucleotide with subsequent addition of a non-radioactive label (Scheme 7b).²²



Ribonucleic acids (and oligoribonucleotides) can be cleaved at the internucleotide bond from the 3'-end of the polyribonucleotide chain by combined treatment with periodate and primary amines or by treatment with sodium periodate in an alkaline medium (see Scheme 5).^{4,13} Such a treatment yields an oligo- or a polynucleotide 'shortened' by one nucleotide unit from the 3'-end. The whole cycle of conversions can be repeated. A base identified by conventional analytical methods is split off from the product of conversion of the original terminal nucleotide unit by treatment with an acid (pH < 3) or an alkali (pH > 11). This property of dialdehyde derivatives of RNA is the basis for a method for determination of nucleotide sequences in short oligoribonucleotides. Stepwise degradation from the 3'-end was used for the analysis of terminal sequences in various tRNA and tobacco mosaic virus RNA.⁴

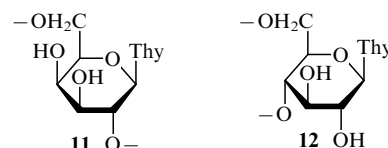
The effects of several basic amino acids and primary amines, pH and temperature on the rate of hydrolysis of the phosphodiester bond in the dialdehyde derivatives of some oligoribonucleotides have been studied.⁴ It was found that the cleavage of the required phosphodiester bond in the presence of lysine, cyclohexylamine or methylamine occurs most efficiently at elevated temperature (45 °C), while that in the presence of aniline is the most efficient at 24 °C (at pH 6–9).⁴ No side reactions were observed at room temperature. A rise in temperature may favour side reactions, such as cleavage of ψ U units and heterocyclic nuclei of other nucleosides.⁴

b. Introduction of the aldehyde groups into any position of the oligonucleotide strand

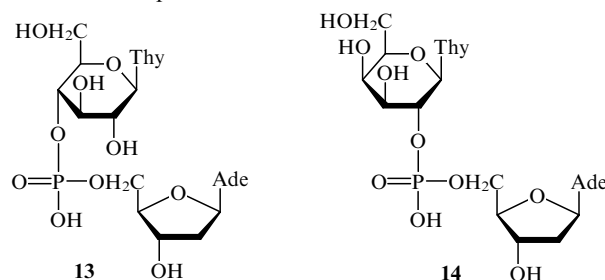
It is not until very recently that the methods for the introduction of aldehyde groups into any position of the oligodeoxyribonucleotide have been developed. Two types of oligonucleotides were used: (1) oligonucleotides containing a hexopyranosyl residue in the oligonucleotide strand^{23–25} instead of a deoxyribose residue and (2) oligonucleotides with an additional ribose residue in the 2'-position of ribose.²⁶ The simplest approach is based on the introduction of galactose residues into the oligonucleotide

strand.²³ Prior to the oligonucleotide synthesis, the hydroxy groups designed for subsequent oxidation are protected with appropriate protective groups. It was suggested²⁴ to introduce both the *cis*-glycol group as a D-galactose residue and the *trans*-glycol group (as a D-glucose residue) into the oligonucleotide.

Preparative syntheses of 1-(3,4-*O*-isopropylidene- β -D-galactopyranosyl)thymine²³ and 1-(2,3-di-*O*-acetyl- β -D-glucopyranosyl)thymine²⁴ from D-galactose and D-glucose, respectively, have been carried out. Then, 14–21-membered oligodeoxyribonucleotides containing a 1-(β -D-glucopyranosyl)thymine (**11**)^{23,25} or a 1-(β -D-galactopyranosyl)thymine (**12**)²⁴ residue at a definite position of the oligonucleotide strand were obtained using standard phosphoramidite procedures.



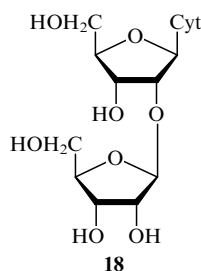
The 1-(β -D-galactopyranosyl)thymine residue was introduced into the oligonucleotide strand through the 2'- and 6'-OH groups, while the 1-(β -D-glucopyranosyl)thymine residue, through the 4'- and 6'-OH groups. The model dinucleoside phosphates, *viz.*, 1-(β -D-glucopyranosyl)thymine-4'-*O*-phosphoryl-(4'-5')-2'-deoxyadenosine (**13**)²⁴ and 1-(β -D-galactopyranosyl)thymine-2'-*O*-phosphoryl-(2'-5')-2'-deoxyadenosine (**14**)²³ were synthesised for detailed studies of periodate oxidation.



The oxidation of the *trans*-diol group in compound **13** with a 10-fold excess of sodium periodate at 20 °C proceeded very slowly; the half-reaction time was 9–10 h.²⁴ The oxidation of compound **14** containing a *cis*-diol group was completed within 1.5 h under these conditions.²³ This circumstance determined the use of oligonucleotides containing a galactopyranose residue for the synthesis of reagents carrying dialdehyde fragments and designed for affinity modification of proteins.

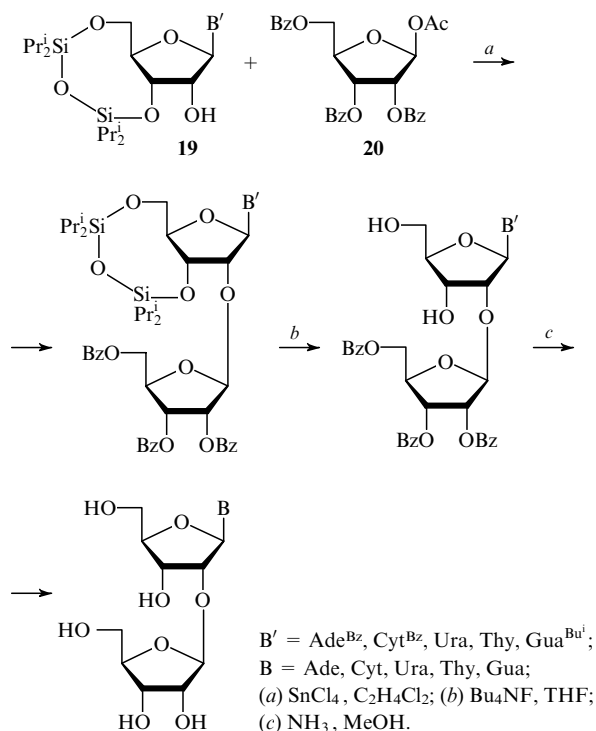
The oxidation of 14-membered galactose-containing oligonucleotides was carried out in 20–200 mM NaIO₄ (1.5–2.5 h, 25–37 °C).²⁵ The yields of the oxidation products (65%–75%) were determined by cleavage of the phosphodiester bond from the 5'-end at the oxidised galactose residue, which was carried out in 10% piperidine (25 min, 95 °C). Under these conditions, oligonucleotides containing a non-oxidised galactose residue remained intact. The structure of oligonucleotides containing an oxidised galactose residue was confirmed by selective cleavage of the phosphodiester bond of the oxidised galactose residue (Fig. 1). This was carried out under conditions of β -elimination analogous to those used for chemical sequencing of RNA.²⁷ The reaction was conducted in 1 M aniline–acetate buffer (pH 4.5) for 15 min at 95 °C.²⁵ In contrast with the oligonucleotides **15**–**17** containing a galactose residue, the 14-membered oligonucleotides containing an oxidised galactose residue (**15***–**17***) in different positions of the oligonucleotide chain were cleaved. Their cleavage gave a ³²P-labelled tetranucleotide (from **15***), a heptanucleotide (from **16***) and an undecanucleotide (from **17***) containing a 3'-phosphate group (see Fig. 1). In control experiments, insignificant degradation of periodate-oxidised oligonucleotides during gel electrophoresis took place.²⁵

Another approach to regiospecific introduction of additional *cis*-diol groups into oligonucleotides is based on the use of nucleoside disaccharide derivatives **18**.^{26, 28, 29}



In these compounds, the *cis*-diol groups are converted into aldehyde groups upon oxidation. Disaccharide nucleosides have been identified in tRNAs as minor components; some antibiotics also involve disaccharide fragments. Synthesis of 2'-*O*-ribofuranosyl nucleosides **18** was carried out in three steps by condensation of 3',5'-*O*-blocked *N*-acylribonucleoside (**19**) and a small excess of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- β -D-ribofuranose (**20**) in the presence of tin tetrachloride^{28, 29} followed by a two-step deprotection. The glycosylation reaction was stereospecific and resulted in the formation of a β -D-glycosidic bond (Scheme 8).

Scheme 8



The periodate oxidation has been studied using a model dinucleoside phosphate **21** containing the disaccharide residue.²⁹

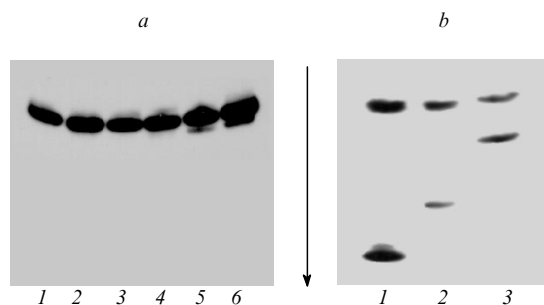
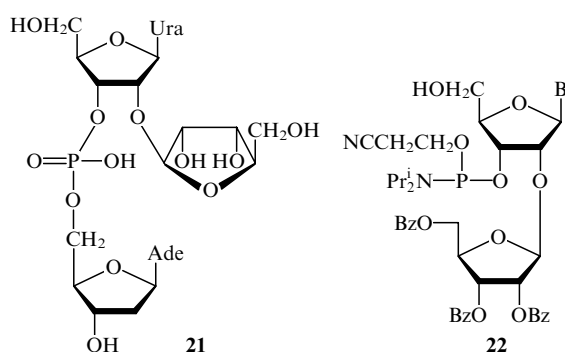


Figure 1. Gel-electrophoretic analysis of stability of the oligonucleotides 5'-GCCAXCCTGGCTCT3' (**15**, **15***), 5'-GCCAACCCXGGCTCT3' (**16**, **16***) and 5'-GCCAACCTGGCXCT3' (**17**, **17***) containing a nonoxidised (**15**–**17**) or oxidised (**15***–**17***) 1-(β -D-galactopyranosyl)thymine residue (X).

(a) Incubation of the oligonucleotides containing a galactose residue: (1, 3, 5) — in aniline–acetate buffer, pH 4.5, 95 °C, 15 min; (2, 4, 6) — in 40 mM Tris–HCl buffer, pH 7.9, 5 mM dithiothreitol, 50 mM NaCl, 15 mM MgCl_2 , 95 °C, 25 min; (1, 2) oligonucleotide **15**; (3, 4) oligonucleotide **16**; (5, 6) oligonucleotide **17**.

(b) Incubation of the oligonucleotides containing an oxidised galactose residue in aniline–acetate buffer, pH 4.5, 95 °C, 15 min; (1) oligonucleotide **15***; (2) oligonucleotide **16***; (3) oligonucleotide **17***.

The model dinucleoside phosphate was oxidised with sodium periodate within 10 min at 20 °C. 14–22-Membered oligonucleotides containing 2'-*O*-ribofuranosylcytidine residues were synthesised using the phosphoramidite method with modified phosphoroamidite (compound **22**).²⁶

DNA duplexes used for affinity modification of some DNA-binding proteins have been formed on the basis of oligonucleotides containing dialdehyde fragments at definite positions of the nucleotide strand.

III. Affinity modification of proteins and polypeptides with periodate-oxidised derivatives of nucleic acids

Periodate-oxidised derivatives of nucleotides containing dialdehyde fragments were used for affinity modification of enzymes that use nucleoside triphosphates as cofactors or substrates and transcription factors. In addition, conjugates of 13- and 15-membered oligodeoxyribonucleotides containing 3'-terminal aldehyde groups with poly(L-Lys) have been synthesised to study the regulation of gene expression.¹⁹ 14- and 22-Membered DNA duplexes with internal dialdehyde fragments were used for covalent cross-linking with restriction endonucleases and methylases (*Eco*RII and *Mva*I²⁵) and RNA polymerase of bacteriophage T7.³⁰

1. Covalent binding of proteins with nucleotide dialdehyde derivatives

The fundamental process that satisfies the bioenergetic requirements of living organisms is versatile for practically all the objects of the living nature. It consists in the hydrolysis of one of pyrophosphate bonds in adenosine 5'-triphosphate (ATP) or, less often, guanosine 5'-triphosphate (GTP). Numerous biochemical processes occur by virtue of energy released upon hydrolysis of nucleoside triphosphates.

2',3'-Dialdehyde derivatives of ATP, ADP, GTP and GDP (oATP, oADP, oGTP and oGDP, respectively) were used for affinity modification of some enzymes, mainly for the study of their cofactor-binding or active sites.

The ATP dialdehyde derivative was cross-linked to mitochondrial ATPase and histone kinase in order to study the active sites of these enzymes.^{31, 32} Pyruvate carboxylase, acetyl-CoA carbox-

ylase and NAD-dependent isocitrate dehydrogenase require ATP for their cofactor function (the catalytic reaction utilises the energy of ATP hydrolysis). These enzymes have several substrates and cofactors. oATP and oADP were used for covalent binding of these enzymes with the allosteric site as well as for the analysis of interaction of this allosteric site with other sites.^{8,33,34} The phosphate group of ATP is added to the 5-ribulose phosphate fragment by phosphoribulokinase to give ribulose-1,5-diphosphate. oATP was used for affinity modification of the binding site in one of phosphoribulokinase substrates.³⁵

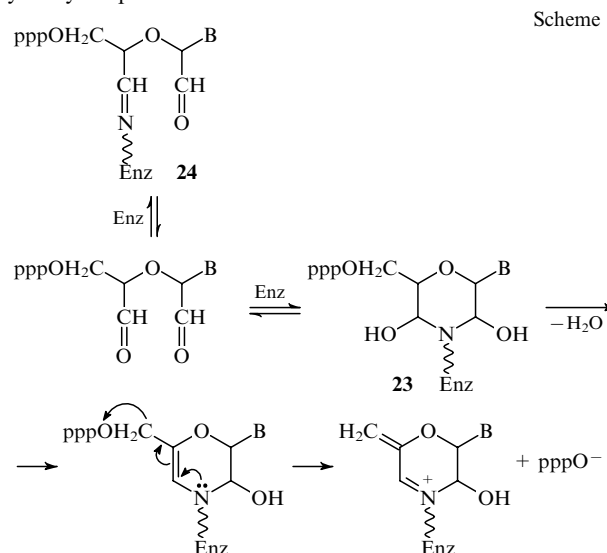
Binding of aminoacyl-tRNA with ribosomes requires the elongation factor EF-Tu. This reaction is accompanied by hydrolysis of GTP. GTP 2',3'-dialdehyde derivative was covalently linked to the elongation factor EF-Tu in order to identify the binding site for the cofactor.³⁶ Functioning of a human protein c-H-ras p21 also is accompanied by GTP hydrolysis. This protein, which is localised in the cytoplasmic membrane, accepts external signals stimulating cell growth and transmits them to target proteins localised inside the cell, thus promoting its growth and division. In order to investigate the interaction of GTP and GDP with this protein in more detail the latter was subjected to affinity modification with periodate-oxidised GTP and GDP derivatives.³⁷ A periodate-oxidised derivative of 1,N⁶-ethenoadenosine-5'-monophosphate (oEAMP) was used for covalent addition to alkaline phosphatase from human placenta.³⁸

Depending on the object of investigation, proteins and periodate-oxidised components of NA are used for cross-linking in various ratios (Table 2). The time of incubation of proteins with the monomeric analogues of NA containing aldehyde groups varied, on the average, from 5 min to 2 h. In kinetic studies of the oADP interaction with isocitrate dehydrogenase, the incubation time varied from 1 to 8 h.³⁴ The kinetic curve of inactivation of the tetrameric enzyme was biphasic: the fast phase is coupled with covalent binding of oADP with one enzyme subunit, and subsequent slow phase consists in covalent binding of oADP with the remaining three subunits of the enzyme and results in its complete inactivation.

Traditionally, NA components that contain a radioactive label (¹⁴C, ³H or ³²P) were used for covalent binding with proteins. The degree of affinity modification was estimated from the radioactivity after electrophoresis in 8%–10% polyacrylamide gel

containing 0.1% SDS,³¹ gel filtration^{19,32} or washing of filters containing reaction mixtures.³⁶ The degree of affinity modification of pyruvate carboxylase with various concentrations of oATP was determined from the residual activity of the enzyme.⁸ The conditions for the preparation of the covalent complexes and subsequent specific cleavage of the covalently bound proteins are listed in Table 2.

Let us consider the mechanism of reaction of the NH₂ groups of proteins with dialdehyde derivatives of monomeric components of NA proposed by Gregory and Kaiser³⁹ (Scheme 9). As can be seen from Scheme 9, the reaction of the NH₂ group of a protein with a periodate-oxidised nucleotide derivative yields either a dihydroxymorpholine derivative **23** or a Schiff's base **24**.



Enz is enzyme.

It was pointed out^{31,33–35} that stable morpholine derivatives of enzymes with oATP or oADP are formed without reduction. Following addition of an oxidised derivative of a nucleotide to the enzyme, splitting of the tri- or di-phosphate anion upon β-elimination occurs faster than in the absence of the enzyme due to the involvement of the electron pair of the nitrogen atom of the

Table 2. Conditions for the preparation of covalent complexes of proteins with periodate-oxidised derivatives of mononucleotides and for specific cleavage of cross-linked proteins.

Protein or polypeptide (concentration)	Modified analogue of NA (concentration)	Reducing agent	Amount of the reducing agent	Duration of reduction / min	Enzymes or chemical reagents for specific cleavage of the protein fragment	Ref.
Mitochondrial adenosine triphosphatase (100 µg ml ⁻¹)	Mg-oATP (9.4 or 2.5 µmol)	—	—	—	—	31
NAD-dependent isocitrate dehydrogenase (0.4–0.5 mg ml ⁻¹)	oADP in the presence of MnSO ₄ (0.2 mmol litre ⁻¹)	—	—	—	pronase, carboxypeptidase A, carboxypeptidase B, aminopeptidase	34
Pyruvate carboxylase (10–20 un ml ⁻¹ or 13.3 un mg ⁻¹)	Mg-oATP (2 mmol litre ⁻¹)	NaBH ₄	10-fold excess with respect to oATP	35	trypsin, chymotrypsin, pronase, α-aminopeptidase	8
Histone kinase	20-fold excess of oATP relative to the enzyme	NaBH ₄	20-fold excess with respect to oATP	60	trypsin	32
Elongation factor from <i>T. thermophilus</i> (20 mmol litre ⁻¹)	ATP ^a (10 mmol litre ⁻¹)	NaBH ₃ CN	20 mmol litre ⁻¹	1	BrCN	36

^a The oxidation with sodium periodate was carried out after incubation of the elongation factor EF-Tu and ATP (incubation time 10 min, oxidation time 1 min).

morpholine derivative in the splitting of the tri(di)phosphate anion (see Scheme 9).

According to other reports,^{8,32,36} the reduction of intermediate products (a dihydroxymorpholine derivative or a Schiff's base) with borohydrides (NaBH_4 or NaBH_3CN) is necessary for stable covalent binding of the enzyme with the nucleotide.

So what is the information that one may derive from cross-linking of proteins with periodate-oxidised mononucleotides? In the first place, specific cleavage of a protein covalently bound with a nucleotide by enzymes or by chemical reagents provides information about the location of amino acids or a protein fragment that form the active or cofactor-binding site of the enzyme. Enzymic hydrolysis is conventionally carried out with trypsin or other specific proteases, while chemical cleavage of proteins at the methionine residues is performed with BrCN (see Table 2).

Enzymic hydrolysis of a modified and reduced conjugate yields a small peptide covalently bound with the nucleotide and then the amino acid sequence of the peptide is determined. To this end, the peptide cross-linked to a radiolabelled oATP is subjected to acid hydrolysis, dansylation and separation by two-dimensional gel electrophoresis followed by identification of dansyl amino acids.³² The mobility of the radiolabelled dansylated derivative coincided with that of the synthetic dansylated derivative of the covalent adduct of lysine with oATP. The amino acid sequence of the peptide cross-linked with oGDP or oGTP was determined using the Edman degradation.³⁷

The lysine residues involved in the covalent binding with periodate-oxidised nucleotide derivatives were identified after proteolysis of products of cross-linking of oATP to histone kinase³² and pyruvate carboxylase⁸ as well as of oGDP and oGTP to the protein c-H-ras p21.³⁷ It was suggested that the lysine residues present in the active or cofactor-binding sites of enzymes are responsible for the binding of the phosphate groups of ATP due to the basic properties of the ϵ -amino group of lysine.

As it has been noted above, treatment of the protein–nucleotide conjugate with BrCN results in the cleavage of the covalently bound protein at the methionine residues (Met). Since these residues are rare in occurrence, large protein fragments are usually formed. This method allowed one to demonstrate that the GTP-binding domain of the elongation factor Tu is localised in the N-terminal part of the protein.³⁶

Affinity modification of active or cofactor-binding sites of pyruvate carboxylase,⁸ mitochondrial ATPase,³¹ isocitrate dehydrogenase,³⁴ phosphoribulokinase³⁵ and alkaline phosphatase from human placenta³⁸ with ATP, ADP or ϵAMP 2',3'-dialdehyde derivatives led to the inhibition of these enzymes. There are several nucleotide analogues that contain a reactive group and can be used for covalent linking to nucleotide-binding sites of proteins. However, only some of them are inhibitors that can specifically bind with the active site. Site-directed modification should meet two criteria. Let us consider these criteria with oATP as an example. First, ATP must protect the protein from inactivation with oATP. Second, oATP must serve as a substrate for this enzyme. Wherever these two criteria were met, it was demonstrated that oATP is a site-directed inhibitor of mitochondrial ATPase³¹ and phosphoribulokinase,³⁴ whereas o ϵAMP is a site-directed inhibitor of alkaline phosphatase from human placenta.³⁸ The dependence of inactivation of multisubunit proteins, e.g., pyruvate carboxylase⁸ and NAD-dependent isocitrate dehydrogenase,³⁵ on the concentration of oATP or oADP and the effects of other cofactors and substrates of enzymes (multisubunit proteins have several substrates and cofactors) on the affinity modification of these proteins with oATP or oADP have been studied in a number of papers. The affinity modification of these proteins with dialdehyde derivatives of nucleotides allowed one to suggest the relative arrangement of the active and cofactor-binding sites of the enzymes.^{8,35}

Thus, in some cases affinity modification of proteins with periodate-oxidised derivatives of nucleotides has made it possible to establish the active and cofactor-binding sites of enzymes that

are covalently bound with periodate-oxidised derivatives of mononucleotides and to suggest the location of the oATP-(cofactor-) binding sites in multisubunit proteins.

2. Affinity modification of proteins and polypeptides with oligonucleotides containing dialdehyde fragments

Methods for cross-linking of histones to DNA containing randomly introduced aldehyde groups were developed in the 1980's by Mirzabekov *et al.* in structural studies of chromatin.^{40–45} The aldehyde groups could be introduced into DNA in several ways. One of them is based on acid treatment of DNA, which results in its depurination and concomitant liberation of the aldehyde group in the sugar moiety. However, this approach can hardly be applied to covalent cross-linking of DNA to proteins, because low pH values prevent the formation of DNA–protein complexes. Yet another method for the random introduction of the aldehyde groups into DNA strands is based on methylation of DNA purines with dimethyl sulfate and subsequent depurination.⁴⁰ In order to identify contacts of DNA with histones, cell nuclei were treated with dimethyl sulfate, then depurination was carried out in a neutral medium followed by reduction with sodium borohydride.^{41–43} Such a treatment resulted in the covalent binding of the aldehyde groups of DNA with the histone amino acid residues interacting with DNA. The same approach was used to establish DNA–protein contacts in complexes of RNA polymerase with the promoter *lacUV5*,⁴⁶ of *lac* repressor with DNA⁴⁷ and in the cowpox virus.⁴⁸

The interaction of DNA duplexes and oligonucleotides containing dialdehyde fragments with proteins and polypeptides has been studied recently.^{19,25,30} The aldehyde groups were introduced regiospecifically both into terminal and nonterminal positions of the oligonucleotide strand. The possibility to introduce aldehyde groups into any position of the oligonucleotide strand has made it possible to investigate template-driven enzymes (RNA polymerases) and enzymes recognising specific sequences in DNA (DNA restriction–modification enzymes). The obvious advantage of dialdehyde reagents is their specificity with respect to adjacent lysine ϵ -amino groups. Special mention should be also made of the ability of these reagents to form stable covalent complexes with the protein after their reduction. The proximity of definite sugar residues of DNA to the lysine residues of the active or DNA-binding sites of proteins can be established by means of introduction of the aldehyde groups into a definite sugar residue of the DNA duplex and subsequent cross-linking of the modified duplex to the proteins.

The specificity of the dialdehyde fragment with respect to the lysine amino group was used for efficient covalent binding of poly(L-Lys) with two aldehyde groups I in the 3'-terminus of an oligonucleotide.¹⁹

Probing of the functional sites of the DNA restriction-modification enzymes *EcoRII* and *MvaI* which recognise the sequence



in DNA, was carried out.²⁵ The restriction endonuclease *EcoRII* (*R.EcoRII*) cleaves the phosphodiester bonds at the positions indicated by the arrows. The DNA-methyltransferases *EcoRII* (*M.EcoRII*) and *MvaI* (*M.MvaI*) methylate the inner cytosine residues at C(5) (*M.EcoRII*) or at N(4) (*M.MvaI*). The cross-linking of these enzymes to DNA duplexes (substrate analogues) that contain an oxidised 1-(β -D-galactopyranosyl)thymine residue was carried out.²⁵ The modified sugar residue was introduced either into the recognition site (duplex **25***) or into the flanking nucleotide sequences (duplexes **26*** and **27***).



Table 3. Conditions for the preparation of covalent complexes of DNA-binding proteins with oligonucleotides containing dialdehyde fragments.

Protein or polypeptide (concentration)	Modified analogue of NA (concentration)	Reducing agent	Amount of the reducing agent	Duration of reduction / min	Yield of cross-linked products (%)	Ref.
Poly(L-Lys) (80 nmol)	oligodeoxyribonucleotides: 5'CATTGTTGATTACTGTC*3', 5'AACGAGGCACATTC*3' (40 nmol), where C* is the oxidised cytidine residue	NaBH ₃ CN	10 µmol	120	25–30	19
<i>Eco</i> RII or <i>Mva</i> I methylases (<i>M.Eco</i> RII — 3.16 µmol litre ⁻¹ ; <i>M.Mva</i> I — 3.3 µmol litre ⁻¹)	14-membered DNA duplex containing an oxidised galactose residue (0.23 µmol litre ⁻¹) (duplexes 25* and 27*)	NaBH ₄	3.75 mmol litre ⁻¹	40	9–20	25
Restriction endonuclease <i>Eco</i> RII (3.16 µmol litre ⁻¹)	14-membered DNA duplex containing an oxidised galactose residue (0.23 µmol litre ⁻¹) (duplex 27*)	NaBH ₄	3.75 mmol litre ⁻¹	40	4	25
RNA polymerase of bacteriophage T7 (0.1–0.5 µmol litre ⁻¹)	22-membered DNA duplex containing an oxidised 2'- <i>O</i> -ribofuranosylcytidine residue (0.1–0.5 µmol litre ⁻¹)	NaBH ₄	0.05 µmol litre ⁻¹	60	—	30

cross-linked product did not depend on the presence of the cofactor (Mg²⁺ ions). This led the authors²⁵ to assume that cross-linking of DNA duplexes containing aldehyde groups to *R.Eco*RII occurs not at the active site.

None of the DNA duplexes containing an oxidised 2'-*O*-ribofuranosylcytidine unit was able to cause affinity modification of T7 RNA polymerase.³⁰ However, covalent cross-linking of the DNA duplex containing an oxidised 2'-*O*-ribofuranosylcytidine residue at position +2 of the consensus promoter to the mutant form of T7 RNA polymerase (Tyr639 → Lys) did take place. In wild type enzyme, Tyr639 is apparently involved in the NTP binding and should be located in close proximity to the initiation site, which suggests that Lys639 is the residue that was subjected to modification.³⁰

The first results of affinity modification of DNA-binding proteins are important for determining specific DNA–protein contacts and for studying the structure of active centres of enzymes as well as for elucidating the mechanisms of catalysis by restriction-modification enzymes and RNA polymerases.

IV. Conclusion

Introduction of reactive aldehyde groups into NA makes it possible to use them for attachment of fluorescent or any other label. In addition, oligonucleotides containing dialdehyde fragments are convenient for the synthesis of antisense oligonucleotides. Affinity modification of proteins with DNA duplexes containing regiospecifically introduced aldehyde groups proceeds with sufficiently high yields and results in stable covalent bonds. The results of cross-linking of this type of reagents to proteins allow one to recommend them as an efficient and flexible tool in the study of a broad range of DNA–protein interactions.

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Dioxiranes: from oxidative transformations to chemiluminescence

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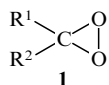
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Abstract. Experimental data on the chemistry of a new class of highly effective oxidation reagents, dioxiranes, are summarised. The main methods used to generate dioxiranes and reactions in which dioxiranes have been proposed as intermediates are considered. The full notion about an important property of dioxiranes, *i.e.* the ability to oxidise rapidly, selectively and under mild conditions various classes of organic compounds (alkanes, alkenes, compounds containing heteroatoms, organometallic substrates, *etc.*) is given. Various aspects and mechanisms of these reactions are discussed. The attention is focused on the analysis of mechanisms of dioxirane decomposition in the absence of oxidisable substrates. One of the most attractive aspects of the dioxirane chemistry, chemiluminescence, is considered (the mechanisms of the generation of excited products during both thermal and catalytic decomposition and upon photochemical activation are discussed). The bibliography includes 401 references.

I. Introduction

The chemistry of three-membered cyclic peroxides, dioxiranes **1**, has swiftly developed during the last twelve years.



In 1985, when successful synthesis of a number of 'isolated alkyl dioxiranes'† had been reported,¹ these compounds became available for wide employment. Since then, they have been in the

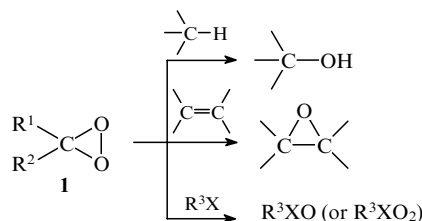
† From here on, the term 'isolated dioxirane' implies a solution of dioxirane in the corresponding ketone or in a solvent isolated from the reaction mixture. This term, which is generally accepted in the literature and reflects features of the peroxide method for the synthesis of dioxiranes (see Section II), is used in order to distinguish the cases where isolated dioxiranes are used from those when dioxiranes are generated *in situ* and are not isolated from the reaction mixture.

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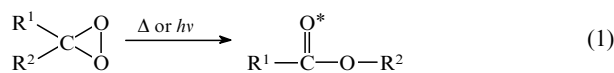
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centre of chemists' attention and the number of publications devoted to them has constantly increased. What is the reason for this interest? The main cause is the exceptionally high reactivity of these compounds, which is remarkably combined with high selectivity of oxidation. The most typical reactions of dioxiranes include oxidative functionalisation of alkanes, alkenes and their functionally substituted derivatives containing heteroatoms X

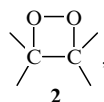


It is this fact that attracts the attention of chemists engaged in organic synthesis to oxiranes. The most often used derivatives are dimethyldioxirane **1a** and methyl(trifluoromethyl)dioxirane **1b**; the oxidative properties of these compounds have been the subject of numerous publications including several excellent reviews,^{2–9} devoted mainly to synthetic aspects.

However, this does not exhaust the properties of dioxiranes. Chemiluminescence (CL) is another, equally important feature of these compounds. A fairly attractive feature of dioxiranes, found recently, is that they are capable of forming products in electronically excited states upon both thermal decomposition and photochemical activation.^{6, 10–17}



The research along this line started only recently, most of the studies being performed by the authors of this review. Even these few studies allow one to appreciate the great opportunities and prospects opened for researchers in the wonderful world of chemiluminescence of dioxiranes. Although it is difficult to predict the extent to which dioxiranes would be able to compete with their chemical relatives, 1,2-dioxetanes **2**^{18–22}



it can be claimed with confidence that these three-membered cyclic peroxides have already occupied a special place in the world of shining reactions.

The great interest in dioxiranes is also due to the fact that they represent an isomeric form of carbonyl oxides $R^1R^2C^+ - O - O^-$ (**3**), which are oxidants and important reactive intermediates in many oxidative processes.^{23–32} Despite the fact that the behaviours of dioxiranes and carbonyl oxides are substantially different, both should be taken into account in consideration of the mechanisms of some oxidation processes. Moreover, photocyclisation of carbonyl oxides **3** is the main method used to synthesise dioxiranes **1** in a matrix.³³

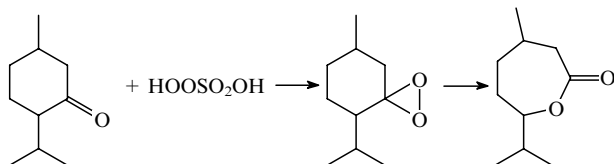
The mechanism of decomposition of dioxiranes in the absence of easily oxidisable partners also presents interest. The mechanism of their reactions with alkanes, which has unexpectedly become the object of sharp debates, is equally interesting (see, for example, Refs 34–39).

There are grounds for believing that dioxiranes can be formed in the upper atmosphere,^{1, 3, 40} upon interaction of alkenes with ozone.^{41–44} Study of gas-phase reactions of dioxiranes with polyaromatic hydrocarbons (PAH)^{3, 45–47} including those yielding carcinogens (which can affect the environment) could provide deeper insight into the processes occurring in the atmosphere.

This review covers these and many other aspects. We hope that it would present interest not only for organic chemists but also for specialists in physical chemistry.

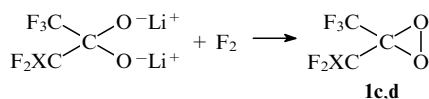
II. Synthesis and spectral characteristics of dioxiranes

The history of the dioxirane chemistry covers almost a century. In 1899, Baeyer and Villiger,⁴⁸ who studied the reaction of menthone with monoperoxydisulfuric acid, postulated that the formation of the corresponding lactone is preceded by the formation of a cyclic oxygen-containing intermediate, dioxirane.



Now this reaction is named after the authors. They were the first to introduce the term 'dioxirane' into scientific literature. The next mention of dioxiranes dates back to 1910, when Harries⁴⁹ suggested that decomposition of 1,2,3-trioxolanes, resulting from ozonisation of alkenes, affords carbonyl oxide and a peroxide and ascribed a dioxirane structure to the latter product.

Only many years after these two publications had appeared, was the first dioxirane really prepared and characterised. This was done by Talbot and Thompson⁵⁰ in 1972. The authors reported on the synthesis of perfluorodimethyldioxirane **1c** and chlorodifluoromethyl(trifluoromethyl)dioxirane **1d** by oxidation of the corresponding dialkoxides with fluorine. However, this method has not been further developed.



X = F (**c**), Cl (**d**).

The dioxiranes **1c** and **1d** were isolated using low-temperature gas chromatography; they were coloured pale yellow both in the liquid and solid states (the absorption maximum of the dioxirane **1c** lies at $\lambda = 306$ nm).⁵⁰ The compound **1c** was described as unstable and explosive.⁵⁰

At present, two main lines in the dioxirane synthesis can be distinguished: (1) the peroxide method, which is used most often and successfully to prepare dioxiranes and (2) non-peroxide

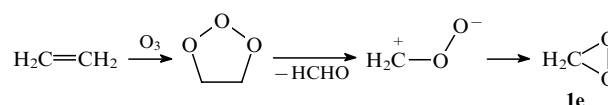
methods (e.g., ozonolysis of hydrocarbons, photooxidation of diazo compounds in a matrix and some other methods.)

1. Non-peroxide methods for the synthesis of dioxiranes

When considering the known non-peroxide methods for the generation of dioxiranes, we dwelt not only on the studies the authors of which succeeded in isolating dioxiranes and obtaining their spectral characteristics but also on those in which dioxiranes were only suggested as possible intermediates (the latter type is represented by a few examples).

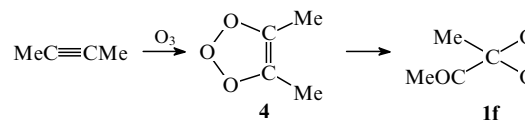
a. Ozonolysis of saturated and unsaturated compounds

In 1977 two groups of researchers working independently^{41–44} presented convincing experimental evidence (obtained by microwave spectroscopy and mass spectrometry) for the formation of the simplest dioxirane **1e** in the gas-phase ozonisation (-130 to -75 °C) of ethylene. Dioxirane **1e** was also detected among the products of ozonolysis of propene, vinyl fluoride and but-1-ene.

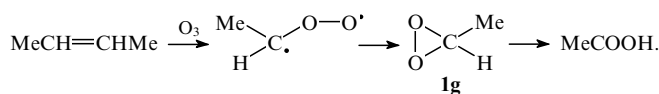


The microwave spectroscopy data showed that dioxirane **1e** has a shorter C–C bond (1.3878 Å) and a longer O–O bond (1.5155 Å) than ethylene ozonide, in which the corresponding bond lengths are 1.416 and 1.461 Å.

A large variety of reactions of ozonisation of unsaturated substrates involving dioxiranes have been reported.^{51–59} Thus Keay and Hamilton^{51, 52} carried out ozonisation of but-2-yne in CH_2Cl_2 (-70 °C). By varying the temperature and adding portions of methanol to the solvent, the researchers isolated three different products, capable of epoxidising alkenes; the first compound was identified as the peroxy acid $MeC(O)OOH$, the second one was identified as trioxolene **4**, and the structure of dioxirane **1f** was attributed to the third compound.



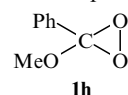
Pryor *et al.*⁵³ carried out a similar reaction in the presence of nitron as a spin trap; they detected the adduct of the nitron with the acetyl radical formed from the dioxirane **1f**. Bufalini *et al.*⁵⁴ interpreted the formation of acetic acid in the ozonisation of but-2-ene as being due to the following sequence of reactions:



Eastman *et al.*^{55, 56} explained in a similar way the formation of methyl acetate and an ester of formic acid in the gas-phase ozonisation of tetramethylethylene and cyclohexene.

O'Neal and Blumstein⁵⁷ proposed a general mechanism of gas-phase ozonolysis based on participation of the biradical form of carbonyl oxide and the subsequent transformation of the biradical into dioxirane. Conversely, Vaccani *et al.*⁵⁸ suggested direct formation of dioxirane from 1,2,3-trioxolane during the gas-phase reaction of ozone with vinyl chloride.

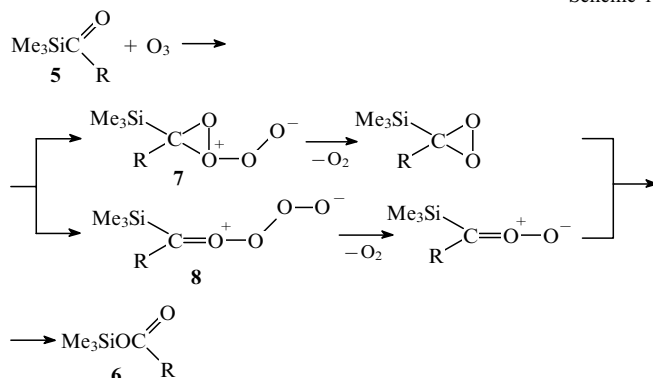
The liquid-phase ozonisation of 1,2-dimethoxy-1,2-diphenylethene gave (methoxy)phenyldioxirane **1h**, which was studied by ¹³C NMR spectroscopy.⁵⁹



In several studies, dioxiranes have been considered as intermediates in ozonisation of saturated compounds. Thus ozonolysis of ketones **5** occurs presumably⁶⁰ via an attack by ozone on the

carbonyl group of **5** to give compounds **7** or **8**, which eliminate an oxygen molecule being thus converted into either carbonyl oxide or dioxirane (Scheme 1).

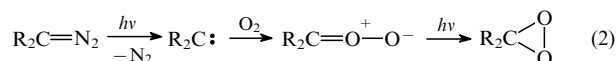
Scheme 1



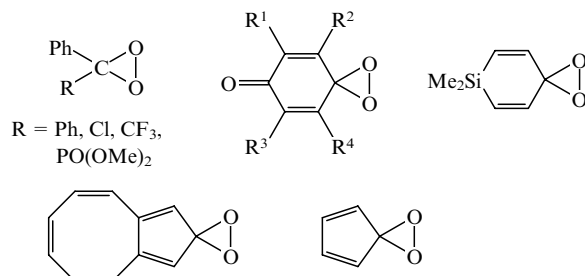
It has been suggested⁶¹ that the formation of anhydrides in the ozonisation of some α -diketones occurs by a similar scheme.

b. Cyclisation of carbonyl oxide to dioxirane in a matrix

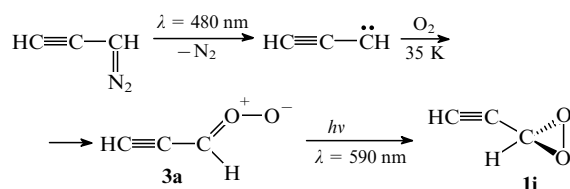
Yet another aspect of the dioxirane chemistry is related to low-temperature photochemistry. In a series of studies,^{28, 33, 62–72} a new pathway to dioxiranes has been found, which is based on low-temperature irradiation of carbonyl oxides in an argon matrix.



This method was used to prepare diphenyldioxirane, chloro(phenyl)dioxirane, phenyl(trifluoromethyl)dioxirane, a series of substituted dioxiranes based on quinone *O*-oxides, silicon-containing dioxiranes, *etc.*^{28, 33, 62, 65–77}

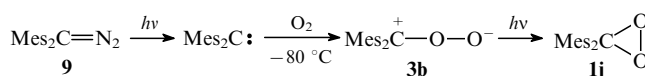


Evidence has been obtained for the formation of unsubstituted dioxirane **1e** in the oxidation of carbene $:CH_2$ in an oxygen-containing matrix.⁷⁸ Photocyclisation of propynal *O*-oxide **3a** to give propargyldioxirane **1i** has been reported.⁷⁹



Despite the fact that photooxidation of diazo compounds made it possible to detect several dioxiranes, this method for their synthesis has not found wide application because it requires thorough control of the photolysis conditions, temperature and the solvent (in order to avoid side reactions of carbenes) and because carbene and carbonyl oxide are unstable. The lifetimes of these species have to be sufficiently long and, in addition, photodecomposition of the diazo compound and photocyclisation of carbonyl oxide have to occur at those wavelengths where the dioxirane is stable in order to avoid its rearrangement into an ester. Until recently, dioxiranes obtained in this way could be studied only at low temperatures.

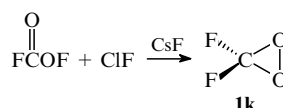
However, in 1994, Sander *et al.*⁸⁰ succeeded in preparing the relatively stable dimesityldioxirane **1j** at quite plausible temperatures (about -80°C). This compound was synthesised from dimesityldiazomethane **9** via the corresponding carbonyl oxide **3b**, the lifetime of which is several orders of magnitude longer than that of diphenylcarbonyl oxide.



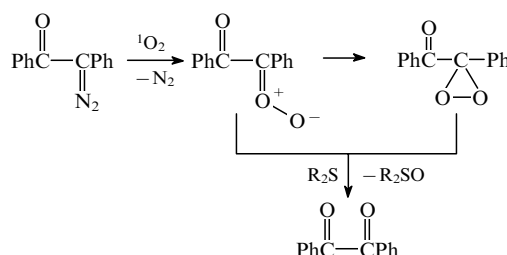
An advantage of this system is that the dioxirane **1j** does not absorb in the spectral range needed to synthesise it. Later, Sander *et al.*⁸¹ proposed several convenient procedures for the synthesis of dimesityldioxirane **1j**, resulting in the formation of this compound both in solution and in the crystalline state (melting point $62–64^\circ\text{C}$).

c. Formation of dioxiranes in other peroxide systems

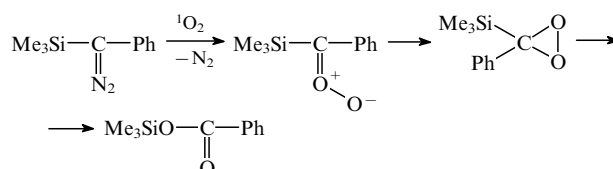
Among various non-peroxide methods for the synthesis of dioxiranes, studies by Russo and DesMarteau^{82, 83} deserve attention. They prepared difluorodioxirane **1k**, which is stable in the gas phase at room temperature over a period of several days, and characterised it by IR spectroscopy (the boiling point of the dioxirane **1k** is -80 to -90°C , and the melting point is $< -160^\circ\text{C}$).



In some studies dioxiranes are considered to be possible intermediates in various chemical reactions. Thus in a study of the oxidation of acyl-substituted diazo compounds by singlet oxygen, Ando *et al.*^{84, 85} concluded that this reaction can give both carbonyl oxide and dioxirane; it is these compounds that are responsible for the oxidation of sulfides.



Apparently, the photosensitised oxidation of phenyl(tri-methylsilyl)diazomethane with singlet oxygen also occurs via a dioxirane.⁸⁶



Dioxiranes have been suggested as intermediates in the decomposition of α -azo hydroperoxides by pyridine,^{87–90} oxidation of some azines⁹¹ and ylides^{92, 93} by singlet oxygen, in the reaction of the $T(F_2C:)$ carbene with O_2 in the presence of alkenes⁹⁴ and in the decomposition of some endoperoxides.^{95, 96}

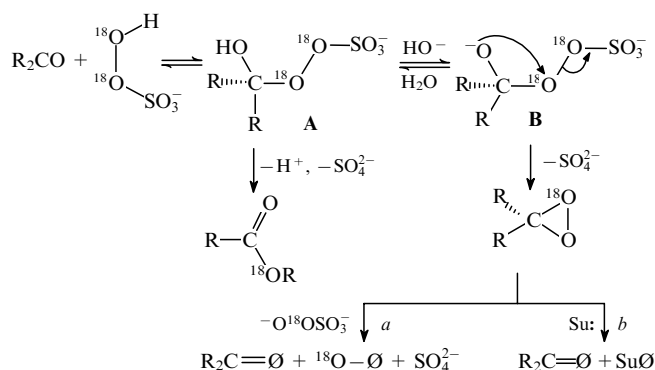
Steinfatt,^{97–100} who observed chemiluminescence during the reaction of geminal dichloro-derivatives of hydrocarbons with Na_2O_2 , suggested that luminescence is due to a dioxirane formed as the key intermediate in this reaction. A dioxirane intermediate has been postulated to interpret the mechanism of bioluminescence of bacteria.¹⁰¹ Recently, we suggested that chemiluminescence in the $Ph_2CCl_2-NaOH-H_2O_2$ system, which is similar to the Steinfatt systems, is also associated with a dioxirane¹² (studies

dealing with the chemiluminescence of dioxiranes are described in greater detail in Section V).

2. Peroxide method for the synthesis of dioxiranes

Despite the existing successful examples where dioxiranes have been synthesised using the procedures described above, the peroxide method for the synthesis of dioxiranes is still the most convenient and the most widely used in synthetic practice. The discovery of this method was preceded by the publication of Montgomery,¹⁰² who found that some ketones catalyse decomposition of monoperoxysulfuric acid (Caro's acid) and accelerate various oxidative transformations involving this acid. Montgomery suggested that dioxirane is formed as an intermediate in the catalytic decomposition of H_2SO_5 . Somewhat later,^{103–108} the presence of dioxirane in the H_2SO_5 – R_2CO system has been proved by the isotopic dilution method using the ^{18}O isotope (Scheme 2).

Scheme 2



Su: is substrate, O is 50% ^{16}O and 50% ^{18}O .

It was in the above series of studies^{103–107} that the researchers showed for the first time that dioxirane itself is also a strong oxidant, which is able, for example, to accomplish highly efficient epoxidation of alkenes (Scheme 2, pathway *b*). The reactions were carried out *in situ* in the system ' KHSO_5 [or $\text{K}_2\text{SO}_4 \cdot \text{KHSO}_4 \cdot 2\text{KHSO}_5$ (oxone)]–ketone–substrate (Su):' at $\text{pH} \approx 7.5$. The necessity of maintaining a constant pH value is due to the fact that $\text{pH} > 7.5$ leads to an increase in the concentration of the $-\text{O}-\text{OSO}_3^-$ dianion, which reacts with dioxirane (Scheme 2, pathway *a*) to destroy the latter, whereas at $\text{pH} < 7.5$, deprotonation of intermediate **A** is virtually terminated and the formation of intermediate **B** and then of dioxirane becomes unlikely.

However, the main difficulty lay in the fact that dioxirane itself could exist *in situ* only together with the corresponding ketone, oxone, H_2O and other reagents needed to maintain pH; of course, this created certain problems hampering the use and investigation of dioxirane. Therefore, the main challenge was to isolate dioxirane from the reaction mixture. This was attained in 1985 by Murray and Jeyaraman,¹ who developed a procedure for the preparation of the individual dioxirane **1a** and some other alkyl dioxiranes (ethylmethyldioxirane, diethyldioxirane, methyl-*n*-propyldioxirane, *n*-butylmethyldioxirane, *etc.*). This study was the first to make dioxiranes accessible for investigations and to open up the way for their extensive use.

A key point in the Murray method¹ was the fact that the reaction of oxone with the initial ketone was carried out in a stream of an inert gas and under a slightly reduced pressure; this made it possible to separate dioxirane as a vapour, which was then collected in cooled traps. Later, this procedure was somewhat modified;^{109–111} however, the basic principle remained the same. This method was also used to prepare the dioxirane **1b**,¹¹¹ which proved even more reactive than **1a**.

It is noteworthy that the Murray procedure for the preparation of dioxiranes is fairly simple and can be performed almost in any laboratory (see, for example, Ref. 110). It should only be borne in mind that the reactants need to be thoroughly purified

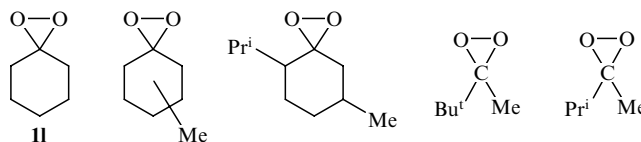
from possible impurities in order to avoid decomposition of dioxirane (see Section III) and that drying agents, if required, should be chosen with caution because it has been noted (see, for example, Refs 2, 112 and 113) that some drying agents affect the stability of the dioxirane **1a** and shorten its lifetime. Therefore, when the purpose of the study does not imply thorough drying, it is better to avoid this procedure and to remove water by decanting the solution from H_2O crystals at a low temperature (-75°C).

The drawbacks of the peroxide Murray method are that it yields dioxiranes only in small amounts and that the initial ketone is distilled from the reaction mixture together with the dioxirane. Thus the concentrations of the dioxiranes **1a** and **1b** in the initial ketone are only 0.06–0.12 and 0.65–0.82 mol litre⁻¹, respectively. The concentrations of other alkyl dioxiranes prepared by this procedure are even lower.¹ The attempts to increase the concentration of the dioxirane **1a** by varying the synthesis conditions and the experiments on its distillation failed.³ Thus, acetone is an immutable 'companion' of the dioxirane **1a** in all its chemical transformations.

However, in the case of the dioxirane **1b**, the initial ketone, 1,1,1-trifluoropropanone (TFP), has been completely separated. For this purpose, the dioxirane obtained was dissolved in the corresponding solvent ($\text{CCl}_2\text{FCClF}_2$, CCl_4 , CH_2Cl_2 , *etc.*) and the solution was washed with doubly distilled water. The initial ketone, which reacts with water forming a hydrate, is extracted into the aqueous phase, whereas the dioxirane **1b** remains in the organic phase.¹¹⁴ To obtain more concentrated solutions, frozen solutions of the dioxirane **1b** (77 K) were slowly evaporated ($< 10^{-2}$ Torr) and then recovered in cooled traps.¹¹⁴

A similar concentration procedure has been developed by Messegueur *et al.*^{115,116} for the dioxirane **1a**. The method is based on the fact that **1a** is more lipophilic than acetone. Although complete removal of acetone was not attained in this case, extraction of an acetone solution of the compound **1a** with an organic solvent (CCl_4 , CH_2Cl_2 , CHCl_3) followed by washing of the organic extract with a phosphate buffer (pH 7) made it possible to obtain more concentrated solutions of the dioxirane **1a** (0.23–0.35 mol litre⁻¹).

In conclusion, another study by Murray *et al.*¹¹⁷ should be mentioned; the researchers reported a procedure for preparation of a number of dioxiranes (0.2–0.8 mol litre⁻¹) from ketones poorly soluble in water.



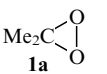
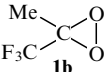
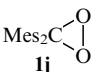
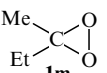
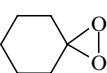
Unfortunately, the peroxide method described above cannot be used for the synthesis of 'heavier' dioxiranes with bulky substituents, in particular, phenyl-substituted dioxiranes.

3. Identification and analysis of dioxiranes

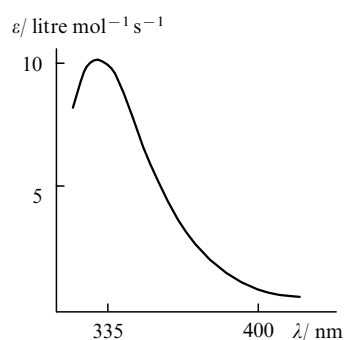
NMR, UV and IR spectroscopy are the most informative methods, used most often to identify dioxiranes. As can be seen from Table 1, common features of dioxiranes include a characteristic signal (δ 100 ppm) for the carbon atom bound to the peroxide group in the ^{13}C NMR spectrum and a relatively weak absorption band in the near UV region ($\lambda = 300$ – 380 nm), ending in the visible region, which is due to the 'forbidden' $n-\pi^*$ transition and is responsible for the pale yellow colour of dioxirane solutions (Fig. 1).

Configurations of dioxiranes are determined using their reactions with methyl phenyl sulfide and triphenylphosphine, iodometric titration and spectrophotometry (the latter method is applicable provided that the extinction coefficient of dioxirane is known).

Table 1. Main spectroscopic characteristics of some dioxiranes (the data were taken from Refs 1, 3, 81, 109, 111 and 117).

Dioxirane	<i>T</i> /°C	δ /ppm				$\lambda_{\max}$ /nm	ϵ /litre mol ⁻¹ s ⁻¹
		¹ H	¹³ C	¹⁷ O	¹⁹ F		
 1a	0	1.65	102.3 ($\overline{\text{COO}}$); 22.69 ^a (Me)	302 ^b		335	10
 1b	-20	1.97 ^c	97.32 ($\overline{\text{COO}}$); 14.51 ^c (Me); 122.2 (CF ₃)	297 ^c	-81.5 ^d	347	9 ^c
 1j	-40	2.19 (12H, <i>o</i> -Me) 2.24 (6H, <i>p</i> -Me) 8.82 (4H, aryl)	103.0 ($\overline{\text{COO}}$); 20.9 (<i>p</i> -Me); 21.6 (<i>o</i> -Me); 130.6 (<i>m</i> -C)			206, 274	10 ^{4.6} , 10 ^{3.2}
 1m	—		103.9 ^c ($\overline{\text{COO}}$)			333	126 ^c
 1l	-17		104.51 ($\overline{\text{COO}}$) 33.36, 24.68 (signals of the other carbon atoms)			345	

^a ¹³C NMR spectra were recorded relative to Me₄Si. ^b Acetone labelled by the ¹⁷O-isotope was used as the initial ketone. ^c The measurements were performed in 1,1,1-trifluoropropanone. ^d ¹⁹F NMR spectra were recorded relative to CFCl₃. ^e The measurements were performed in methyl ethyl ketone.

**Figure 1.** Absorption spectrum of the dioxirane **1a**.

4. Thermochemistry of dioxiranes

The data obtained by microwave spectroscopy^{41–44} for unsubstituted dioxirane **1e** indicate that this compound contains the longest peroxide bond (1.52 Å) among such bonds known so far. This strained character of the peroxide ring should favour the homolytic cleavage of the O–O bond to give the biradical intermediate



According to theoretical calculations, the activation energy of this process is ~15 kcal mol⁻¹, whereas the activation barrier to the back reaction (cyclisation) is negligibly small,⁴ < 1 kcal mol⁻¹ (note that in a study¹¹⁸ which is considered in more detail below, the activation energy of cyclisation of the biradical has been suggested to be ~10 kcal mol⁻¹). The results of studies of various energy states of dioxirane **1e**, the corresponding biradical and the carbonyl oxide indicate that dioxirane **1e** cannot pass into carbonyl oxide without substantial energy expenditure, because the energy of the carbonyl oxide is much higher.⁴ Indeed, no examples of this transformation are known. The back reaction, which also requires additional activation energy, equal to

~22 kcal mol⁻¹, occurs on irradiation of dioxiranes.^{28, 29, 33, 62, 65–77, 80, 81}

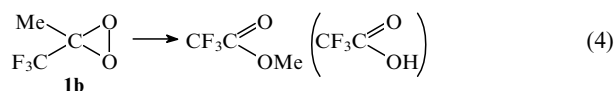
III. Thermal decomposition of dioxiranes

Despite the substantial progress attained in the studies of oxidative processes of dimethyl- (**1a**) and methyl(trifluoro-methyl)dioxiranes **1b**, the behaviour of these compounds in solutions in the absence of easily oxidisable substrates is still enigmatic and contradictory and remains the least studied aspect in the chemistry of dioxiranes. At present, facts are being accumulated along this line; however, they are often fairly contradictory. In fact, there is still no general agreement concerning either the products of decomposition of the dioxirane **1a** or its stability (the values for the time needed for decomposition of the dioxirane **1a** at room temperature reported in the literature^{109, 112, 119} range from 7 h¹⁰⁹ to 26 days¹¹²).

This situation is due to the properties of dioxiranes; apparently, their decomposition is a complex process depending on numerous factors and conditions.

1. The products and mechanism of decomposition of methyl(trifluoromethyl)dioxirane

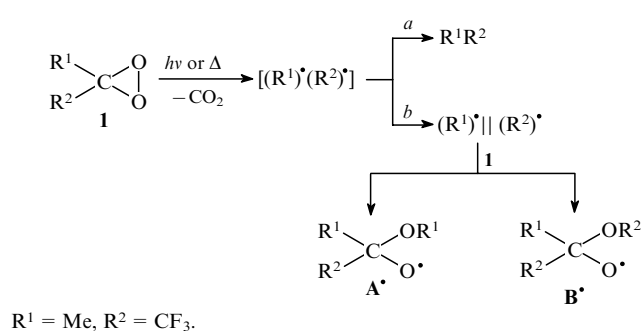
Decomposition of methyl(trifluoromethyl)dioxirane **1b** in the initial ketone gives methyl trifluoroacetate (MTFA) and trifluoroacetic acid, formed upon its hydrolysis, as the major products.¹¹¹



The half-life of the dioxirane **1b** in the initial ketone is ~20 h at 15 °C (at -20 °C, the decrease in the concentration is ~6% over a period of 48 h).¹¹¹ In addition, it was noted¹¹¹ that decomposition of the dioxirane **1b** at 0 °C follows complex kinetics corresponding to a mixed first and second order.

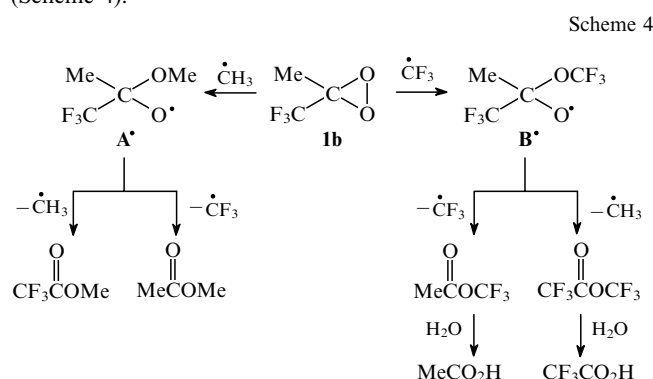
Later, when solutions of the dioxirane **1b** in inert solvents were obtained, the full picture of its decomposition occurring at elevated temperatures or on exposure to UV radiation was identified.¹¹⁴ Whereas at low temperatures the dioxirane **1b** is

rather stable in inert solvents (at $-20\text{ }^{\circ}\text{C}$, the decrease in its concentration in CCl_4 or CH_2Cl_2 is 5%–6% over a period of 168 h), at elevated temperatures ($60\text{ }^{\circ}\text{C}$, CCl_4), it decomposes by almost 50% within 30 min.¹¹⁴ Thorough investigation of the products of thermolysis ($60\text{ }^{\circ}\text{C}$) and photolysis of solutions of the dioxirane **1b** free from the corresponding ketone showed that under these conditions, decomposition occurs by a radical chain mechanism¹¹⁴ and affords MTFA, trifluoromethyl acetate (TFMA) and methyl acetate (MA). Apart from the esters listed above, the reaction mixture contains acetic and trifluoroacetic acids, which, in the opinion of the authors cited,¹¹⁴ have resulted from hydrolysis of TFMA and trifluoromethyl trifluoroacetate (TFMTFA), respectively. In addition, evolution of CO_2 was noted in all cases. These facts and the fact that in the presence of O_2 , the photolytic process is substantially retarded and the formation of esters is markedly depressed provide strong evidence for the chain radical mechanism of decomposition of the dioxirane **1b** (Scheme 3).



In conformity with the Scheme 3, decomposition of methyl-(trifluoromethyl)dioxirane gives rise to the radical pair $[\dot{\text{C}}\text{H}_3 \dot{\text{C}}\text{F}_3]$, which then either recombines according to pathway *a* or generates free radicals $\dot{\text{C}}\text{H}_3$ and $\dot{\text{C}}\text{F}_3$ (pathway *b*); these radicals, in turn, attack dioxirane yielding alkoxy radicals **A•** and **B•**. Pathway *a* is realised when methyl(trifluoro-methyl)dioxirane is photolysed in a matrix. In this case (unlike experiments in solution), 1,1,1-trifluoroethane is a major product of decomposition of dioxirane.

Radicals **A•** and **B•** undergo β -cleavage to give esters with the regeneration of alkyl radicals, which carry the chain (Scheme 4).¹¹⁴

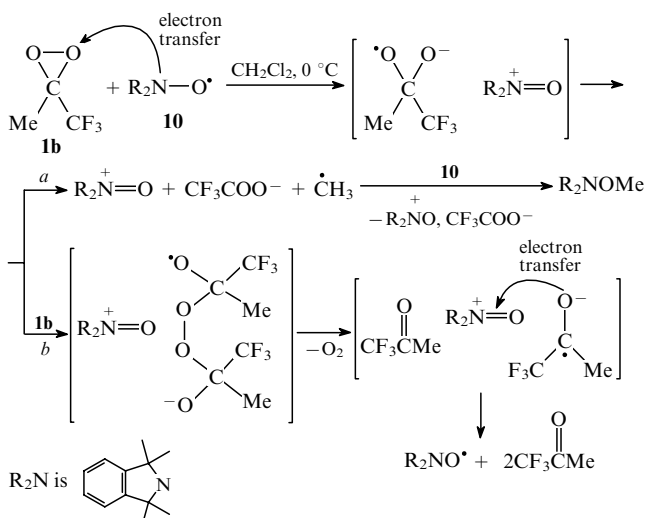


It is of interest that no radical chain processes are involved in the vacuum flash pyrolysis ($500\text{ }^{\circ}\text{C}$) of the dioxirane **1b**,¹¹⁴ which gives only MTFA. Apparently, in this case, dioxirane simply isomerises to ester according to reaction (4).

The radicals formed upon decomposition of the dioxirane **1b** were detected at low temperatures using 1,1,3,3-tetramethyl-1,3-dihydroisindolin-2-yloxyl **10** as a spin trap.¹²⁰ However, the adduct of the nitroxide **10** and the $\dot{\text{C}}\text{H}_3$ radical is formed apparently *via* the dioxirane radical anion, resulting from the transfer of an electron from the nitroxide **10** to the dioxirane **1b**

(Scheme 5, pathway *a*).¹²⁰ Yet another channel of consumption of the radical anion is pathway *b*.

Scheme 5

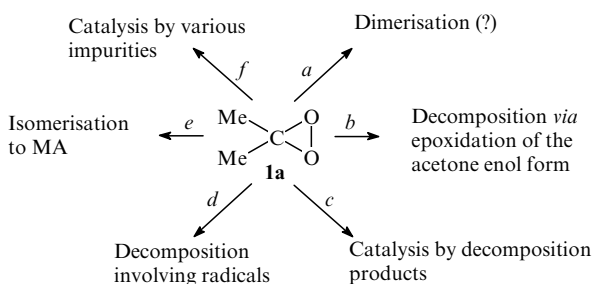


The decomposition of the dioxirane **1b** can also be induced by various impurities. Thus it has been noted¹²¹ that the presence of even traces of metals can cause rapid decomposition of dioxiranes. Messeguer *et al.*¹²² have found that catalytic amounts of dialkyl ethers (*e.g.*, diethyl or dihexyl ether) induce rapid decomposition of the dioxirane **1b** in a radical chain process. This finding appears very important because the same researchers reported¹²² that these ethers are contained in the initial TFP even after distillation. However, they can be removed. Thus when TFP is washed with water and an inert solvent, the ethers are accumulated in the organic phase, whereas TFP passes into the aqueous phase as hydrate.

2. The products, kinetics and mechanism of decomposition of dimethyldioxirane

Several routes for decomposition of dioxiranes **1a** can be found in the literature (Scheme 6).

Scheme 6



Evidently, the realisation of one or another channel of transformation of the dioxirane **1a** depends on a whole series of conditions such as temperature, the content of O_2 , the presence of impurities, *etc.* Some of these factors can be controlled; the influence of some other factors can be reduced (for example, by thorough purification of the initial compounds). Table 2 contains data on the products of decomposition of the dioxirane **1a** and on the reaction mechanisms that have been invoked by the researchers in order to interpret the results obtained and that are considered in detail below.

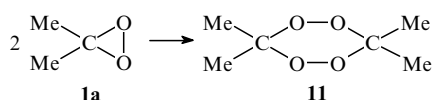
Table 2. Products of decomposition of dimethyldioxirane (**1a**) under various conditions.

Reaction conditions	Proposed mechanism (Scheme 6)	Decomposition products	Ref.
Room temperature, no special purging with oxygen or an inert gas	<i>a</i>	diperoxide 11	1
	<i>b</i>	hydroxyacetone (12) + MA ^a	119
	the mechanism is not discussed	MA ^a	112
Vacuum flash pyrolysis, 150–180 °C	<i>e</i>	MA	112
In boiling acetone	<i>d</i>	MA + 1-(acetyl-oxy)propan-2-one	112
Decomposition in the presence of BF ₃	pathways <i>b</i> and <i>e</i> occur in parallel	MA + 12	112
Room temperature	<i>e</i>	MA	15
Decomposition in the presence of CCl ₃ Br, 20 °C	<i>d, e</i> and <i>f</i>	MA ^b , 1-(acetyl-oxy)propan-2-one, CH ₃ CO ₂ H, CH ₃ Br, CHCl ₃ , CH ₃ OH, ClCH ₂ C(O)CH ₃	37
Decomposition in the presence of the Ru(II) tris-(bipyridine) complex, 40 °C	<i>e</i> (see ^c)	MA	15

^a Some quantity of MA was already present in the initial solutions of **1a**.
^b Methyl acetate was the major product. ^c In this case, we are dealing with catalysed isomerisation of dioxirane to MA according to the electron transfer mechanism (see Section V).

a. Dimerisation of dimethyldioxirane

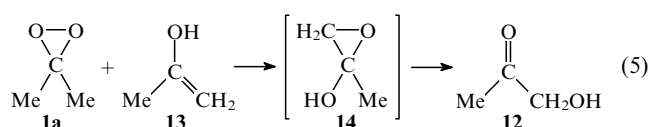
The first data on the products of decomposition of dimethyldioxirane **1a** were published in 1985. Murray *et al.*¹ reported on the conversion of the dioxirane **1a** into cyclic diperoxide **11**:



Later, however, they were unable to reproduce their own results¹¹² and suggested that compound **11**, which they had observed previously, must have been formed as a side product during the synthesis of dioxirane.

b. Decomposition with participation of the enol form of acetone

Decomposition of the dimethyldioxirane **1a** at room temperature has been reported¹¹⁹ to give hydroxyacetone **12** together with a minor amount of methyl acetate. It was noted¹¹⁹ that solutions of dioxirane always contain some MA, which appears apparently during the synthesis of dimethyldioxirane. Based on this finding, a decomposition mechanism has been proposed, the key stage of which includes the reaction of the dioxirane **1a** with the enol form of acetone **13** followed by rearrangement of the resulting epoxide intermediate to hydroxyacetone **12**.



However, the possible formation of the hydroxy ketone **12** upon direct insertion of an oxygen atom into the C–H bond of acetone or in a free-radical process also cannot be ruled out.¹¹⁹

The contribution of reaction (5) to decomposition of the dioxirane **1a** increases in the presence of BF₃. In the opinion of Murray and Singh,¹¹² boron trifluoride exerts a dual effect: on the one hand, it increases the rate of conversion of **1a** into MA and, on the other hand, it favours an increase in the concentration of the enol **13**, which then reacts with **1a** [reaction (5)] to give hydroxyacetone (see Table 2).

It was also found that solutions of the dioxirane **1a** are sensitive to the presence of bases; the addition of KOH to a solution of dioxirane results in its rapid decomposition, which follows first-order kinetics.¹¹⁹ A similar situation has been observed in the case of a solution of deuterated dioxirane **1a**, which proved to be more stable than the non-deuterated compound ($k_{\text{H}}/k_{\text{D}} \sim 4$).¹¹⁹

c. Catalysis by decomposition products

Many researchers (see, for example, Refs 109, 112, 118, 119, 123) have noted that at high concentrations (≥ 0.06 mol litre⁻¹), decomposition of the dimethyldioxirane **1a** does not follow first-order kinetics; instead, it has a fairly long induction period, which is followed by rapid decomposition (Fig. 2). It was found that the higher the temperature and the dioxirane concentration, the shorter the induction period.^{118, 123} It was suggested that reaction products have a catalytic effect on the decomposition of the dioxirane **1a**. Indeed, comparison of curves 2 and 3 in Fig. 2 shows that **1a** decomposes much faster in the presence of decomposition products. Unfortunately, the products of decomposition of **1a** were not specified in the study cited.¹¹⁸

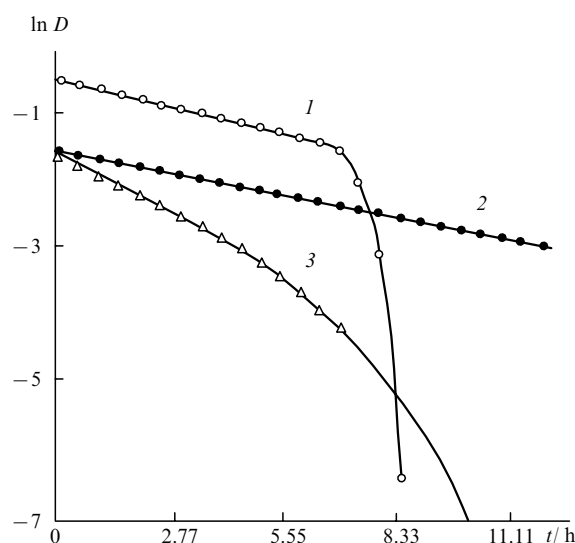


Figure 2. Kinetic curves for the consumption of dimethyldioxirane **1a** in acetone at 50 °C (solutions of **1a** in acetone were used without preliminary dehydration).¹¹⁸

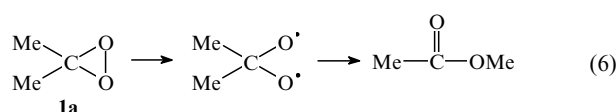
The initial concentration of the dioxirane **1a** (mol litre⁻¹): (1) 0.12, (2) 0.02, (3) 0.02 (in the presence of the products formed upon decomposition of 0.12 mol litre⁻¹ of a solution of the dioxirane **1a**).

When the concentration of the dioxirane **1a** is low (0.02 mol litre⁻¹), its decomposition follows first-order kinetics (Fig. 2, curve 2).^{112, 118, 123} This fact was used¹¹⁸ to determine the activation parameters of the decomposition of **1a** in the temperature range 25–75 °C: $\log k = 12.4 - 24.9/(2.3RT)$. Thus, at 25 °C, $k = 1.53 \times 10^{-6}$ s⁻¹, and the activation energy of decomposition of the dioxirane **1a** is about 9–10 kcal mol⁻¹ higher than the value calculated theoretically (~ 15 kcal mol⁻¹) for unsubstituted dioxirane **1e**.⁴ The latter result was interpreted¹¹⁸ as being due to

the consumption of **1a** in a radical chain process, which is manifested as a sharp acceleration of the reaction. This is quite consistent with the decrease in the induction period following an increase in the temperature¹¹⁸ and also with the substantial effect of argon. Even when the concentration of the dioxirane **1a** is relatively low (0.03 mol litre⁻¹) and the temperature is moderate (20 °C), the induction period in the reaction performed under argon decreases to ~150 min.¹²⁴ It comes as no surprise that the dioxirane decomposition under an atmosphere of O₂, which inhibits the radical chain process, strictly follows first-order kinetics irrespective of the initial dioxirane concentration or temperature (30–49.5 °C).¹³²

e. Isomerisation of dimethyldioxirane to methyl acetate

Although arguments in favour of the radical mechanism of decomposition of the dioxirane **1a** are quite forcible, the existence of a parallel channel of the decomposition of **1a**, namely, its isomerisation to MA *via* a biradical intermediate, can also be considered to be proven.



It was found¹⁴ that reaction (6) occurs under conditions of photolysis of the dioxirane **1a** in a matrix (77 K) (isomerisation is also a major pathway of the low-temperature phototransformation of some other dioxiranes³³). In addition, at higher temperatures, ($T = 150\text{--}180$ °C, vacuum flash pyrolysis), reaction (6) is regarded as the major pathway for decomposition of dimethyldioxirane (remarkably, under these conditions some **1a** remains intact!).¹¹² Apparently, rearrangement to give MA is the main route of decomposition of the dioxirane adsorbed on the Silipor surface from the gas phase.^{11, 16}

However, it is reasonable to suggest that decomposition of the dimethyldioxirane **1a** in solution also involves reaction (6). Its contribution depends most likely on the temperature and other experimental conditions. Due to the influence of impurities and at elevated temperatures, which promote the occurrence of parallel routes of the radical chain decay of the dioxirane **1a**, the fraction of isomerisation should decrease. However, it has been shown experimentally that even under conditions most favourable for a radical chain process (46 °C, absence of O₂), reaction (6) still does occur, because it is this reaction that is responsible for the chemiluminescence observed under these conditions¹³ (this aspect is considered in greater detail in Section V). In our opinion, the contribution of reaction (6) markedly increases at lower temperatures; apparently, at room temperature and below room temperature, it becomes the major route for the dioxirane consumption.

Note that reaction (6) can also be induced by a catalytic influence of various compounds. Thus ruthenium tris(bipyridine) complex Ru(bipy)₃²⁺ and some polyaromatic hydrocarbons, which act as activators of the CL arising by the chemically

initiated electron-exchange luminescence (CIEEL) mechanism, catalyse isomerisation of dioxirane.^{6, 10, 12, 15, 16, 123} Apparently, the Silipor surface also functions as a catalyst.^{11, 16}

e. Catalysed (induced) decomposition of dimethyldioxirane by impurities

Some impurities have an exceptionally significant influence on the stability and the decomposition mechanism of the dioxirane **1a**. These impurities include some metals, traces of dehydrating agents (*e.g.*, molecular sieves,¹¹² MgSO₄, *etc.*) and reactive compounds present in the initial acetone or introduced into a solution of the dioxirane **1a** from the reaction vessel at the stage of its synthesis. Murray² noted that the lifetime of dioxirane depends on the pre-history of the sample and can be sensitive to admixtures of the dehydrating agent used (*e.g.*, Na₂SO₄).

An example of dioxirane decomposition induced by impurities has been reported.³⁷ It was shown that the stability of dimethyldioxirane **1a** is substantially affected by the addition of CCl₃Br. Whereas decomposition of the dioxirane **1a** under ordinary conditions follows first-order kinetics ($k = 6.2 \times 10^{-6}$ s⁻¹), the addition of CCl₃Br, especially with simultaneous removal of O₂ from the system, sharply accelerates the process (Fig. 4), the product composition leaving no doubt as to the participation of free radicals in the dioxirane decomposition in the presence of CCl₃Br³⁷ (Scheme 9).

Presumably,³⁷ CCl₃Br can also participate in the formation of a biradical-ion pair with the dioxirane, resulting from transfer of an electron from the bromide to **1a**. The subsequent reverse electron transfer from the radical anion to the radical cation increases the concentration of biradical **A** and, hence, the probability of formation of the $\dot{\text{C}}\text{H}_3$ radical from it.

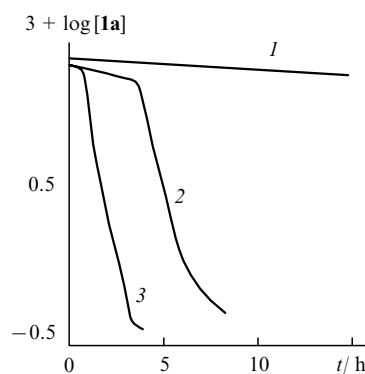
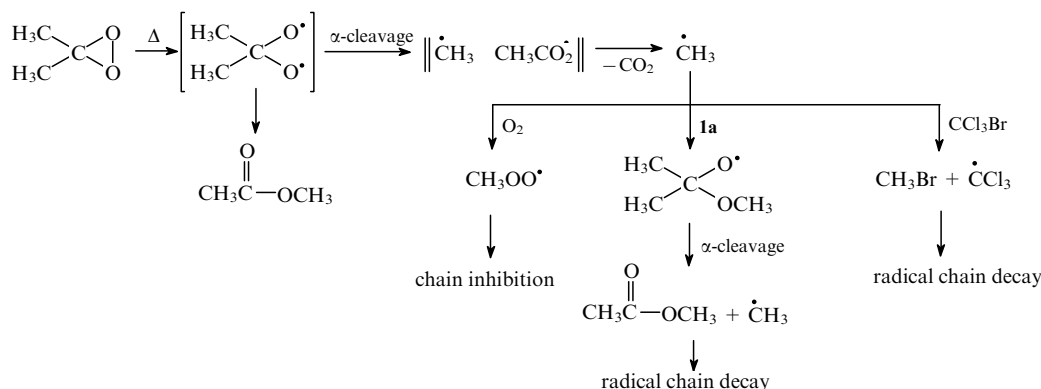
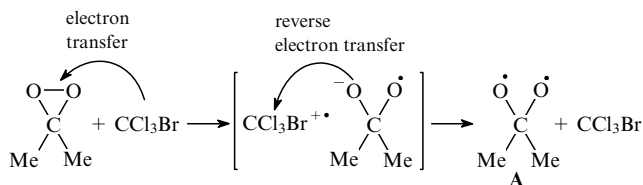


Figure 4. Kinetics of decomposition of dimethyldioxirane (**1a**) in the absence (*1*) and in the presence (*2*, *3*) of an equimolar amount of CCl₃Br; (*2*) under atmospheric conditions, (*3*) under inert atmosphere (N₂).





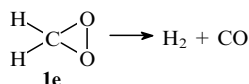
The occurrence of another parallel channel for the transformation of the biradical-ion pair, resulting in the formation of $\cdot\text{CCl}_3$ and $\text{BrO}^{\cdot}$ radicals, capable of participating in the radical chain decay of dioxirane, also cannot be ruled out.³⁷ It was noted^{37,121} that traces of metals can cause rapid decomposition of the dioxirane **1b**. Recently we have confirmed experimentally that this warning is also true for the dioxirane **1a**. It was found¹⁵ that even catalytic amounts of ruthenium(II) $[(4-24) \times 10^{-5} \text{ mol litre}^{-1}]$ induce rapid decomposition of the dioxirane **1a**. It can be anticipated that other metals would also influence the stability of dioxiranes.

The stability of dioxiranes can be affected not only by traces of metals and dehydrating agents but also by organic impurities. The radical chain decay of methyl(trifluoromethyl)dioxirane **1b** in the presence of dialkyl ethers (for example, diethyl and dihexyl ethers)¹²² has been already mentioned. The addition of ethers to dimethyldioxirane **1a** has a similar influence, although it is less pronounced.¹²² Unfortunately, since the boiling points of dialkyl ethers and acetone are close, purification of acetone by distillation does not always lead to the desired result. The situation is aggravated by the fact that some impurities can form directly in the reaction vessel and, therefore, they can appear in a solution of dioxirane at the stage of its synthesis. For example, this concerns MA, small amounts of which get into solutions of **1a** in exactly this way.^{112,119} Impurities that have got into a dioxirane solution *via* this route can be involved in the radical decomposition of dioxirane; hence, the different lifetimes of the dioxirane **1a** synthesised by various researchers and the non-reproducibility of the kinetic data^{15,109,112,118,119,123,132} can be due to different natures and amounts of non-controllable impurities able to accelerate decomposition of the dioxirane **1a** and promote the formation of different decomposition products (see Table 2). This resembles the situation observed in the study of the kinetic and activation parameters of decomposition of tetramethyldioxetane (TMD). In these studies, the so-called 'false solvent effect' had been discovered, manifested as a sharp acceleration of the reaction on passing from aprotic solvents (benzene, CCl_4) to alcohols (MeOH and EtOH) and poor reproducibility of the kinetic data in alcoholic solutions.^{21,133} The reason was that admixtures of transition metal ions were present even in distilled solvents.^{21,134,135} Treatment of alcoholic solutions of TMD with complexonates improved the reproducibility, and the kinetic and activation parameters acquired values typical of aprotic solvents.

However, in the case of the dioxirane **1a**, the situation must be more complicated. Thermal decomposition of dimethyldioxirane **1a** is a complex process, its mechanism depending on numerous factors. To elucidate the extent of influence of each factor, further studies are needed.

3. Decomposition of other dioxiranes

The formation of H_2 and CO is the main pathway of decomposition of gaseous unsubstituted dioxirane **1e** (-115°C).^{42,43}

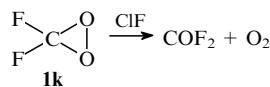


It has been noted that decomposition of dioxirane **1e** follows different channels, resulting in the formation of atomic hydrogen.⁴³

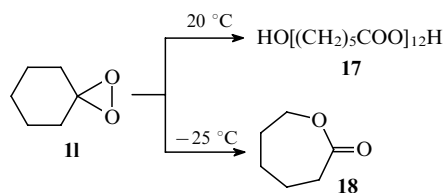
Gaseous difluorodioxirane **1k** is more stable than **1e**. No decrease in its concentration has been noted over a period of

12 h at 22°C and 15 Torr. The unusual stability of the dioxirane has become the subject of a special theoretical study.¹³⁶

When a small amount of ClF is added to difluorodioxirane **1k**, the dioxirane is destroyed fairly rapidly to give COF_2 and O_2 .⁸²

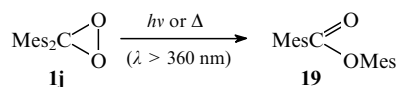


The spirocyclic dioxirane **11** is relatively unstable:¹¹⁷ at room temperature, the yellow colour, typical of dioxiranes, completely disappears in 5–10 min and the solution becomes colourless. Simultaneously, the solution substantially warms up, indicating the exothermic character of the decomposition of **11**. Interestingly, instead of the expected lactone **18**, decomposition of the dioxirane **11** at room temperature gives its linear oligomer **17** as the major product (90%).



However, at lower temperatures the reaction gives the lactone **18**.¹¹⁷ This example clearly illustrates the statement that the reaction temperature can dictate the predominance of one or another channel of dioxirane decomposition.

Dimesityldioxirane **1j** can exist both in solution and in the crystalline state.^{80,81} In both cases, the dioxirane **1j** isomerises to the corresponding ester, mesityl mesitoate **19**:



The dioxirane **1j** is relatively stable at room temperature (its concentration decreases by 14% over two weeks) and virtually stable at -20°C . However, on exposure to radiation, it completely isomerises into the ester **19** in several minutes.^{80,81} The stability of the dioxirane **1j** under ordinary conditions is due to the facts that its molecule is sterically hindered and the O—O bond is relatively strong and, in addition, it is the shortest (1.503 Å) among the O—O bonds in dioxiranes.⁸¹

IV. Dioxiranes as oxidants

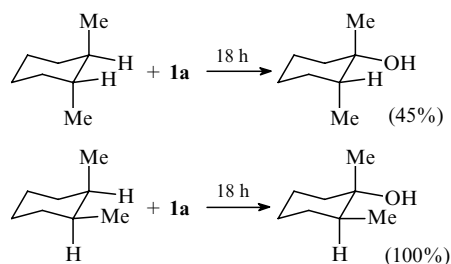
Highly selective oxidation of organic compounds of various classes is a well-studied aspect of the chemistry of dioxiranes, which is becoming more and more significant in organic synthesis. This feature, discovered even in the first studies on *in situ* generation of dioxiranes,^{103–107} has fully come to light in the subsequent studies carried out using pure solutions, most often of the dioxiranes **1a** and **1b**. The main types of oxidative transformations involving **1a** and **1b** include oxidation of alkanes, alkenes, their functionally substituted derivatives containing heteroatoms (O, S, N, P), and organometallic compounds.

1. Oxidation of saturated compounds

Highly selective oxidation of saturated compounds to the corresponding hydroxy- and oxo-derivatives is one of the most important and most difficult problems in organic chemistry.¹³⁷ At present, peroxy acids, hydroperoxides, ozone, catalytic systems including transition metals and some other compounds are used most often for this purpose.^{138–144} Dioxiranes, capable of oxidising selectively and under mild conditions non-activated C—H bonds in alkanes, occupy a unique place in the series of organic oxidants.

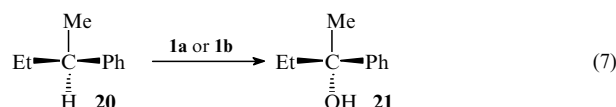
The reactions of dioxiranes with alkanes give rise to the corresponding alcohols. The oxidation of *cis*- and *trans*-1,2-

dimethylcyclohexanes by the dioxirane **1a**, reported by Murray *et al.*,¹⁴⁵ was among the first examples of this reaction.



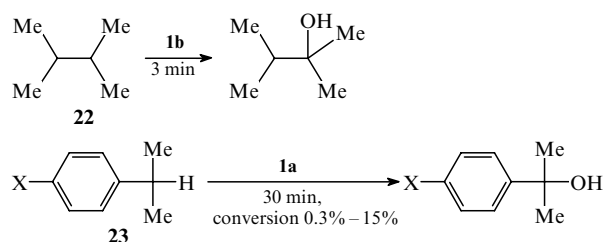
A similar reaction with participation of the dioxirane **1b**, which is more reactive than **1a**, occurs much faster.¹¹¹

Oxidation of optically active (*R*)-(-)-2-phenylbutane **20** to (*S*)-(-)-2-phenylbutan-2-ol **21** by the dioxiranes **1a** and **1b** occurs with retention of the absolute configuration.^{39, 146}



In this reaction, too, methyl(trifluoromethyl)dioxirane **1b** demonstrates obvious advantages over dimethyloxirane **1a**. Thus when the dioxirane **1a** is used, a 50% degree of conversion of the alkane **20** into the alcohol **21** requires a 10-fold excess of **1a**, 2 days, and a temperature of 25 °C, whereas in the case of **1b**, 100% conversion is attained with only a 2-fold increase of the oxidant and takes 1 h at a temperature of 24 °C.

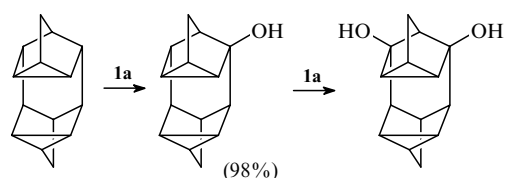
Dioxiranes have also been used successfully for the synthesis of hydroxy-derivatives of 2,3-dimethylbutane **22**, cumene **23** (X = H)^{121, 147, 148} and its derivatives and a series of other alkanes.



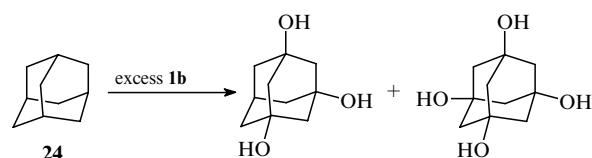
X = H, I, Me, OH, OMe, OPh, COMe.

In all cases (except for norbornane), a tertiary C–H bond in the substrate is oxidised more efficiently than secondary C–H bonds.¹²¹ Non-activated primary and secondary C–H bonds in alkanes can also undergo selective oxidation, for example, in the presence of trifluoroacetic anhydride.¹⁴⁹

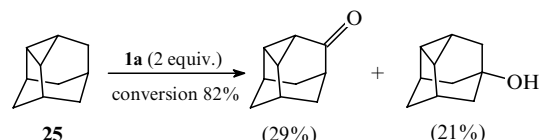
Oxidation of cage compounds yields the corresponding alcohols.^{37, 117, 121, 147, 150–152} Thus oxidation of binor **S** by dimethyldioxirane **1a** gave rise to mono- and dihydroxy-derivatives.



Oxidation of adamantane **24** by the dioxirane **1b** gives predominantly, depending on the ratio of the reactants, either adamantane-1-ol (**1b**:**24** = 1:1) or adamantane-1,3-diol (**1b**:**24** = 2:1).¹²¹ When **1b** was taken in a larger excess, adamantane-1,3,5-triol and adamantane-1,3,5,7-tetraol were obtained.

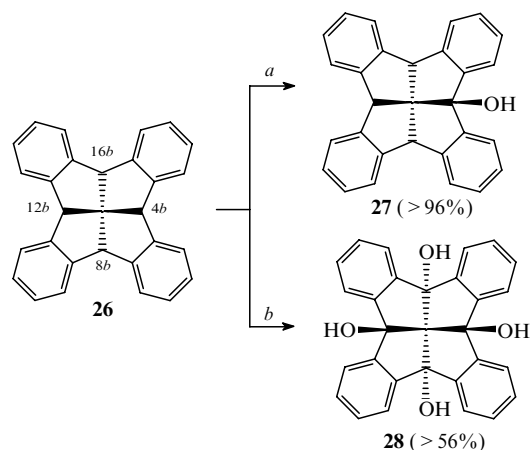


The dioxirane **1a** has also been used to oxidise adamantane^{37, 151} and its derivatives¹⁴⁷ and also 2,4-didehydroadamantane **25**¹⁵² to the corresponding alcohols; however, it is much less reactive than **1b**.



It is of interest that the dioxirane **1b** is 4 times more reactive towards the oxidation of adamantane than **1a**.¹¹⁷

The dioxiranes **1a** and **1b** have been used to synthesise¹⁵³ hydroxy- and polyhydroxy-derivatives of several centropolyindans [triptindan, 1,1'-(*o*-phenylene)-2,2'-spirobiindan, 10-methyltribenzoquinacene, fenestrindan, *etc.*]. Thus oxidation of fenestrindan **26** by the dioxirane **1b** in the CH₂Cl₂–CF₃C(O)Me–Bu^tOH system affords, depending on the reaction conditions, either alcohol **27** or tetraol **28**.¹⁵³

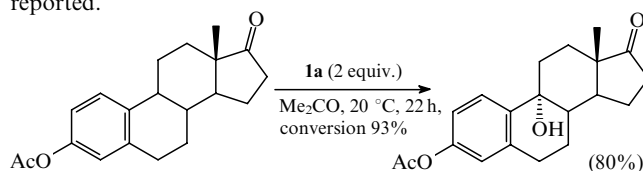


(a) 1.5 equiv. **1b**, CH₂Cl₂:CF₃C(O)Me:Bu^tOH = 9:1:1, –10 °C, 25 min, conversion 56%;

(b) 10 equiv. **1b**, CH₂Cl₂:CF₃C(O)Me:Bu^tOH = 5:4:1, –10 °C, 25 min, conversion 97%.

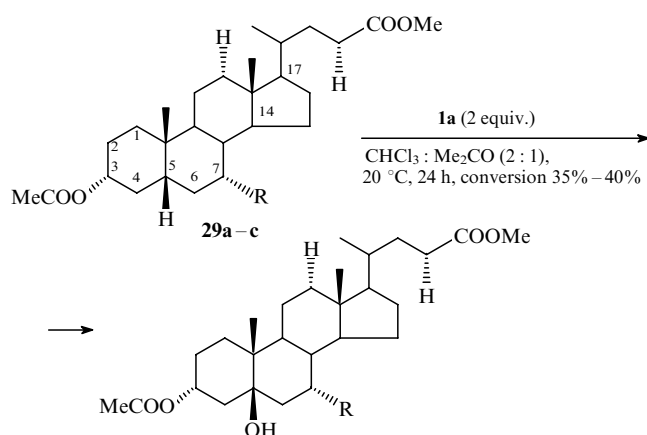
The alcohol **27** reacts with the dioxirane **1b** (1.7 equiv. of **1b**; CH₂Cl₂:CF₃C(O)Me = 9:1, 0 °C, 15 min, conversion 60%) to give a diol, 4b,8b-dihydroxyfenestrindan (yield >88%).³⁸

Hydroxylation of several natural products,^{154–158} for example, estrone acetate,¹⁵⁶ by the dioxiranes **1a** and **1b** has been reported.



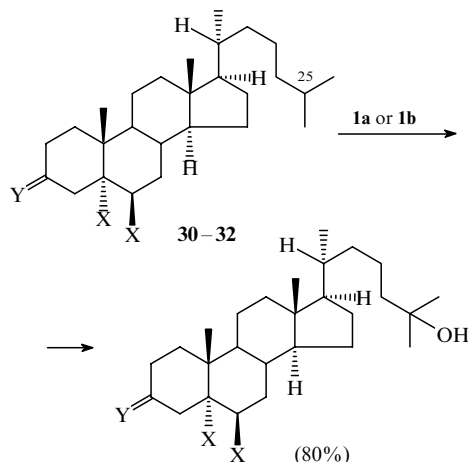
The reactions of a ~0.16 M solution of the dioxirane **1a** in a CHCl₃–Me₂CO mixture with a number of 5β-H-cholic acids (lithocholic **29a**, ursodeoxycholic **29b**, chenodeoxycholic acid **29c**, *etc.*) have been studied.¹⁵⁷ In all cases, oxidation of the C–H bond in the 5β position occurred. However, whereas lithocholic acid **29a** reacts relatively rapidly, the corresponding 5β-hydroxy-derivative being the only reaction product,¹⁵⁷ the acids **29b** and **29c**, containing an electron-withdrawing acetoxy group at the C(7) atom, react slowly because the 5β position is

deactivated and, apart from the 5 β -hydroxy-derivative, the reaction gives, the 14 α - and 17 α -hydroxylation products.¹⁵⁷



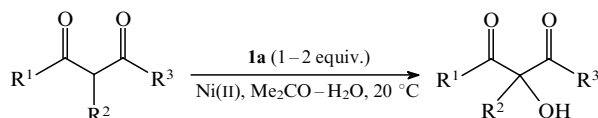
R = H (**a**), β -OCOMe (**b**), α -OCOMe (**c**).

Cholestane derivatives, for example, 5 α -cholestan-3-one **30**, 3 β -acetoxy-5 α -cholestan-3-one **31** and 3 β -acetoxy-5 α ,6 β -cholestan-3-one **32** are also oxidised by dioxiranes at the C(25) position to give the corresponding alcohols.¹⁵⁸



30: Y = O, X = H;
31: Y = β -OAc, H, X = H;
32: Y = β -OAc, H, X = Br.

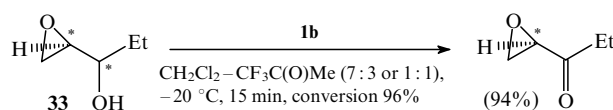
The rate of oxidation of C–H bonds by dioxiranes can depend on ‘external’ factors. Whereas oxidation of 1,3-dicarbonyl compounds by even a substantial excess of the dioxirane **1a** requires about three days,¹⁵⁹ the same reaction carried out in the presence of Ni(II) salts as the catalyst occurs markedly faster, the reaction time being reduced to several hours.¹⁶⁰



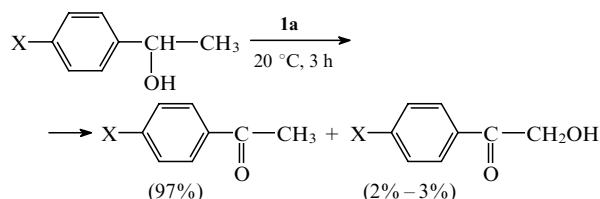
This reaction is one of the few examples of ‘external’ interference in the course of oxidative reactions involving isolated dioxiranes. Previously, acid catalysis has been used¹⁶¹ to accomplish selective oxidation of methoxybenzenes by the dioxirane **1a** to the corresponding *p*-benzoquinones.

In some cases, the alcohols formed from alkanes are oxidised by excess dioxirane to give the corresponding ketones.¹²¹ Several secondary alcohols have been oxidised¹⁶² to the corresponding ketones (yields 92%–99%) by the dioxirane **1b** (oxidation of secondary alcohols proceeds more smoothly and requires less time than the oxidation of primary alcohols). A remarkable selectivity was found in the reaction of the dioxirane **1b** with 2-norborneol:

the *endo*-isomer was found to be 40 times more reactive than the *exo*-isomer.¹⁶² Oxidation of chiral α -epoxy alcohols **33** by dioxiranes does not affect the oxirane groups and occurs with retention of the configuration of the asymmetric centre adjacent to the hydroxy group.¹⁶²

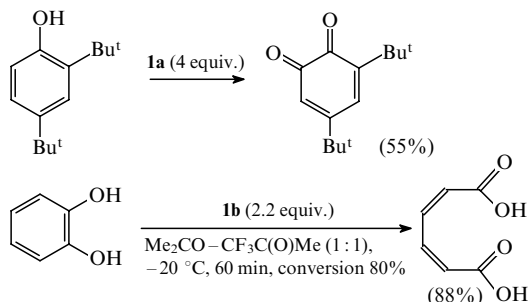


On treatment with dimethyldioxirane **1a**, several *para*-substituted α -methylbenzyl alcohols have been converted into the corresponding acetophenones in good yields.¹⁶³

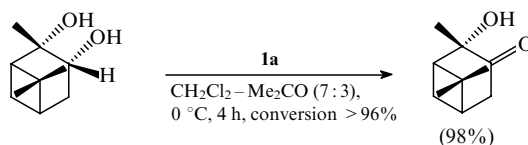


X = H, F, Cl, Br, Me, OMe, CN.

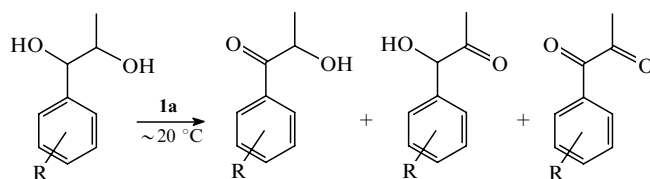
Oxidation of simple phenols by dioxiranes affords complex mixtures of products;¹⁶⁴ the best results were obtained in the reactions of dioxiranes with substituted phenols and catechol.^{164, 165}



Aliphatic diols (including optically active ones) react with the dioxiranes **1a** and **1b** to give α -hydroxy ketones.^{166, 167} It is noteworthy that oxidation of (+)-pinane-2,3-diol to (–)-2-hydroxypinan-3-one occurs with virtually complete retention of the configuration (the optical yield of the ketone is >97%).¹⁶⁶

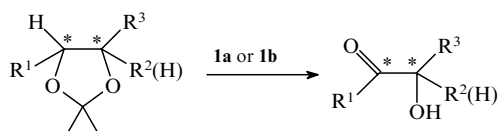


Oxidation of non-symmetrical 1,2-diols results in their complete conversion to the corresponding mono- and dioxo derivatives (regioselectivity of the process depends considerably on the nature of the substituents).¹⁶⁸

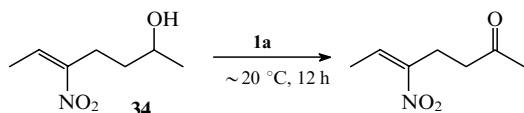


R = H, *p*-OMe, *o*-OH, *o*-NO₂, *p*-NO₂.

Optically active *O*-isopropylidene derivatives of 1,2-diols are converted into 2-hydroxy ketones, formed in high optical yields and with retention of the optical purity.¹⁶⁹



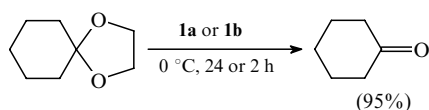
Depending on the reaction conditions and the nature of the substrate, oxidation of allylic alcohols by dioxirane **1a** occurs as either epoxidation of the double bond^{106,107} or competing oxidation of the hydroxy group to an oxo group.¹⁷⁰ In the oxidation of unsaturated nitro alcohols **34**, the double bond remains intact because it is deactivated by the NO₂ group.¹⁷¹



The deactivation effect is also manifested in the oxidation of nitro diols: the hydroxy group remote from NO₂ is oxidised, whereas the OH group occurring in the α - or β -position to the NO₂ group remains intact.¹⁷¹

When dioxiranes are made to react with allyl hydroperoxides, the corresponding epoxy hydroperoxides are formed.¹⁷²

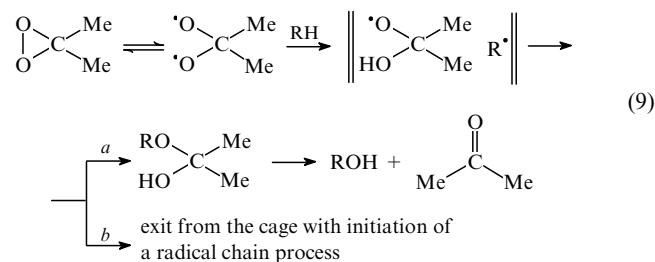
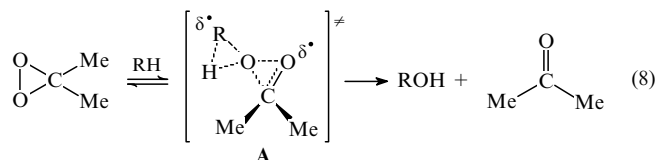
Oxidation of aliphatic esters with the dioxirane **1b** affords oxo and hydroxy derivatives.¹⁷³ Acetals and cyclic and acyclic ethers are also oxidised by dioxiranes to give the corresponding carbonyl compounds,¹⁷⁴ whereas aldehydes are converted into the corresponding carboxylic acids;¹ oxidation of substituted benzaldehydes by the dioxirane **1a** follows a radical mechanism.¹¹⁹ Ethylene ketals undergo oxidative cleavage.¹⁷⁴



The reaction of diphenylmethane with dimethyldioxirane affords Ph₂CO (92%). In this case, the methylene carbon atom, which is absolutely inert under other circumstances, can be oxidised because the CH₂ unit is activated by the two phenyl groups.¹⁷⁵ Phenylcyclopropanes and halophenyl-substituted cyclopropanes do not react with the dioxirane **1a**,¹⁷⁶ whereas bicyclo[4.1.0]heptane and *exo*-9-bromobicyclo[6.1.0]nonane are converted into the corresponding ketones.¹⁷⁶

Dioxiranes have also been used to oxidise vegetable oil components,¹⁷⁷ caffeine and purine nucleosides.¹⁷⁸

At present, two possible mechanisms for the reaction of dioxiranes with alkanes are being discussed in the literature, namely, insertion of an oxygen atom into the C–H bond of the substrate (by analogy with the oxenoid mechanism, proposed previously for the oxidation by ozone¹⁷⁹) [reaction (8)] and a free-radical mechanism [reaction (9)].



In the former case, oxidation of the substrate by a dioxirane passes through the formation of transition state **A** [reaction (8)], while in the latter case, dioxirane first undergoes homolytic cleavage at the O–O bond, the dioxirane biradical abstracts an H atom from the substrate and then the radicals either undergo intracage recombination [reaction (9), pathway (a)] to give the oxidation products or leave the cage and initiate a radical chain process [reaction (9), pathway (b)], or both pathways occur in parallel.

The main argument favouring the former mechanism is the high selectivity of a large number of reactions of oxidation of saturated hydrocarbons by dioxiranes, which could hardly be expected in the case of a radical chain mechanism. The selectivity of the reactions of the dioxiranes **1a** and **1b** with *cis*- and *trans*-1,2-dimethylcyclohexanes,^{111,145} 2-norborneols¹⁶² and with the *para*-substituted isopropylbenzenes **23**^{121,145,147,148} have already been noted above. The oxidation of 3-methyltetrahydropyran is equally selective:¹⁷⁴ an oxygen molecule is inserted exclusively at the two α -positions, whereas in the case of a radical mechanism, the β -positions of the substrate would also undergo oxidation. Oxidation of *R*-(–)-2-phenylbutane **20** occurs with retention of the configuration [reaction (7)], whereas in the case of a radical chain process, at least partial racemisation would be observed. The relatively large negative values of activation entropy¹⁴⁶ (Table 3) provide more evidence for the formation of an ordered transition state of type **A** [reaction (8)].

Table 3. Rate constants (k_2 /litre mol^{–1} s^{–1}) and activation parameters for the oxidation (E_a /kcal mol^{–1}; $\Delta S^\ddagger$ /cal mol^{–1} K^{–1}; $\Delta G^\ddagger$ /kcal mol^{–1}) of 2-phenylbutane with the dioxirane **1b**.¹⁴⁶

Solvent	$T/^\circ\text{C}$	$k_2 \times 10^2$	E_a^a	$\log A$	$\Delta S^\ddagger^a$	$\Delta G^\ddagger$
CH ₂ Cl ₂	–15.0	2.83				
	0.0	7.34	9.7±0.2	6.6±0.2	–30±2	17.4
	9.9	15.10				
CF ₃ C(O)Me	–19.8	0.55				
	0.0	2.58	11.3±0.2	7.4±0.2	–26±2	17.9
	9.7	5.82				

^a Found from the plot for $\log k_2$ vs $1/T$ (in K).

The formation of transition state **A** is supported by the data¹⁸⁰ on the reaction of dimethyldioxirane **1a** with *cis*-1,2-dimethylcyclohexane in various solvents (Table 4). The reaction is facilitated by proton-donating solvents, which stabilise the spiro transition state.

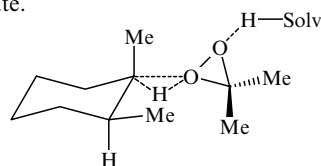


Table 4. Second-order rate constants for the reaction of dimethyldioxirane (**1a**) with *cis*-1,2-dimethylcyclohexane.¹⁸⁰

Solvent	$k_2 \times 10^3$ /litre mol ^{–1} s ^{–1}	Relative reactivity
MeC(O)Me	1.37±0.03	1.00
MeC(O)Et	1.29±0.01	0.94
MeC(O)OEt	1.02±0.02	0.74
CH ₂ Cl ₂	3.08±0.06	2.25
CHCl ₃	4.44±0.13	3.24
CDCl ₃	4.05±0.04	2.96

Note. The reaction was carried out in a solvent–acetone mixture (1 : 1) at 0 °C.

Kinetic data provide additional evidence supporting the 'insertion' mechanism; reactions described in numerous studies^{8, 37–39, 121, 145–147, 151, 162, 180} obey second-order kinetics (first-order kinetics with respect to each reactant). The fairly moderate primary kinetic isotope effect observed in the oxidation of cyclohexane-*d*₁₂ ($k_{\text{H}}/k_{\text{D}} \approx 2$)¹²¹ also points to a molecular mechanism of the reaction. In those cases where the reaction rate is limited by radical abstraction of a hydrogen atom from an *sp*³-hybridised carbon atom, the primary isotope effect increases substantially and can be greater than 10.^{181, 182}

Comparison of the relative reactivity of the dioxiranes **1a** and **1b** with respect to cumene and ethylbenzene^{121, 145} with the reactivity of the BuO[•] radical showed that dioxiranes are more selective; this also provides evidence for reaction (8). Finally, the mechanism of insertion is in good agreement with the results of theoretical calculations.¹⁸³

Despite all the above facts, which attest to the insertion mechanism, the radical reaction mechanism [reaction (9)] has been still considered in a number of recent publications.^{34–36, 184–190} An early publication that considered the radical character of the interaction of the dioxirane **1a** with alkanes and appeared in 1989¹¹⁹ dealt with the influence of O₂ on the products formed upon oxidation by dimethyldioxirane **1a** of a series of substituted benzaldehydes. The radical mechanism has been considered as a possible mechanism of oxidation of *para*-substituted α -methylbenzyl alcohols.¹⁶³

Later, the Minisci's research group³⁴ has obtained data on the strong influence of oxygen and inhibitors on the rate and the products of oxidation of a number of alkanes by the dioxirane **1a**. Thus it was found that the degree of conversion of alkanes in oxygen-free systems is much lower than that attained under ambient conditions, the corresponding alkyl acetates being formed as the major reaction products. Meanwhile, in the presence of O₂, the formation of acetates is largely suppressed. Trapping by TEMPO made it possible to detect the corresponding adducts with alkyl radicals. However, it was noted that TEMPO could induce decomposition of the dioxirane. This assumption has later been confirmed in another study.¹²⁴

When the reaction of the dioxirane **1a** with cyclohexane and adamantane was carried out in the presence of chinaldine, adducts of the trap with alkyl radicals were isolated.¹⁸⁴ The reactions of alkanes and adamantane with the dioxirane **1a** in the presence of CBrCl₃ resulted in a set of halo-containing products, their ratio being dependent on the **1a**:CBrCl₃ ratio.³⁵ These and other experimental facts led Minisci *et al.*^{34, 35, 184–186} to the conclusion that in the presence of alkanes, the compound **1a** undergoes radical chain decomposition induced by the alkyl radicals that have left the cage according to pathway *b* [reaction (9)]. The radical chain model has later been extended to reactions of dimethyldioxirane **1a** with esters and aldehydes.¹⁸⁴

The high selectivity of the oxidation of alkanes by dioxiranes was attributed to the unusual selectivity of the dioxirane biradical, compared with other alkoxy radicals; this biradical can selectively abstract an H atom from the substrate, which leads subsequently to the formation of the reaction products [reaction (9), pathway *a*]. Meanwhile, oxygen present in the system reacts with the radicals having left the cage [reaction (9), pathway *b*] and thus prevents the development of a radical chain process.³⁴

Analysis of the kinetic features of the oxidation of cumene by dimethyldioxirane **1a** and the products and the thermochemistry of the process also attest in favour of the radical character of the reaction.³⁶ An indirect proof of the formation of radicals is the slight chemiluminescence (obviously, caused by recombination of peroxy radicals¹⁹¹) in the visible region of the spectrum, which accompanies the reaction in question when it is carried out in the presence of oxygen.¹⁸⁷ According to the radical mechanism being discussed, chain decomposition of the dioxirane **1a** (in the absence of O₂) is responsible for its 'idle' consumption; therefore, the yields of the products of oxidation of cumene based on the converted dioxirane are relatively low.³⁶ A radical mechanism has also been

proposed for reactions of the dioxirane **1a** with isopentane¹⁸⁹ and adamantane.¹⁹⁰

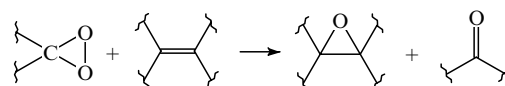
However, it can be easily seen that a radical chain mechanism for the reactions of dioxiranes with saturated hydrocarbons is at variance with the kinetic curves and with the high selectivity of oxidation reactions, which can be perfectly explained in terms of the insertion mechanism [reaction (8)]. These contradictions were partially eliminated in the study by Curci *et al.*,³⁷ which dealt with the oxidation of adamantane **24** by the dioxirane **1a** under various conditions. When the **1a**:**24** molar ratio was $\sim 1:1.2$, the oxidation gave an alcohol, 1-AdOH (91.5%), and a diol, 1,3-Ad(OH)₂ (4.5%). However, the reaction in the presence of CCl₃Br (*i.e.*, under the conditions used in the above-mentioned study by Minisci *et al.*³⁵) was appreciably less selective and yielded a series of side products: 1-AdBr (42.3%), 1-AdCl (9.2%), 2-AdBr (10.5%), 2-AdCl (2.5%), 2-AdOH (2.0%), adamantanone (<0.5%), *etc.*³⁷ The reaction kinetics, which corresponded to the simple second order without CCl₃Br (both in air and under an atmosphere of N₂), became more complex in the presence of this additive. It was also found that the addition of CCl₃Br induces rapid radical decomposition of the dioxirane **1a**.³⁷

Curci, Adam, *et al.*^{37–39} suggested that, when there are no factors able to induce decomposition of dioxirane (various admixtures, for example, metal ions, irradiation with light, *etc.*) and when there is no O₂, the radical chain mechanism is not involved in the oxidation of alkanes. The influence of drying agents (*e.g.*, MgSO₄) and impurities introduced together with drying agents can also be regarded as destabilising factors of this type. Other factors that should also be taken into account include temperature (it is reasonable to expect that at higher temperatures, the proportion of radical processes would increase and thus the process selectivity would decrease) and the nature of the substrate being oxidised (structural features, C–H bond strength, *etc.*).

An interesting view on the mechanism of reactions of dioxiranes with saturated hydrocarbons has been expressed by Asensio *et al.*¹⁹² A thorough study of the primary kinetic isotope effect and the products of the reaction of the dioxirane **1a** with cyclohexane and methylcyclohexane at various reaction conditions, both in solution (0 °C, Ar atmosphere) and in the gas phase (25 °C) showed that the radical chain process actually does contribute to the oxidation of cyclohexane and methylcyclohexane under experimental conditions but the major reaction products — cyclohexanone (in the case of cyclohexane) and the corresponding alcohol (in the case of methylcyclohexane) — are formed by the insertion mechanism.¹⁹² The researchers suggested that the formation of free radicals can be due to a change in the electronic configuration of dioxirane [namely, transition into the triplet (π, π^*)³ state with the properties of a biradical] induced by interaction with an alkane. Depending on the energy and the route of this interaction, the process follows either a radical chain mechanism (β -cleavage of the biradical to give methyl radicals) or an insertion mechanism [reaction (8)].¹⁹²

2. Oxidation of unsaturated compounds

Epoxidation of compounds containing double bonds is the best studied oxidative reaction of dioxiranes, which is often used for synthetic purposes.



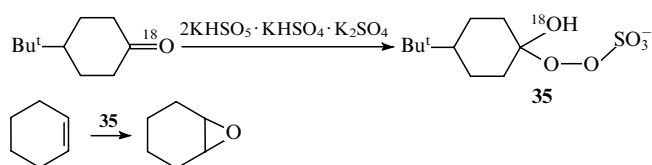
These reactions usually proceed at high rates, give products in good yields and are stereospecific. Yet another advantage of these reactions is that the possibility of conducting them under mild conditions (low temperatures, neutral medium) is combined with the possibility of isolating unstable epoxides; this can be seen taking the synthesis of pH-sensitive oxaspiropentanes from the corresponding methylenecyclopropanes as an example.¹⁹³ Dioxiranes efficiently epoxidise alkenes containing electron-donating

substituents,^{104, 107, 194–196} which obviously makes them better epoxidising agents compared to other peroxides because dioxiranes are more reactive; this allows the synthesis of relatively labile epoxides. The fact that dioxiranes are able to oxidise electron-unsaturated alkenes is equally significant.^{103, 104, 197–199} Although these reactions are usually rather slow, the use of excess dioxirane makes it possible to attain high yields of epoxides.

Epoxidation can be carried out both using isolated dioxiranes and *in situ*.^{103, 104, 106, 107, 200–205} In the latter case, the pH of the medium should be strictly controlled (7.3–7.5). The procedures using isolated dioxiranes are not faced with this problem. In some cases, phase transfer catalysts are used (for example, for water-insoluble substrates). In this respect, the *in situ* procedure with the use of Caro's acid derivatives (peroxomonosulfates) seems quite promising.²⁰⁶ In this procedure, dioxiranes are generated in a homogeneous organic medium, which substantially facilitates the oxidation. An advantage of the *in situ* method is that ketone is virtually not consumed in the reaction (only the oxone is consumed) and can be quantitatively recovered after its completion.

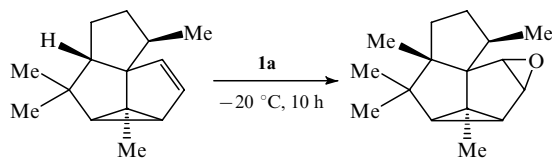
The *in situ* reactions in which the corresponding optically active ketones are used as the precursors of dioxiranes present considerable interest.^{107, 203–205} Thus the use of (+)-3-(trifluoroacetyl)camphor or *R*-(+)- and *S*-(-)-4,4,4-trifluoro-3-methoxy-3-phenylbutan-2-one as the initial ketones allowed asymmetric epoxidation of prochiral alkenes (*trans*- β -methylstyrene, *trans*-oct-2-ene, *cis*-2-methyloctadec-7-ene) with optical yields of 12%–20%.²⁰³ Enantioselective epoxidation of *trans*-stilbene and its 4,4'-dialkyl-substituted homologues catalysed by chiral ketones in the presence of oxone (2KHSO₅·KHSO₄·K₂SO₄) at ~20 °C affords the corresponding epoxides (yields 90%–95%) with 75%–93% enantiomeric purity.²⁰⁴

Regarding the *in situ* oxidation, it is noteworthy that, based on the experiments with ¹⁸O isotope labelling, it has been suggested that the dioxirane intermediate is not responsible for the *in situ* epoxidation of alkenes.²⁰⁷ Thus in the epoxidation of cyclohexene, it is not dioxirane that acts as the main oxidation agent but rather the product of addition of the HOOSO₃⁻ anion to the carbonyl group of the transferring ketone — compound **35** (corresponding to intermediate **A** in Scheme 2).²⁰⁷

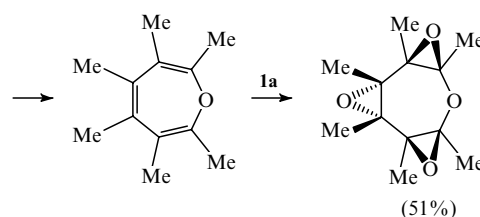
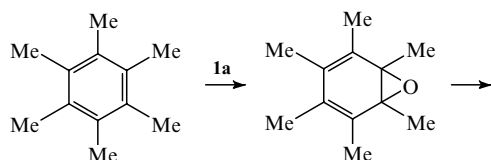


The reactions of dioxiranes (both *in situ* and in a pure state) with *cis*- and *trans*-alkenes are stereoselective: *cis*- and *trans*-alkenes are converted into *cis*- and *trans*-epoxides, respectively (the *cis*-compounds are more reactive).^{103, 104, 107, 195, 196, 208}

Treatment of strained polycyclic alkenes with the dioxirane **1a** resulted in the synthesis of the corresponding epoxides.²⁰⁹

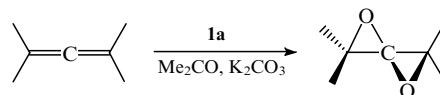


Oxidation of hexamethylbenzene by the dioxirane **1a** gives hexamethylbenzene polyoxides *via* the intermediate formation of 2,3,4,5,6,7-hexamethyloxepine.²¹⁰



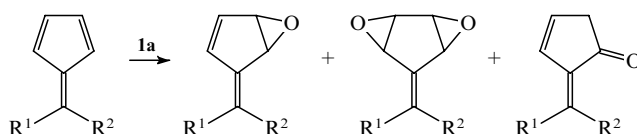
exo,exo,exo-3,6,9-Tris(4-methylphenylsulfonyloxymethyl)-*cis,cis*-cyclonona-1,4,7-triene reacts with this dioxirane in a similar way.²¹¹

The dioxirane **1a** oxidises allenes and their derivatives (allene alcohols and acids) to give the corresponding dioxides.^{212–216}



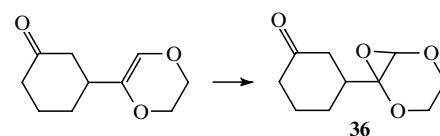
On treatment with the dioxirane **1a**, (*E*)- and (*Z*)-arylideneindolones give the corresponding spiro epoxides in 70%–90% yields (the process is fully diastereoselective).²¹⁷

The reactions of 6,6-disubstituted pentafulvenes, containing conjugated double bonds with different reactivities, with an excess of the dioxirane **1a** afford endocyclic diepoxides in good yields. When the reactants are taken in stoichiometric amounts, a mixture of mono- and diepoxides is formed²¹⁸ (the exocyclic double bond remains intact, pointing to an electrophilic nature of **1a** in the oxidation).

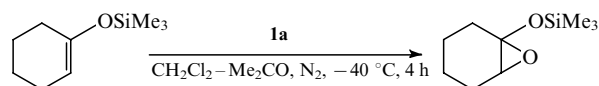


Dioxiranes are able to oxidise allyl alcohols,¹⁰⁶ alkenyl hydroperoxides,¹⁷² vinylsilanes²¹⁹ and unsaturated ketones, acids and esters^{220, 221} to give the corresponding epoxy derivatives in good yields.

Oxidation of 4-dioxenylcyclohexanone gives rise to epoxide **36**.²²²



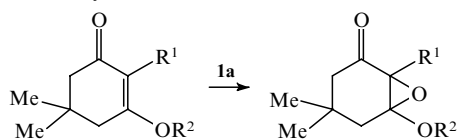
Oxidation of silyl ethers of enols by peroxides, resulting in the formation of α -hydroxy ketones, has been suggested to occur *via* intermediate epoxide.²²³ This type of epoxide also proved to be produced from silyl ether, phosphates and esters of enols as well as from γ,δ -unsaturated 5- and 6-membered lactones on treatment with the dioxirane **1a**. These compounds can be isolated in a pure state.²²⁴



High yields (92%–97%) of spiro oxiranes have also been detected in the oxidation of enol ethers, for example alkoxy(aryl)methylidenadamantanes and methoxy(2-naphthyl)methylidene-2-bornane by the dioxirane **1b**.²²⁵ Note for comparison that synthesis of epoxy esters and strained oxaspiroalkanes involving peroxy acids often does not lead to acceptable results, because the oxiranes formed in the reaction rearrange in the presence of acids to give α -alkoxy or α -hydroxy ketones.

The ability of the dioxiranes **1a** and **1b** to epoxidise electron-unsaturated alkenes can be illustrated by the oxidation of 4-substituted (*E*)-ethyl cinnamates by the dioxirane **1a**.¹⁹⁸ Enol ethers of

β -diketone, which are relatively inert, can also be quantitatively epoxidised by the dioxirane **1a**.¹⁹⁹



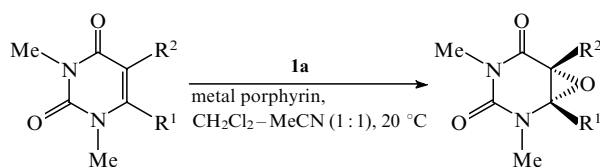
$R^1 = H, Me$; $R^2 = Et, Bu, Ph$.

The corresponding epoxides are also formed in the oxidation of enol phosphates,²²⁶ γ -methylene- γ -butyrolactones²²⁷ and acyl- and allylferrocenes.²²⁸

Epoxidation of primary and secondary alkenylammonium salts by the dioxiranes **1a** and **1b** gives rise to epoxy derivatives; on treatment with sodium carbonate, they are readily converted into epoxyalkylamines, formed in good yields.²²⁹ The epoxidation rate is lower than that in the case of epoxidation of simple alkenes because the double bonds are deactivated due to the ammonium groups.

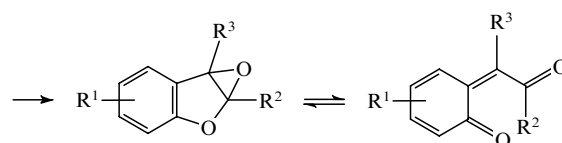
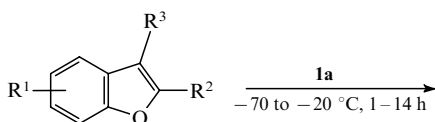
Adam *et al.*²³⁰ were able to detect the low-temperature NMR signals of epoxides of *cis*- and *trans*-(2-methyloxiranyl)benzamide, which result from oxidation of (*E*)- and (*Z*)-*N*-propenylbenzamides by the dioxirane **1a**.

Examples of catalytic epoxidation of alkenes by dioxiranes have been reported in several studies.^{231–233} Thus epoxidation of 2,2-dimethyl-2*H*-chromenes by the dioxirane **1a** in the presence of chiral Mn(III)(salen) complexes (Jacobsen catalysts) occurs enantioselectively. Selective synthesis of epoxides of uracil derivatives (important intermediates in oxidative transformations of DNA) catalysed by metal porphyrins has been described.²³³ (The attempt to prepare uracil epoxides without a catalyst using the dioxirane **1a** as the oxidant was less successful; the yields of the corresponding epoxides were low and side products formed²³⁴). The reaction was carried out in CH_2Cl_2 –MeCN (1 : 1) at 20 °C in the presence of imidazole.



Other dioxiranes also possess high oxidative potentials.^{1, 81, 82, 117, 235} Thus ethylmethyldioxirane **1m** has been used to epoxidise natural triglycerides in the butan-2-one–water two-phase system in the presence of the 18-crown-6 ether,²³⁵ while difluorodioxirane **1k** has been employed to epoxidise fluorinated alkenes $CF_3CF=CF_2$ and $F_2C=CFCl$ (the yields of epoxides are >95%).⁸²

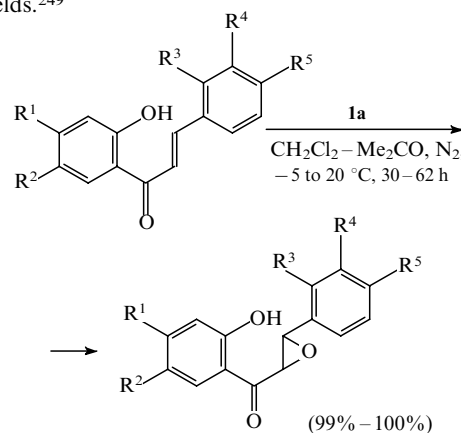
Special mention should be made of those studies that are valuable not only for synthetic purposes but also from the medical or biological viewpoint. For example, this is true for several works^{236–245} dealing with epoxidation of furans by dioxiranes. Benzofurans are known to be toxic for animals and humans. Their toxicity may be due to the presence of labile epoxides, resulting from oxidation of the furan ring.^{236, 246, 247} However, benzofuran epoxides had not been detected even at low temperatures. This became possible only using the dioxirane **1a**.^{236–243} This reagent was employed to prepare epoxides of substituted benzofurans, occurring in equilibrium with the corresponding quinonemethides.



$R^1 = H, Me, OMe, Cl, MeCO$; $R^2 = H, Me, CH_2OH, CH(OMe)Ph, CO_2Et$; $R^3 = H, Me, Bu^t, C_6H_3R^4R^5-3,4$ ($R^4 = H, NO_2$; $R^5 = H, MeO$).

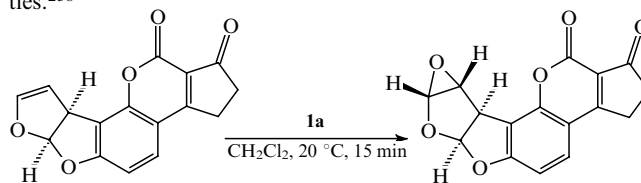
Using the dioxirane **1a**, regio- and stereoselective oxidation of the C(3) = C(4) enol bonds in the molecules of biologically active triterpenes containing a norquinonemethide fragment (*e.g.*, pristimerin, tingenone) was attained.²⁴⁸

Oxidation of steroids, flavones and chalcones by dioxiranes is equally important.^{249–257} Chalcone epoxides are significant building blocks in organic synthesis; they play an important role in the biosynthesis of many flavonoid systems. Oxidation of hydroxychalcones by the dioxirane **1a** resulted in the formation of epoxide products, unstable in acidic or alkaline media, in high yields.²⁴⁹



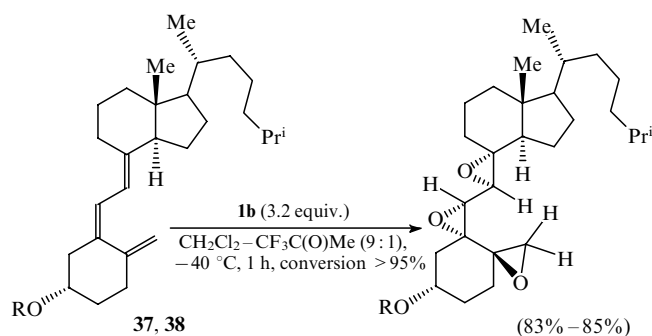
R^1	R^2	R^3	R^4	R^5
H	Cl	H	H	H
H	H	H	H	Cl
H	H	MeO	H	H
H	H	H	MeO	H
Me	H	H	H	H
H	Me	H	H	MeO
H	Cl	H	H	MeO

Epoxidation reaction has been successfully used to prepare the 8,9-epoxide of the aflatoxin B₁, noted for its carcinogenic properties.²⁵⁸



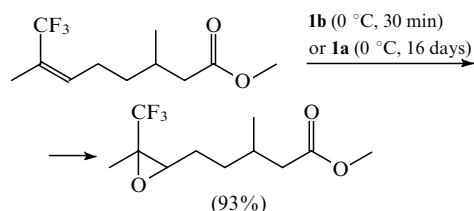
The reactions of the dioxiranes **1a** and **1b** with vitamin D₃ and its 3-*O*-acylated derivatives were reported to be highly selective.²⁵⁹ The reaction of 3 β -acetyl- (**37**) and 3 β -(*p*-bromobenzoyl)-derivatives (**38**) of vitamin D₃ with methyl(trifluoromethyl)dioxirane **1b** gives rise to the corresponding (*R,R,R*)-triepoxides.

On treatment with the same dioxirane, vitamin D₂ and its 3 β -*O*-acetyl-derivative are converted into the corresponding (*R,R,R,R*)-tetraepoxides.²⁶⁰

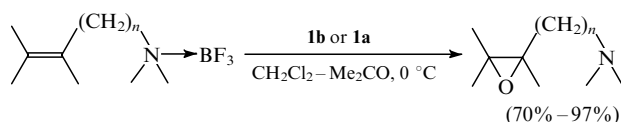


R = Ac (37), *p*-BrC₆H₄CO (38).

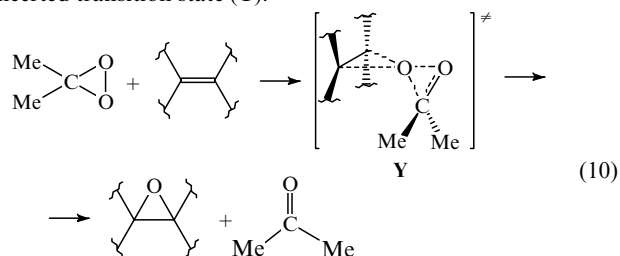
Mention should be made of interesting studies^{261, 262} in which dioxiranes have been used to synthesise epoxy-derivatives of insect juvenile hormones, which play an important role in the growth and development of insects. An example of epoxidation of a compound containing a CF₃ group at a double-bond carbon atom has been reported.²⁶²



Epoxidation of aminoalkenes is used to prepare indole alkaloids. However, epoxidation of this type of substrates by traditional reagents is hampered by the predominant oxidation of the nitrogen atom. Only recently,²⁶³ were epoxides of several tertiary amines containing alkenyl groups synthesised chemoselectively using dioxiranes in the presence of BF₃·Et₂O.



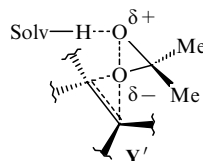
The reactions of dioxiranes with alkenes (Table 5) is described by a second-order equation^{39, 116, 195, 196, 198, 264, 265} (*cis*-isomers react approximately 10 times faster than *trans*-isomers). Based on experimental data, a reaction mechanism has been proposed,¹⁹⁶ which includes a stage of formation of a spiro-type concerted transition state (Y).



This mechanism is in good agreement with the results obtained by Murray and Gu²⁶⁴ concerning the influence of solvents on the rates of epoxidation of *trans*-ethyl cinnamate and cyclohexene; analysis of the kinetic data in terms of the Kamlet–Taft equation, which takes account of the ability of a solvent to act as a hydrogen bond donor (HBD) or acceptor (HBA), showed that HBD solvents increase the rate of epoxidation, whereas HBA solvents retard this process.²⁶⁴ Transition state Y', which is similar to Y but takes into account the solvent effect on the reaction rate, explains well the characteristic features observed.

Table 5. Second-order rate constants for epoxidation of di- and mono-substituted alkenes by the dioxirane **1a** in dry acetone (according to Ref. 195).

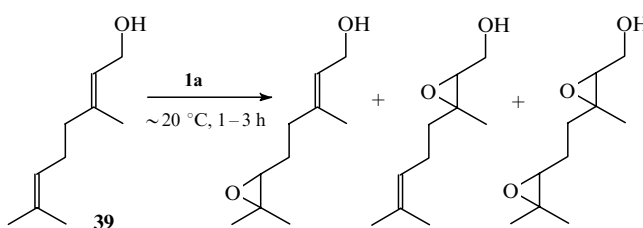
Alkene	$k_2 \times 10^2 / \text{litre mol}^{-1} \text{s}^{-1}$	Relative reactivity
<i>cis</i> -Hex-3-ene	47±3	8.3
<i>trans</i> -Hex-3-ene	5.7±0.4	1.0
<i>cis</i> -4,4-Dimethylpent-2-ene	33±2	5.8
<i>trans</i> -4,4-Dimethylpent-2-ene	2.3±0.1	0.4
<i>cis</i> -2,5-Dimethylhex-3-ene	39±2	6.8
<i>trans</i> -2,5-Dimethylhex-3-ene	2±1	0.4
<i>trans</i> -2,2,5,5-Tetramethylhex-3-ene	0.024±0.004	0.004
Cyclohexene	48±2	8.4
<i>cis</i> -1-Phenylpropene	18±2	3.2
<i>trans</i> -1-Phenylpropene	29±2	5.1
<i>cis</i> -Stilbene	4.0±0.1	0.70
<i>trans</i> -Stilbene	4.3±0.2	0.75
Indene	22±1	3.9
4-Methoxystyrene	57±3	10.0
4-Methylstyrene	25±1	4.4
Styrene	13±1	2.3
4-Bromostyrene	8.9±0.3	1.6
3-Nitrostyrene	3.0±0.3	0.53
3,3-Dimethylbut-1-ene	3.3±0.1	0.58
3-Methylbut-1-en-3-ol	1.6±0.2	0.28



In fact, HBD solvents (MeOH, CDCl₃, AcOH) stabilise the negative charge on the oxygen atom involved in H-bonding with a solvent molecule and thus facilitate epoxidation. Conversely, HBA solvents destabilise the transition state, which decelerates the reaction. This assumption accounts for the fact that addition of water (which can be regarded as an HBD solvent) increases the epoxidation rate.¹⁹⁵ The relatively large negative values of the entropy factor $\Delta S^\ddagger$ also support the assumed formation of an ordered spiro transition state.²⁶⁴

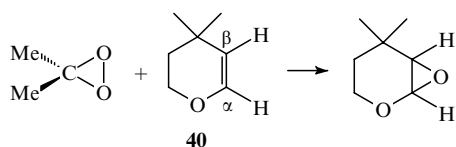
The data obtained by Messeguer *et al.*,¹¹⁶ who studied the influence of solvents on the epoxidation of *cis*-stilbene by more concentrated solutions of the dioxirane **1a** (see Section II), are in good agreement with the results of Murray and Gu²⁶⁴ with the only difference that in the former case,¹¹⁶ the effect was more pronounced due to the use of acetone-free solutions of **1a**.

The solvent effect, like the influence of substituents, is manifested not only as a change in the reaction rate but also as a change in the diastereoselectivity and regioselectivity of epoxidation.^{266–268} It was shown^{266, 267} that diastereoselectivity of epoxidation of substituted cyclohexenes by the dioxirane **1a** is determined by the substrate structure and the solvent, which includes steric effects, dipole–dipole interactions, effects of hydrogen bonding and other factors. A similar solvent effect is involved in the epoxidation of acyclic allyl alcohols,²⁶⁸ in particular, geraniol **39**.



In a polar medium, MeOH–Me₂CO (9 : 1), the ratio of the 6,7- and 3,2-monoepoxides is 88 : 12, whereas in a less polar system, CCl₄–Me₂CO (9 : 1), it is equal to 51 : 49.²⁶⁸ In fact, the Δ^6 double bond in the alcohol **39** is more nucleophilic than the Δ^2 bond, deactivated by the OH group; hence, it is the Δ^6 bond that will be attacked predominantly by dioxirane. Methanol stabilises the transition state due to the formation of a hydrogen bond, so that the contribution of the geraniol OH group to the stabilisation of the transition state is minimised.²⁶⁸ Conversely, in non-polar CCl₄, the external stabilisation is much less pronounced and the transition state is largely stabilised by the OH group belonging to the alcohol **39** molecule, resulting in a higher yield of the 2,3-epoxides.²⁶⁸

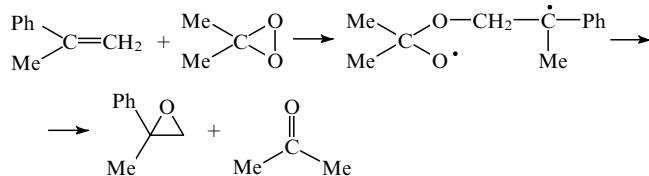
An interesting situation is observed when 4,4-dimethyl-2,3-dihydro- γ -pyran **40** is oxidised by the dioxirane **1a**.²⁶⁹



Measurements of the secondary kinetic isotope effect showed that in the transition state *en route* to the epoxide, the degree of rehybridisation of the β -carbon atom is higher than that of C $_{\alpha}$. Hence, this reaction does not proceed *via* a symmetrical transition state but occurs as a non-synchronous concerted process.²⁶⁹ This result cannot be extended to simple alkenes in which the electron densities at the C $_{\alpha}$ and C $_{\beta}$ atoms are identical. In fact, the experimental values for the α - and β -isotope effects found for the reactions of **1a** with 3-methyl-1-phenylbut-2-ene and 2,2,7,7-tetramethyl-*cis*-oct-4-ene and their deuterated analogues support the formation of a concerted transition state of the spiro type.²⁷⁰

Study of the epoxidation kinetics also confirms the electrophilic mechanism of the reaction: Hammett correlations for a series of substituted styrenes¹⁹⁵ and 4-substituted (*E*)-ethyl cinnamates¹⁹⁸ give the values $\rho^+ = -0.9$ and -1.153 , respectively. Study of the kinetics of epoxidation of chalcones (anhydrous acetone, 30 °C) showed that electron-donating substituents at 4 and 4'-positions accelerate the reaction (for 4- and 4'-substituted chalcones, $\rho^+ = -1.03$ and -0.182 , respectively).²⁶⁵

As noted above, experimental results point to a molecular mechanism of the epoxidation of alkenes by dioxiranes [reaction (10)]. However, arguments for a free radical mechanism of epoxidation have also been reported.¹⁸⁵ Thus the oxidation of α -methylstyrene by the dioxirane **1a**, in addition to the epoxide (35%) and α -phenylpropionaldehyde (51%), resulting from its rearrangement, gave the allyl alcohol PhC(CH₂OH) = CH₂ (6%) and the corresponding aldehyde PhC(CHO) = CH₂ (5%). It was suggested¹⁸⁵ that alkenes can induce homolysis of dimethyldioxirane **1a** and the formation of epoxides can be explained in terms of a radical mechanism.



These data, which contradict the molecular mechanism of the reaction, have been specially considered in the study by Adam, Curci, *et al.*³⁹ The results obtained by these researchers³⁹ indicated that the reactions of alkenes with dioxiranes involve no radical processes. In particular, the reaction of the dioxirane **1a** with α -methylstyrene obeys second-order kinetics both under ordinary conditions and under an inert atmosphere (N₂), the corresponding epoxide being the only reaction product (neither allyl alcohol nor the aldehyde were detected even under conditions most favourable for radical chain processes, *viz.*, in the presence of

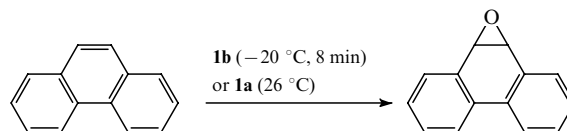
CBBrCl₃ at 56 °C). Investigation of epoxidation of *trans*-cyclooctene and 2-vinylcyclopropane also supported the hypothesis that no radical chain processes are involved.³⁹

These examples indicate once again that, in all probability, in the absence of factors that could induce a radical chain process, oxidation of alkanes and alkenes by dioxiranes does not include radical pathways of transformation.^{37–39}

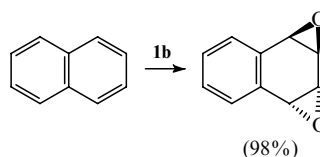
3. Oxidation of polyaromatic hydrocarbons

Study of the chemical transformations of PAH on treatment with dioxiranes is an exceptionally important problem, if for no other reason than that many PAH are hazardous carcinogens. The mutagenic and carcinogenic action of PAH is preceded by a metabolic activation process,²⁷¹ comprising a complex sequence of oxidative transformations, unstable arene oxides being the most significant intermediates in these processes. These important intermediates are prepared in most cases using multistage syntheses. The use of direct oxidation by classical reagents (peroxy acids, hypochlorites, *etc.*) is often restricted because many arene oxides are sensitive to acids, water or nucleophiles.

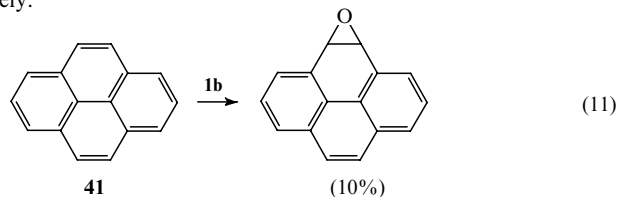
Dioxiranes are convenient reagents for oxidative functionalisation of PAH.^{1, 3, 40, 47–47, 272, 273} Thus the reactions of the dioxiranes **1a** and **1b** with phenanthrene in solution afford the corresponding oxide in 83% and 96% yields, respectively.^{1, 272}



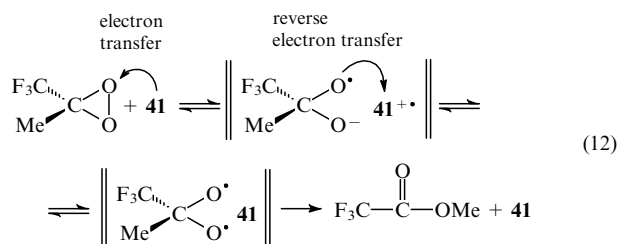
Another typical example is the reaction of the dioxirane **1b** with naphthalene, which gives *anti*-1,2:3,4-dioxide.²⁷²



However, the reaction with pyrene **41** occurs less effectively.²⁷²



Among the products of reaction (11), CF₃COOMe (a product of decomposition of the dioxirane **1b**, see Section III) was also detected, and the EPR spectrum of the system (–30 °C) contained a signal for the pyrene radical cation.²⁷² It was suggested²⁷² that the low yield of the oxidation products is due to the competing electron transfer reaction, giving rise to CF₃COOMe.



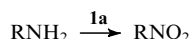
An essentially similar mechanism has been proposed to interpret the chemiluminescence of dioxiranes in the presence of some activating agents, which is discussed in detail in Section V.

In view of the formation of dioxiranes in gas-phase ozonisation of unsaturated hydrocarbons,^{41–44} the relatively high concentrations of O₃, alkenes and PAH in the atmosphere and the carcinogenic properties of PAH, Murray *et al.*^{1,3,40,46} suggested that reactions of dioxiranes with PAH might be responsible for the formation of carcinogenic compounds in the atmosphere. To verify this hypothesis, gas-phase oxidation of PAH under conditions close to the atmospheric conditions was carried out.^{3,46,47} A gas stream of the dioxirane **1a** in acetone or a Me₂CO–CH₂Cl₂ mixture was directed at PAH supported on silica gel. Although in most cases, the yield of the resulting oxides was lower than that in the case of liquid-phase oxidation, this experiment demonstrated that dioxiranes can be involved in possible atmospheric reactions with PAH. Moreover, when PAH deposited on silica gel were oxidised by the O₃–Me₂C=CMe₂ gas mixture,⁴⁷ the reaction gave products similar to those obtained when the dioxirane **1a** is used as the oxidant (ordinary ozonolysis does not yield this type of products under these conditions).

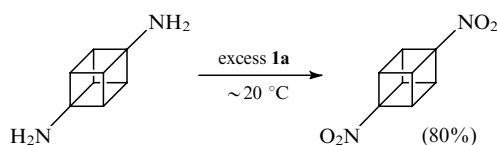
4. Oxidation of compounds containing heteroatoms

a. Nitrogen-containing compounds

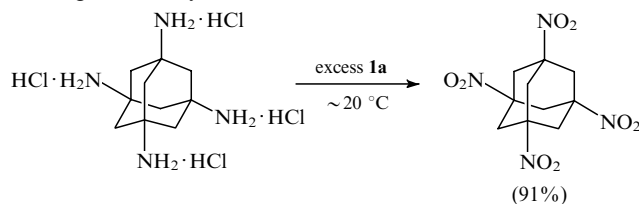
Oxidation of primary amines by dimethyldioxirane **1a** occurs rapidly (taking from several minutes to several hours) and affords the corresponding nitro compounds.^{274,275}



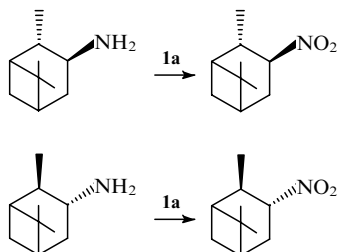
Polyamines are also converted into nitro compounds. Thus 1,4-diaminocubane reacts with **1a** to give 1,4-dinitrocubane.²⁷⁵



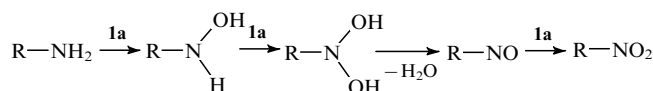
The latter compound can also be obtained by the reaction of the dioxirane **1a** with 1,4-diisocyanatocubane (however, in this case, the presence of H₂O is required).²⁷⁶ Yet another typical example of oxidation of polyamines is the transformation of 1,3,5,7-tetraaminoadamantane,²⁷⁵ which is extremely explosive although thermally stable.



Chiral amines are converted into the corresponding nitro compounds with retention of the configuration.²⁷⁷

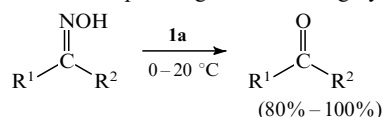


Presumably,²⁷⁴ oxidation of primary amines includes several stages, hydroxylamines and nitroso compounds being formed as intermediate products; the process can be partially controlled at the stage of formation of hydroxylamine.²⁷⁸

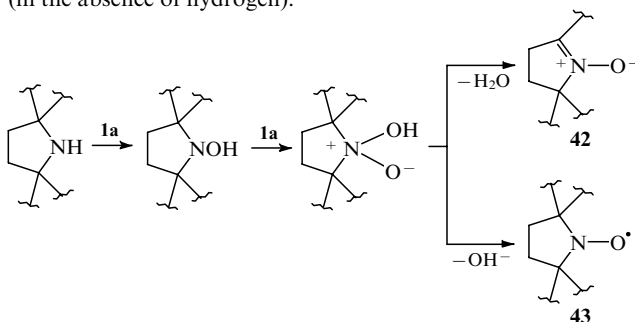


This sequence of reactions can include either insertion of oxygen into the N–H bond (similar to the insertion into C–H bonds of saturated hydrocarbons) or formation of an intermediate such as *N*-oxide followed by its rearrangement into hydroxylamine.²⁷⁷

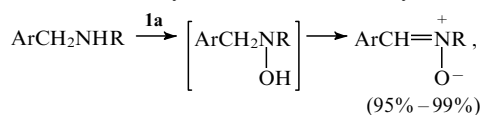
Nitro compounds are not always the only reaction products. Thus oxidation of some aliphatic primary amines by the dioxirane **1a** (either isolated or *in situ*) gives, depending on the reaction conditions, oximes, nitrosoalkanes, nitroalkanes and oxaziridines.²⁷⁹ In some cases, the corresponding nitrones, arising upon oxidation of intermediate imines, can also be found among the reaction products.²⁷⁹ Oxidation of ketoximes by the dioxirane **1a** gives the corresponding ketones in high yields.²⁸⁰



Secondary amines react with the dioxirane **1a** (1:1) to give hydroxylamines.²⁸¹ When excess dioxirane is used, the process affords either nitron **42** (in the presence of hydrogen at the α-position in relation to the amino group) or stable nitroxide **43** (in the absence of hydrogen).²⁸²



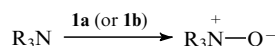
A series of nitrones have been prepared by the reaction of the dioxirane **1a** with aryl-substituted secondary amines.^{283,284}



while oxidation of *N*-methylaniline gives rise to dinitrone.²⁸⁴

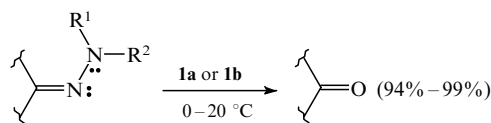
Nitroxides are formed in good yields when secondary amines are oxidised by dioxiranes generated *in situ* in the system Me₂CO–(2KHSO₅·KHSO₄·K₂SO₄)–CH₂Cl₂–H₂O–Bu₄NHSO₄ (phase transfer catalyst).²⁸⁵

Tertiary amines including pyridines are oxidised by the dioxiranes **1a** and **1b** to give *N*-oxides.^{3,105,263,286,287}



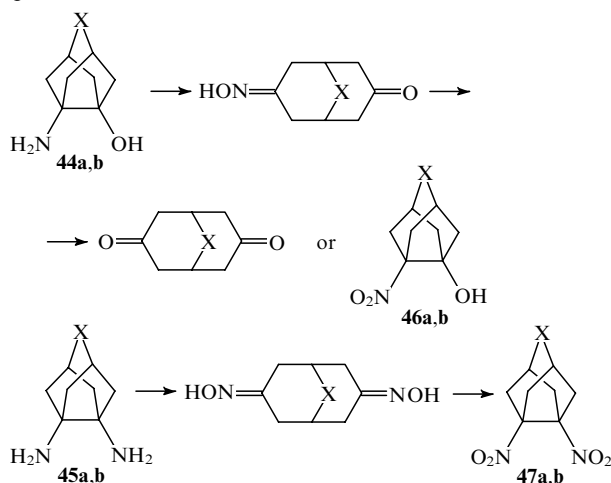
It is noteworthy that some *N*-oxides cause decomposition of dioxiranes,^{3,263,286} which gives singlet oxygen²⁸⁶ (see Section V).

Dioxiranes proved to be convenient reagents for the recovery of the initial ketones from derivatives of hydrazones,²⁸⁸ which are often used in organic chemistry to isolate carbonyl compounds from reaction mixtures and to purify them.



Recently²⁸⁹ new versions of the oxidation of amines with participation of the dioxirane **1a** have been found. They include (1) oxidative fragmentation of 2-amino alcohols **44a,b** or 1,2-diamines **45a,b** to give the corresponding mono- and dioximes of bicyclic diketones and (2) intramolecular oxidative transforma-

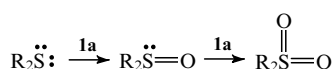
tion of the latter into tricyclic 2-nitro alcohols **46b** and 1,2-dinitro compounds **47a,b**.



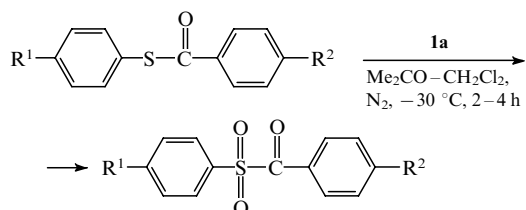
X = CH₂ (**a**), C₆H₄-*o* (**b**).

b. Sulfur- and phosphorus-containing compounds

Dioxiranes selectively oxidise sulfides to the corresponding sulfoxides (equimolar ratio of the reactants) and sulfones (excess dioxirane).



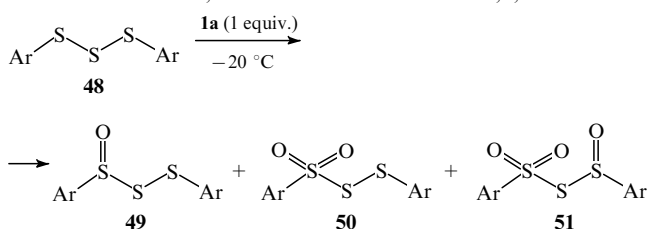
Thus thioesters are quantitatively oxidised by dimethyldioxirane **1a** to give labile α -oxo sulfones.²⁹⁰



Oxidation of (*Z*)-thioaurones, (*E*)-3-arylidene-1-thiochroman-4-ones and (*E*)-3-arylidene-1-thioflavan-4-ones by the dioxirane **1a** gives rise to the corresponding sulfoxides and/or sulfoxides.²⁹¹ The reaction of the dioxirane **1a**, taken in an excess, with ketene *S,S*-acetals, thioacetals and thioketals affords the corresponding bis(sulfoxides) in excellent yields.²⁹² When bis(sulfides) are treated with one, two or three equivalents of dimethyldioxirane, this gives monosulfoxides, bis(sulfoxides) and sulfoxide sulfones, respectively, the ratio of the products depending appreciably on the reaction temperature and the order in which the reactants are mixed.²⁹²

The corresponding sulfides and sulfones are formed in high yields in the chemoselective oxidation of the pentacarbonyl[amino(arylthioalkyl)carbene]chromium(0) complex by the dioxirane **1a**.²⁹³

Low-temperature (−20 °C) oxidation²⁹⁴ of bis(*p*-methoxyphenyl)trisulfane **48** results in the formation of monooxide **49** and a small amount of 1,1-dioxide **50** and trisulfane-1,1,3-trioxide **51**.

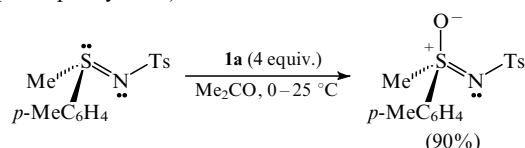


Ar = 4-MeOC₆H₄.

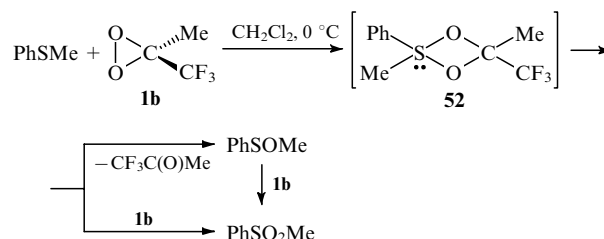
High enantiomeric yields have been attained in the oxidation of prochiral sulfides to chiral sulfoxides by dioxiranes generated *in situ*.²⁹⁵

In reactions with sulfides, dioxiranes act as electrophilic reagents; the Hammett correlations found for the oxidation of a series of methyl 4-*R*-phenyl sulfides to sulfoxides and oxidation of sulfoxides to sulfones gave the values $\rho^+ = -0.77$ and -0.76 , respectively, the reactions of dioxiranes with sulfides being faster than those with sulfoxides.²⁹⁶ Using the reaction with thianthrene 5-oxide as an electrophilicity test,²⁹⁷ Adam and Golsch²⁹⁸ also confirmed the electrophilic nature of the dioxirane **1a** as an oxidant.

This is indicated by the fact that the rate of oxidation of sulfolimines containing electron-donating substituents in the aromatic nucleus by the dioxirane **1a** is markedly higher than the rate of oxidation of sulfolimines with electron-withdrawing substituents.²⁹⁹ It is noteworthy that the above-described method proved to be convenient for the synthesis of chiral sulfoxylimines (optical purity 80%).



When considering the mechanism of oxidation of sulfur-containing compounds, mention should be made of a study³⁰⁰ dealing with the oxidation of methyl phenyl sulfide by the dioxirane **1a** and postulating the formation of a hypervalent sulfurane intermediate **52**.

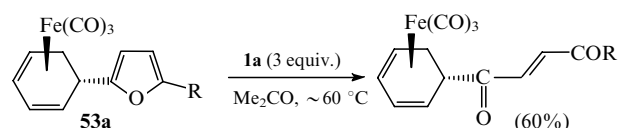


Among the few examples of oxidation of phosphorus-containing compounds by dioxiranes, the reaction of methyl(trifluoromethyl)dioxirane **1b** with triphenylphosphine, resulting in the phosphine oxide, deserves attention; this reaction is used to determine dioxirane concentrations.

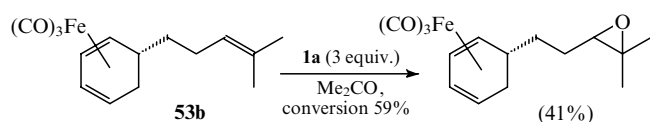
c. Oxidation of organometallic compounds

The above oxidative transformations involving dioxiranes also take place during oxidation of metal-containing compounds.³⁰¹ In the majority of cases, these reactions are highly chemoselective, because they are not accompanied by oxidative decomposition of metal complexes.

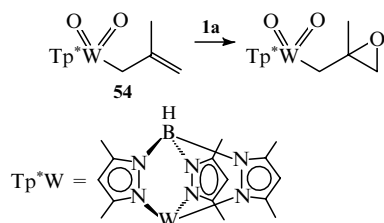
Oxidation of tricarbonyl iron complexes **53a**, containing a furylcyclohexadiene ligand is accompanied by opening of the furan ring and gives rise to the corresponding carbonyl compound.³⁰²



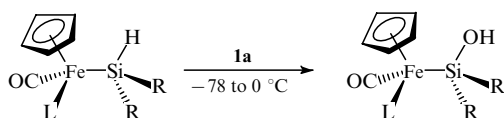
Oxidation of iron complex **53b** having a similar structure yields a 1:1 mixture of diastereoisomeric epoxides. The most plausible results were attained at elevated temperatures (at low temperatures, oxidative decomposition of the complex upon direct oxidation of iron occurs as a side reaction).³⁰³



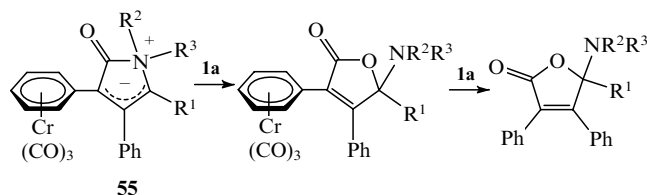
The reaction of the tungsten alkene complex with the dioxirane **1a** results in the quantitative formation of the corresponding epoxide.³⁰⁴



Ferrohydrosilanes react with **1a** to give the corresponding ferrosilanol.^{305, 306}

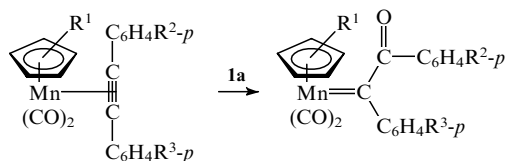


The reaction of the ylide (η^6 -arene)chromiumtricarbonyl complex **55** with the dioxirane **1a** gives the corresponding lactone complex, which is converted in the metal-free lactone on further addition of the oxidant.³⁰⁷

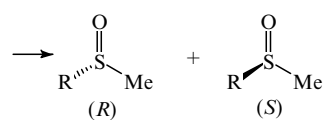
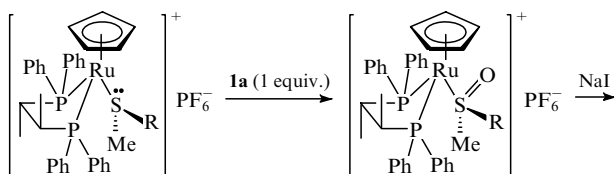


$\text{R}^1 = \text{H, Me, Ph; R}^2 = \text{R}^3 = \text{Me, R}^2 - \text{R}^3 = (\text{CH}_2)_5, \text{R}^2 = \text{Me, R}^3 = \text{cyclo-C}_3\text{H}_5.$

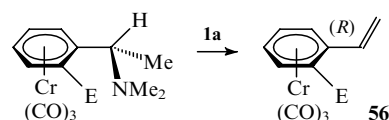
The oxidative capacity of dioxiranes is clearly illustrated taken as an example the transformation of tolane manganese-containing complexes into α -oxocarbene complexes (apparently, this reaction proceeds *via* intermediate epoxidation of the alkyne).³⁰⁸



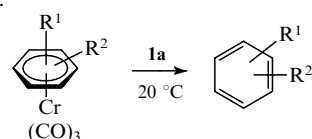
Oxidation of iron and tungsten phosphine complexes gives rise to the corresponding metal phosphine oxides.³⁰⁹ Sulfur-containing metal complexes are also oxidised by dioxiranes.^{310–312} Thus a new approach to the synthesis of chiral sulfoxides *via* diastereoselective oxidation by the dioxirane **1a** of a prochiral thioether incorporated in a metal complex was reported.^{311, 312} A chiral sulfoxide complex of ruthenium is formed as an intermediate in this reaction. The subsequent decomposition of this complex results in the liberation of chiral sulfoxide.



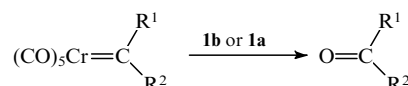
Enantiomerically pure vinyl-substituted complex **56** has been synthesised by the oxidation of chiral amino-containing (η^6 -arene)chromiumtricarbonyl complex by the dioxirane **1a**.³¹³



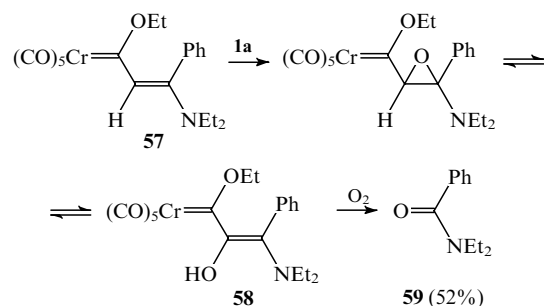
Apart from oxidation of the ligands, dioxiranes can be used for oxidative decomposition of metal complexes. Thus the organic ligands incorporated in the (η^6 -arene)chromiumtricarbonyl complexes are quantitatively liberated on treatment with the dioxirane **1a**.³¹⁴



The reaction of dioxiranes with Fischer carbene complexes follows a similar pathway.^{301, 315–317}

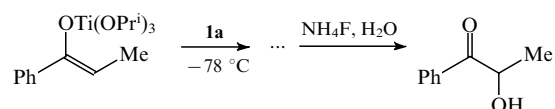


However, in the case of the Fischer complexes **57**, containing conjugated enamine fragments, the reaction loses the above-noted selectivity and yields, instead of the expected enamino ester, amide **59** *via* intermediate **58**.³¹⁷

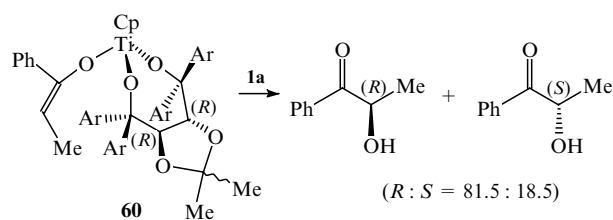


During decomplexation of (η^4 -diene)irontricarbonyl and μ -(η^2 -alkyne)dicobalthexacarbonyl complexes, the process of liberation of organic ligands induced by dioxirane **1a** competes with the oxidation of the unsaturated fragments present in the compounds being liberated.³¹⁸

Lithium, sodium and titanium enolates are converted in most cases into the corresponding α -hydroxy carbonyl products.^{159, 319, 320} It is of interest that the best results are achieved when the reaction is carried out at reduced temperatures.



The stereoselectivity of oxidation of chiral enolates hardly depends on the temperature and the solvent but depends on the nature of the ligands attached to the central metal atom.³²⁰ The highest enantiomeric excess for 2-hydroxy-1-oxo-1-phenylpropane (63% *R*) is attained in the oxidation of the enolate **60** containing a chiral ligand with bulky 1-naphthyl groups, where the steric differences between the two conformers are the most pronounced.³²⁰

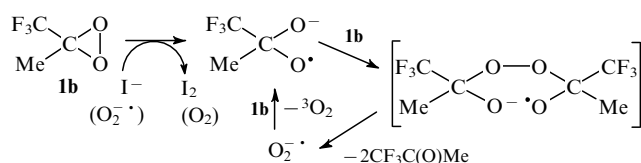


Ar is 1-naphthyl, Cp is cyclopentadienyl.

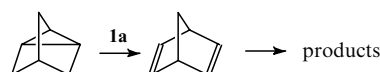
d. Other reactions of dioxiranes

Single-electron transfer reactions involving dioxiranes have been considered to a degree in Sections IV.3 and III.2 in relation to the mechanisms of oxidation of pyrene²⁷² and reactions of dioxiranes with nitroxides.^{120, 124} A typical single-electron transfer reaction is the rapid decomposition of the dioxirane **1b** to give $\text{CF}_3\text{C}(\text{O})\text{Me}$ and O_2 in the presence of catalytic amounts of lithium or tetrabutylammonium iodide.³²¹ Based on experimental data, a chain electron mechanism was proposed for the dioxirane **1a** consumption, according to which the dioxirane accepts an electron from the I^- anion being thus converted into a radical anion, which interacts with a second dioxirane molecule to give a dimeric radical anion; the latter decomposes to ketone and $\text{O}_2^{\cdot -}$. Then the $\text{O}_2^{\cdot -}$ radical anion passes an electron to a new dioxirane molecule and thus closes the catalytic cycle. Thus, the superoxide ion carries the chain, whereas the iodide anion acts as the initiator (Scheme 10).³²¹

Scheme 10

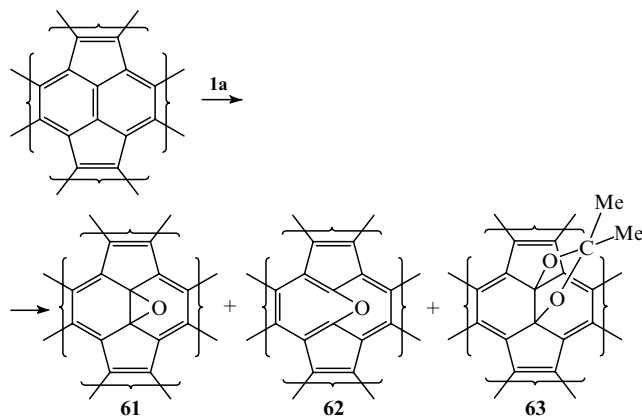


A possible mechanism of the reaction between quadricyclane and the dioxirane **1a** also implies an electron transfer.^{322, 323} It is known that the dioxirane **1a**, even present in small amounts (7.4×10^{-4} mmol), is able to catalyse isomerisation of quadricyclane into norbornadiene.



In addition, it is the electron transfer that is responsible for chemiluminescence observed in the reactions of dioxiranes with PAH and $\text{Ru}(\text{II})$.^{6, 10, 12, 15–17} Note that the capability of dioxiranes to accept an electron is in good agreement with their theoretically calculated electron affinity (2 eV).³²⁴

The reaction of the dioxirane **1a** with fullerene³²⁵ is a unique example of a reaction with an organic substrate in which dioxirane

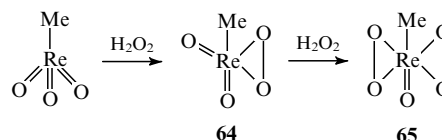


displays its biradical nature; the 1,3-dioxolane derivative **63** was detected among the products of fullerene oxidation, in addition to epoxide **61** and oxo derivative **62**.³²⁵

The use of the dioxirane **1a** to prepare silanol-containing polymers has been reported.³²⁶ These polymers were synthesised by selective oxidation of SiH groups in appropriate polymer precursors.³²⁶

Owing to their oxidising capacity, dioxiranes have found wide use as bleaching or disinfecting reagents.^{327–333}

It is worth noting in conclusion that rhenium peroxides (**64** and **65**) formed in the $\text{MeReO}_3 - \text{H}_2\text{O}_2$ system resemble dioxiranes in their structure and behave remarkably similarly to dioxiranes in the oxidation of alkenes, nitro compounds and alkanes.^{334–340}



V. Chemluminescence and photochemistry of dioxiranes

Study of the dioxirane chemiluminescence started with the pioneering work by Adam and Curci,³⁴¹ who were the first to propose the possibility of CL during isomerisation (at that time, hypothetical) of dimethyldioxirane **1a** to MA [see reaction (6)]. In fact, the sum of the activation energy and enthalpy of this reaction is quite sufficient for an ester to be formed in, at least, the triplet state (Fig. 5); hence, CL is possible.^{4, 5, 341} It was found that reaction (6) should also comply with other criteria necessary for the generation of electronically excited states.³⁴¹ Thus, even before alkyldioxiranes were isolated,¹ Adam and Curci³⁴¹ had discovered a new interesting chapter in their chemistry.

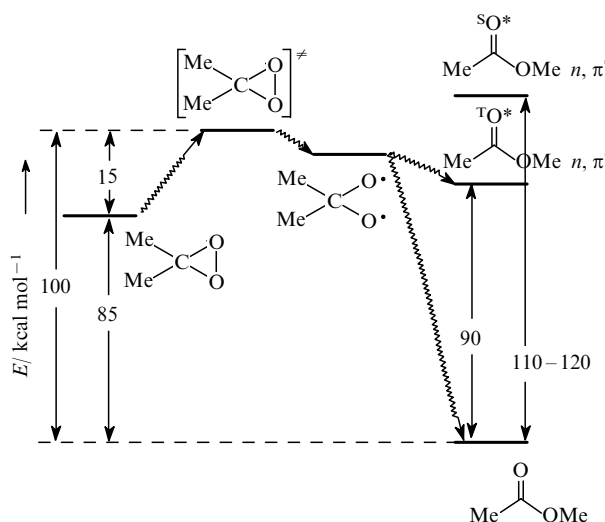
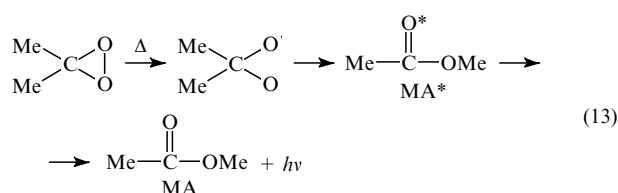


Figure 5. Diagram of the energy levels of the dioxirane **1a** in relation to the product of its decomposition, methyl acetate.

1. Non-activated chemiluminescence

Decomposition of the dioxirane **1a** in solutions under ordinary conditions is not accompanied by CL (despite the theoretical prerequisites). This can be due both to a low efficiency of emission by the electronically excited MA^* in the triplet state and to efficient side 'dark' pathways of decomposition of **1a** (see Sectio-

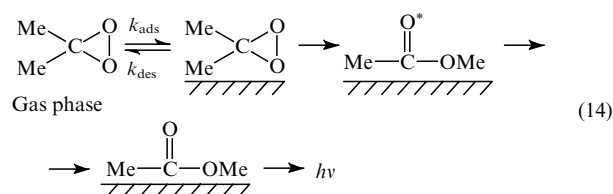
n III). The third reason for the absence of luminescence is associated with efficient emission quenching, in particular, with the presence of traces of O₂ (which is a triplet biradical in its ground state). Dioxxygen does not suppress fluorescence (FL) of electronically excited singlet states but functions as an efficient quencher for triplet states. The removal of dioxxygen from the solution may result in a substantially greater contribution of phosphorescence (PH); this was demonstrated, in particular, in the study of the CL that accompanies decomposition of tetramethyldioxetane (TMD).³⁴² We used a similar expedient and found that thermal (46 °C) decomposition of both non-deuterated and deuterated **1a** in acetone purified from traces of oxygen was actually accompanied by CL in the visible region;¹³ the CL maximum occurs within a band with $\lambda_{\text{max}} = 390$ nm, typical of the phosphorescence of the resulting electronically excited triplet state of methyl acetate (MA*).¹⁴



The decay of CL follows first-order kinetics (for non-deuterated **1a**, $k_{\text{eff}} = 8.5 \times 10^{-3} \text{ s}^{-1}$).¹³ The quantum yield of CL ($\phi_{\text{CL}} = 2.2 \times 10^{-11}$ and 6×10^{-11} Einstein mol⁻¹ for non-deuterated and deuterated dioxirane, respectively) and the yield of excited MA [$\phi^*(\text{MA}) = 10^{-4}\%$] are relatively low[‡] compared, for example, with the ϕ^* values for ketones formed upon decomposition of 1,2-dioxetanes^{21,22} (the yield of excitation of triplet acetone in the decomposition of TMD is 37%). This low ϕ^* value for MA* is evidently due to 'dark' decomposition of **1a** occurring in parallel (in the absence of O₂ at high temperatures) by a radical chain mechanism (see Section III). However, according to energy estimates, the reaction sequence presented in Scheme 7 cannot lead to excitation of MA.¹³ Therefore, reaction (13) is the most probable CL channel. Apparently, this reaction proceeds in parallel with those shown in Scheme 7, but in the absence of O₂, its contribution must be low, which accounts for the low intensity of luminescence. Under 'normal' conditions, isomerisation also occurs, however CL is suppressed almost completely by the O₂ present in the system.

It should be noted that reaction (13), according to which the excited state is formed upon a direct isomerisation event without fragmentation of the molecule, is a very uncommon process.

Decomposition of dimethyldioxirane **1a** upon sorption from the gas phase on the Silipor surface is accompanied by much brighter CL than its decomposition in solution (MA* is the emitter).¹¹



———— Silipor.

In fact, the minimum possible CL characteristics under these conditions were estimated^{16,343} to be two orders of magnitude

‡ Since no data on the yield of emission of MA (ϕ_{emis}) can be found in the literature, this value is assumed to be at least not greater (actually, it must be smaller) than the ϕ_{emis} values for related compounds, ketones, for which $\phi_{\text{emis}} = 10^{-5}$. Thus, from here on, we should imply the minimum possible CL characteristics.

larger ($\phi_{\text{CL}} \geq 4 \times 10^{-9}$ Einstein mol⁻¹; $\phi^*(\text{MA}) > 0.01\%$)[§] than the corresponding values for decomposition of **1a** in oxygen-free acetone solutions.¹³ Among other reasons, this may be due to lower efficiency of quenching processes on the Silipor surface. However, in our opinion, the main reason for the increase in the CL yield on the Silipor surface lies in the mechanism of dioxirane decomposition; whereas in the solution in the absence of O₂ at elevated temperatures, the 'dark' radical chain decomposition (see Scheme 7) is the predominant process, on the Silipor surface, where radical reactions are much less efficient, chemiluminescent isomerisation [reaction (14)] becomes the major channel for the consumption of **1a**.

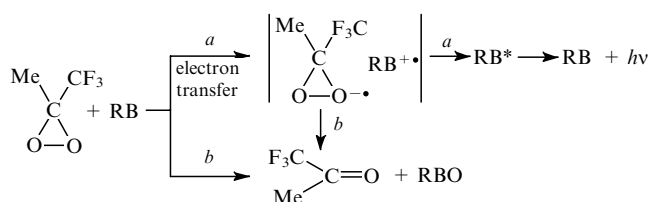
The kinetics of the decay of CL during decomposition of dimethyldioxirane **1a** adsorbed on a Silipor surface is described by a first-order equation; however, the effective rate constant ($k_{\text{eff}} = 0.01 \text{ s}^{-1}$), found from the kinetic curves for CL decay plotted on the semilogarithmic coordinates, scarcely depends on the temperature (in the range 65–90 °C).^{16,343} Evidently, the observed rate constant, which is an effective value, depends not only on the isomerisation constant of the dioxirane **1a** but also on the adsorption equilibrium ($k_{\text{des}}/k_{\text{ads}}$), so that the increase in the rate constant for the desorption of the dioxirane **1a** from the Silipor surface following an increase in the temperature makes up for the increase in the isomerisation rate constant, the k_{eff} value remaining almost invariable.

It is noteworthy that low-intensity chemiluminescence is also observed in a cell containing no Silipor.¹¹ This may be due to both isomerisation of the dioxirane **1a** in the gas phase and its decomposition on the internal surface of the cell. The addition of Silipor to a solution of the dioxirane **1a** in acetone causes a short burst of luminescence, characterised by a relatively low intensity.³⁴³

2. Activated chemiluminescence

Luminescence activation by polyaromatic hydrocarbons is widely used to study the CL arising during oxidation of hydrocarbons^{344–348} or decomposition of 1,2-dioxetanes.^{21,22,349–352} Taking the reaction of the dioxirane **1b** with rubrene (RB) as an example, Adam, Curci, *et al.*⁶ demonstrated the applicability of the luminescence activation method to detection of CL during decomposition of dioxiranes.

Scheme 11



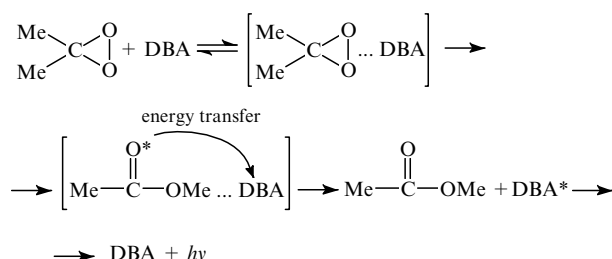
It was suggested that rubrene activates the CIEEL mechanism (Scheme 11, pathway *a*). In addition to CIEEL, there is also another channel of dioxirane consumption, namely, oxidation of rubrene (Scheme 11, pathway *b*), which decreases the CL intensity.⁶ Detection of the EPR signal of the radical cation **41**^{•+}, formed in the reaction of pyrene with the dioxirane **1b** by reaction (12), is an additional argument pointing to the CIEEL mechanism in the chemiluminescence reactions of dioxiranes.²⁷²

The reaction of the dioxirane **1a** with PAH is also accompanied by CL. Thus CL has been discovered in the thermolysis of the dioxirane **1a** (35 °C, Ar) in the presence of 9,10-diphenylanthracene (DPA), 9,10-dibromoanthracene (DBA) and anthracene (A).¹⁰ In all cases, the activators acted as the emitters of the observed luminescence (the maximum CL intensity increases in

§ The CL characteristics were estimated under the assumption that all the dioxirane present in the cell with Silipor is accumulated on the sorbent surface; in reality, this proportion can be only several percent and, hence, the real CL yield and $\phi^*(\text{MA})$ are an order of magnitude greater.

the sequence $I_A < I_{DPA} < I_{DBA}$). The mechanism of activation of CL depends on the nature of the activator. Based on experimental results, it has been suggested^{10,343} that anthracene and 9,10-diphenylanthracene, which are oxidised during the reaction, activate the CIEEL mechanism, and 9,10-dibromoanthracene activates luminescence by the mechanism of energy transfer from MA^* to the activator (Scheme 12).

Scheme 12



In the presence of DBA, the CL decay follows first-order kinetics; however, the observed rate constant depends on the activator concentration, which implies that 9,10-dibromoanthracene catalyses the dioxirane decomposition.^{123,343} However, anthracene and DPA influence the process kinetics in a more complicated way than DBA: the curve for the luminescence decay has two sections, 'fast' and 'slow' (Fig. 6).^{123,343} It can be suggested that decomposition of the dioxirane **1a** accounts for only the 'fast' section of the curve (section 1), whereas an intermediate labile compound (perhaps, of the peroxide type), resulting from oxidation of the activators by the dioxirane, is responsible for the luminescence in the slow section (section 2). Indeed, after the CL kinetics had reached section 2 (Fig. 6) and acetone had been completely evaporated from the reaction cell, the addition of a new portion of acetone restored the luminescence intensity nearly up to the previous level.^{123,343} Similar kinetics observed in the presence of anthracene may be due to analogous reasons.

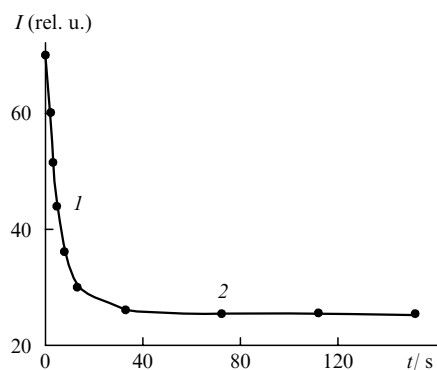


Figure 6. Kinetic curve for the decay of luminescence in the presence of DPA. $[DPA]_0 = 6.7 \times 10^{-4}$ mol litre⁻¹, $[1a]_0 = 2 \times 10^{-2}$ mol litre⁻¹, acetone, 35 °C.

Besides PAH, luminescent metal compounds can also be used to activate the CL of dioxiranes. Thus the reaction of $Ru(bipy)_3Cl_2$ with dimethyldioxirane **1a** in solution is accompanied by bright CL,¹⁵ emitted by $Ru(II)^*$ (Fig. 7).

The CL decay obeys a first-order equation, the observed first-order rate constant for the CL decay (k_{CL}) being proportional to the $Ru(II)$ concentration: $k_{CL} = k_1 + k_2[Ru(II)]$. The activation parameters found from the temperature dependence of the bimolecular rate constant for the reaction k_2 are the following: $E_a = 9.6 \pm 1.6$ kcal mol⁻¹, $\log A = 9.1 \pm 1.0$. It can be seen that the reaction of $Ru(II)$ with the dioxirane **1a** has a markedly lower (by ~ 13 – 14 kcal mol⁻¹) activation energy than non-catalysed

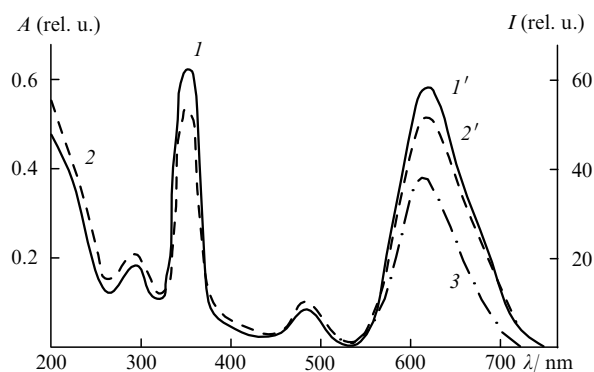
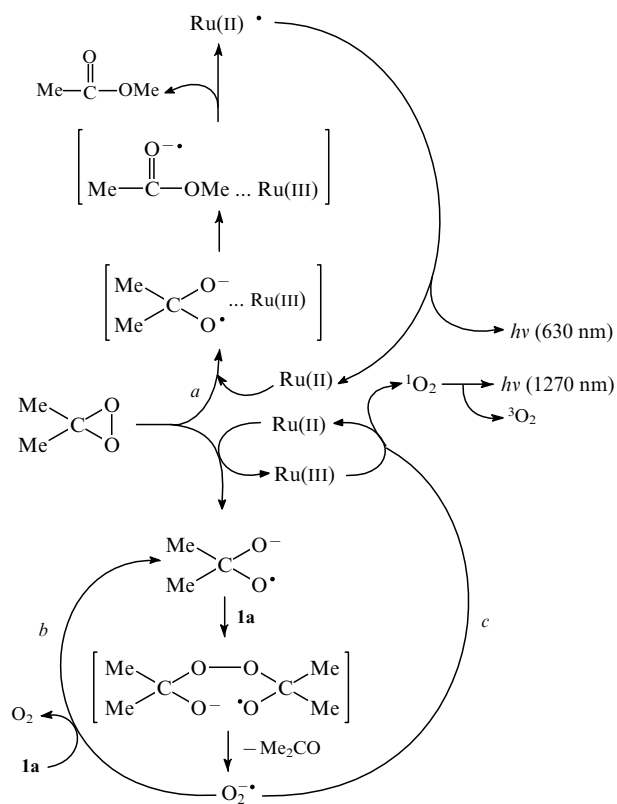


Figure 7. Absorption (*I*, 2) and photoluminescence (*I'*, 2') spectra of $Ru(II)$ ($[Ru(II)] = 5 \times 10^{-6}$ mol litre⁻¹, CH_3CN , 25 °C): (*I*, *I'*) before the reaction with the dioxirane **1a**; (2, 2') after the reaction with **1a** ($[1a] = 2 \times 10^{-2}$ mol litre⁻¹); (3) chemiluminescence spectrum ($[Ru(II)] = 1.25 \times 10^{-4}$ mol litre⁻¹, $[1a] = 6 \times 10^{-3}$ mol litre⁻¹).

decomposition,^{8,118} because the ruthenium complex substantially catalyses the dioxirane decomposition. For $[Ru(II)] = 1.25 \times 10^{-4}$ mol litre⁻¹, the rate of catalysed decomposition of the dioxirane **1a** at 40 °C is greater than the rate of non-catalysed decomposition by a factor of 170 (!).¹⁵

Apparently, the activation of $Ru(II)^*$ luminescence and at least one pathway of the dioxirane decomposition catalysed by the ruthenium complex (Scheme 13) occur by the CIEEL mechanism, as has been shown for the reaction of $Ru(II)$ with 1,2-dioxetanes.^{353–357}

Scheme 13



Comparison of the photoluminescence and absorption spectra of $Ru(II)$ before and after completion of the reaction (see Fig. 7) indicates that the reaction of the $Ru(II)$ complex with dioxirane leads to oxidation of the complex; this, however, has no influence on the CL kinetics and does not distort the results because noticeable changes in the spectra can be observed only when a

4×10^3 -fold excess of the dioxirane **1a** is present, whereas most of the kinetic measurements were carried out at lower ratios of **1a** to Ru(II).¹⁵

The CL quantum yield found from the plot for the light sum *versus* concentration (Fig. 8) using the equation $S = \varphi^*(\text{Ru}) \varphi_{\text{FL}} k_2 [\text{Ru(II)}]_0 [\text{1a}]_0 / (k_1 + k_2 [\text{Ru(II)}]_0)$ is equal to $\varphi_{\text{CL}} = (9.5 \pm 3) \times 10^{-5}$ Einstein mol⁻¹, and the yield of excitation of Ru(II) (with allowance for the fact that the yield of ruthenium emission $\varphi_{\text{FL}} = 0.0095$) equals $\varphi^*(\text{Ru}) = 0.01 \pm 0.005$.¹⁵ The CL characteristics obtained indicate that the dioxirane **1a**–ruthenium complex system is a fairly bright chemiluminescence system. However, the $\varphi^*(\text{Ru})$ value for the reaction of Ru(II) with 1,2-dioxetanes is much greater (0.2).³⁵⁷ Among other factors, the low ruthenium excitation yield in the CIEEL reaction of Ru(II) with the dioxirane **1a** may be due to the existence of a parallel channel for the dioxirane consumption, which yields no excited Ru(II). Below we demonstrate that this channel actually exists.

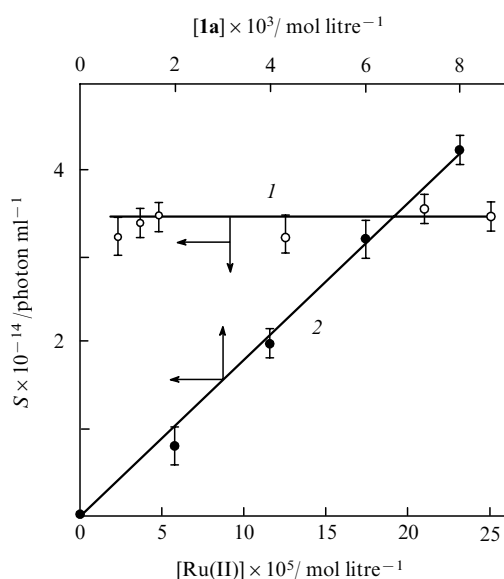


Figure 8. Chemiluminescence light sum in the reaction of the dioxirane **1a** with Ru(II) *vs* the concentration of Ru(II) (straight line 1) ($[\text{1a}] = 6 \times 10^{-3}$ mol litre⁻¹) and the concentration of **1a** (straight line 2) ($[\text{Ru(II)}] = 1.25 \times 10^{-4}$ mol litre⁻¹).

The catalytic activity of Ru(II) increases appreciably on excitation of the complex,¹⁵ which is in good agreement with the theory of electron transfer. In fact, the k_2 value is known to depend on the oxidation potential of the activator (E_{Ox}) and the reduction potential of the peroxide (E_{Red}) according to the following equation:

$$k_2 = A \exp \left[-\frac{E_{\text{Ox}} - E_{\text{Red}} - e^2/\epsilon R_0}{RT} \right], \quad (15)$$

where e is the electron charge, ϵ is the dielectric constant of the solvent and R_0 is the distance between ions in the transition state. Since the oxidation potential of Ru(II)* decreases by the energy of excitation,³⁵⁸ i.e., $E_{\text{Ru(II)}^*/\text{Ru(III)}} = E_{\text{Ru(II)/Ru(III)}} - E^* = 1.29 - 2.12 = -0.83$ V, then, in conformity with Eqn (15), an increase in k_2 by several orders of magnitude should be expected. In fact, the Stern quenching constant (K), found from the linear section of the kinetics of quenching of Ru(II)* by dioxirane using the Stern–Volmer equation

$$\frac{\varphi_0}{\varphi} = \frac{\tau_0}{\tau} = 1 + K[\text{Q}], \quad (16)$$

(φ_0 and τ_0 are the quantum yield and the decay time of the luminescence without quencher Q, and $[\text{Q}]$ is the quencher con-

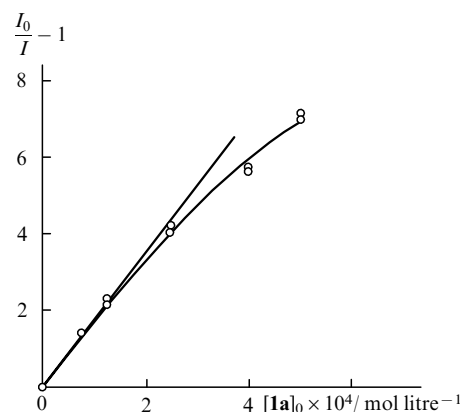
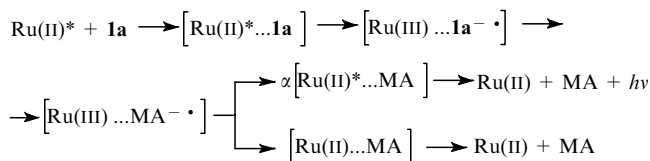


Figure 9. Kinetics of quenching of Ru(II) photoluminescence by the dioxirane **1a** in the coordinates of the Stern–Volmer equation. $\lambda_{\text{excit}} = 450$ nm, $[\text{Ru(II)}] = 2.5 \times 10^{-5}$ mol litre⁻¹, 16 °C.

centration), is the following: $K = k_Q \tau_0 = 1800 \pm 200$ litre mol⁻¹ [k_Q is the rate constant for the interaction of Ru(II)* with **1a**]. From this it follows that the catalytic activity of Ru(II) increases on excitation by a factor of more than 8×10^7 .¹⁵ It can be seen from Fig. 9 that at $[\text{1a}] > 2.5 \times 10^{-4}$ mol litre⁻¹, a negative deviation from the linear Stern–Volmer dependence is observed, obviously, due to the apparent decrease in the quenching efficiency caused by the recovery of the excited Ru(II) complex.



α is the excitation regeneration coefficient.

The calculation of the excitation regeneration coefficient gives the value $\alpha = 0.30 \pm 0.01$, which is much greater than $\varphi^*[\text{Ru(II)}]$ for the reaction of **1a** with non-excited ruthenium. This leads to the conclusion that the contribution of the catalysed isomerisation of **1a** occurring by the reversible electron transfer mechanism (see Scheme 13, pathway *a*) increases markedly.¹⁵

As noted above, the relatively low $\varphi^*[\text{Ru(II)}]$ value for the reaction of Ru(II) with the dioxirane **1a** (compared to this value for the reaction with 1,2-dioxetanes) may be due to the occurrence of a parallel channel of consumption of **1a**, which does not give excited Ru(II). This route actually does exist but this is not a dark reaction! On the contrary, it is accompanied by very bright CL, which occurs in the infrared region (1270 nm), indicating the formation of singlet oxygen in the system.^{17,343} The yield of ¹O₂ based on the decomposed dioxirane **1a** in the Me₂CO–CD₃CN (1 : 2) system is 0.03%. It is notable that the kinetics of the IR CL decay, unlike that for the Ru(II)* luminescence in the visible region of the spectrum, follows a fairly complex pattern (Fig. 10).^{17,343} Thus, the Ru(II)–**1a** system contains two luminescence emitters,^{15,17,343} Ru(II)* in the visible region and ¹O₂ in the infrared region. A possible pathway to ¹O₂ is the reaction of Ru(II) with the dioxirane **1a** by the electron chain mechanism (Scheme 13, pathways *b* and *c*). Pathway *b* is similar to that found in the I⁻–**1b** system (the Adam–Curci system³²¹) (see Scheme 10) with the only difference that in this case, Ru(II) serves as the electron donor. However, unlike the I⁻–**1b** system,³²¹ in the Ru(II)–**1a** system, the oxidised trivalent ruthenium can be reduced to recover the initial divalent species (Scheme 13, pathway *c*), which apparently gives rise to the singlet oxygen [the interaction of Ru(III) with the superoxide ion is known to lead to the generation of ¹O₂].³⁵⁹

Thus, in the reaction of Ru(III) with **1a**, the dioxirane is consumed, in all probability, *via* two competing pathways,

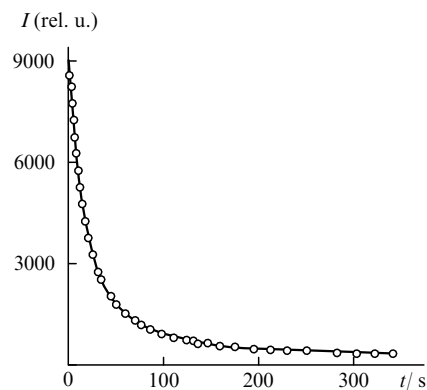


Figure 10. Typical kinetic curve for the decay of the $^1\text{O}_2$ chemiluminescence (IR region) in the reaction between Ru(II) and the dioxirane **1a** (25 °C, Ar, $[\mathbf{1a}]_0 = 5.25 \times 10^{-2} \text{ mol litre}^{-1}$, $[\text{Ru(II)}]_0 = 1 \times 10^{-4} \text{ mol litre}^{-1}$, solvent $\text{Me}_2\text{CO} - \text{CD}_3\text{CN}$ (1 : 2)).

namely, the CIEEL mechanism to give excited Ru(II) (Scheme 13, pathway *a*) and the electron chain decomposition to give singlet oxygen (Scheme 13, pathways *b* and *c*). The reactions of other transition metals with dioxiranes might also give rise to singlet oxygen.[†]

The above-described thermal decomposition of **1a** upon adsorption of the Silipor surface from the gas phase can be substantially enhanced by applying CL activators [DBA, DPA, Ru(II)] on the Silipor surface.^{16, 343} For example, in the presence of Ru(II) or DPA (concentration of the additive $1 \times 10^{-6} \text{ mol g}^{-1}$), the maximum luminescence intensity increases 100- and 10-fold, respectively. The activators function as the luminescence emitters, which are apparently activated in the same way as in solutions.^{16, 343} The CL yield ($0.03 \times 10^{-5} \text{ Einstein mol}^{-1}$)^{165, 343} for the decomposition of **1a** in the presence of Ru(II) applied to the Silipor surface proved to be about three orders of magnitude lower than the CL yield observed in the reaction of **1a** with Ru(II) in solution.¹⁵ Since the electron transfer is controlled by diffusion, this difference can be explained by the decrease in the rate of the diffusion of the reactants on passing from the homogeneous system (solution) to heterogeneous conditions (Silipor–gas phase).

It is of interest that in the **1a**–Ru(II)–Silipor system, no CL from singlet oxygen is observed.¹⁶ Apparently, the diffusion restrictions prevent development of the processes shown by pathway *b* (or *c*) (see Scheme 13).

3. Other chemiluminescence reactions involving dioxiranes and dioxirane intermediates

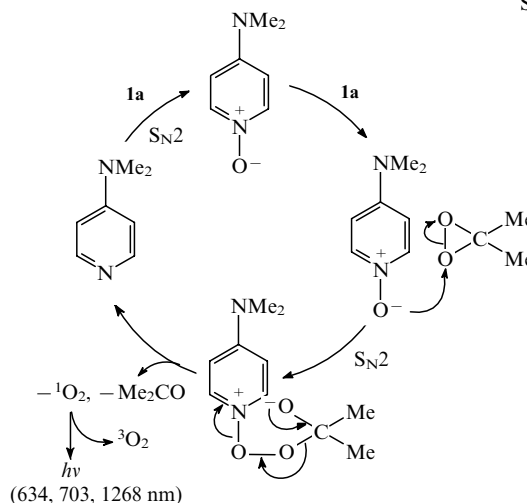
Although the examples of formation of singlet oxygen in decomposition of dioxiranes are still few in number, they deserve attention, because the reactions described below are apparently far from being the last examples in which an extremely efficient oxidant (dioxirane) gives rise to another one, namely, $^1\text{O}_2$, which plays a very significant role in both chemistry and biology.^{360–362}

Even the synthesis of dioxiranes itself is accompanied by the formation of $^1\text{O}_2$.³⁶³ Non-catalysed decomposition of Caro's acid is known to give $^1\text{O}_2$.³⁶⁴ Decomposition of Caro's acid catalysed by ketones is also accompanied by the evolution of oxygen (see Scheme 2). Previously,⁴ this has been suggested to be singlet oxygen; later, this suggestion was confirmed experimentally by Lange and Brauer,³⁶³ who observed CL of singlet oxygen at $\lambda = 1270 \text{ nm}$ during decomposition of Caro's acid induced by

various ketones (acetone, butan-2-one, fluoroacetone, cyclohexanone, *etc.*). In addition to the detailed study of the reaction kinetics, they measured the yield of $^1\text{O}_2$ (in the case of acetone) per HSO_5^- molecule, which proved to be 0.5; this means that all the oxygen evolved is in the singlet state.³⁶³

Adam *et al.*²⁸⁶ were the first to detect the evolution of $^1\text{O}_2$ in the reactions of isolated dioxirane. Previously, Murray³ had noted that some *N*-oxides induce decomposition of **1a** with evolution of oxygen, which may be in the singlet state. Somewhat later, the Messeguer's group²⁶³ found a catalytic effect of *N*-oxides on the decomposition of dioxiranes. Adam *et al.*²⁸⁶ observed the same phenomenon in the oxidation of 4-dimethylaminopyridine by the dioxirane **1a**: 4-dimethylaminopyridine *N*-oxide formed in the reaction induced rapid decomposition of **1a** (Scheme 14). The reaction was accompanied by evolution of $^1\text{O}_2$ (at 37 °C, the fraction of $^1\text{O}_2$ in the total number of O_2 molecules was 5%), which was proved by CL registered in the infrared and visible regions of the spectrum. Luminescence in the visible region might be due to the dimol emission of $^1\text{O}_2$ (634 and 703 nm).²⁸⁶

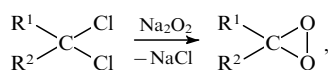
Scheme 14



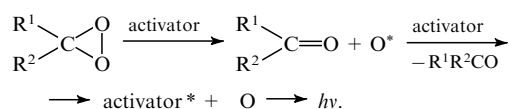
Finally, the third example of evolution of $^1\text{O}_2$ in the reactions of dioxiranes, namely, in the decomposition of **1a** catalysed by the complex $\text{Ru}(\text{bipy})_3\text{Cl}_2$ ¹⁷ was considered in detail above.

When drawing indirect analogy with 1,2-dioxetanes, it is noteworthy that only one example of the formation of $^1\text{O}_2$ during decomposition of 1,2-dioxetane (namely, 3-hydroxymethyl-3,4,4-trimethyl-1,2-dioxetane) has been reported.³⁶⁵ The excitation of O_2 occurs *via* a trivial mechanism consisting in the transfer of energy from the triplet-excited carbonyl fragment (the product of dioxetane decomposition) to oxygen.

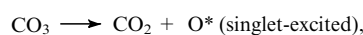
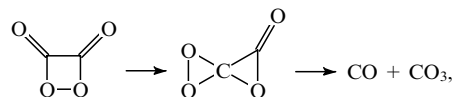
By now we have considered CL of isolated dioxiranes. However, several studies in which dioxiranes are considered as possible intermediates in various chemical and biochemical chemiluminescence systems have also been reported.^{12, 97–101} In the 1980s, Steinfatt^{97–100} published a series of studies, dealing with the reactions of a number of organic *gem*-dichlorides with sodium peroxide and hydroperoxide in the presence of aromatic sensitizers. These reactions were accompanied by fairly bright chemiluminescence. The yield of activated CL in the reaction of Na_2O_2 with 3,3-dichlorophthalide⁹⁷ was $10^{-3} \text{ Einstein mol}^{-1}$ (!). Steinfatt also studied activated CL reactions of 1,8- $\text{C}_{10}\text{H}_6(\text{COCl})_2$ with Na_2O_2 ¹⁰⁰ and Cl_2CO with NaOOH .⁹⁸ The following scheme was proposed to interpret the CL observed:



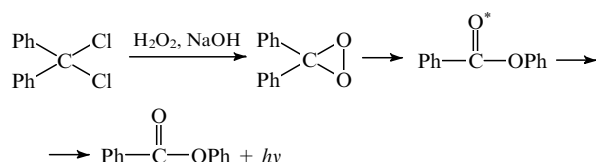
[†]This should depend appreciably on the energy characteristics of the reaction. Thus we were unable to detect CL of singlet oxygen in the reaction of the dioxirane **1a** with Ce(III).^{17, 343} apparently, due to the too high redox potential of the Ce(III)/Ce(IV) pair (1.4 V),³⁵⁸ which precludes the transfer of an electron from Ce(III) to the dioxirane.



Dioxirane was also proposed as an intermediate to explain the CL of peroxyoxalate.⁹⁹



Later¹² we have observed non-sensitised CL in the Ph_2CCl_2 – H_2O_2 – NaOH system, similar to the Steinfatt systems. The maximum of the luminescence intensity was concentrated in the range 400–450 nm, pointing to the possible formation of triplet phenyl benzoate, the product of isomerisation of diphenyldioxirane.¹²



It is significant that CL of diphenyldioxirane (provided that it is actually formed in this system) can be observed even in the absence of luminescence activators. On addition of Ru(II) , the luminescence intensity increases by several orders of magnitude, the maximum intensity being directly proportional to the concentration of the complex. Apparently, in this case, as in the case of isomerisation of dimethyldioxirane **1a**, the CIEEL mechanism is involved.¹²

The formation of a dioxirane intermediate has also been assumed to interpret the mechanism of bioluminescence of bacteria.¹⁰¹ The mechanism of excitation in these reactions cannot yet be considered to be conclusively established. The overall process is known to be catalysed by an enzyme — luciferase (E) — and consists in the oxidation of the reduced form of flavine mononucleotide (FMNH_2) by oxygen with participation of a long-chain aldehyde. A mechanism for the generation of luminescence was proposed¹⁰¹ (Scheme 15); according to this mechanism, the

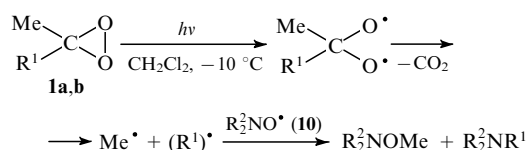
reaction of O_2 with the complex $\text{E} \cdot \text{FMNH}_2$ yields $\text{C}(4a)$ -peroxydihydroflavine **66**, which subsequently reacts with the aldehyde to give a tetrahedral intermediate **67**. These stages are in good agreement with known mechanisms. Presumably,¹⁰¹ the next step includes the formation of a dioxirane intermediate and $\text{C}(4a)$ -hydroxyflavine **68**. After that, there are two pathways for the generation of CL¹⁰¹

— decomposition of dioxirane to give an excited carboxylic acid and subsequent energy transfer on the hydroxyflavine **68**, which acts as the CL emitter; in this case, luminescence is activated by the energy transfer mechanism (Scheme 15, pathway *a*);

— the CIEEL mechanism in which the hydroxyflavine **68** acts as the fluorophore and the electron donor (Scheme 15, pathway *b*).

4. Photochemistry of dioxiranes

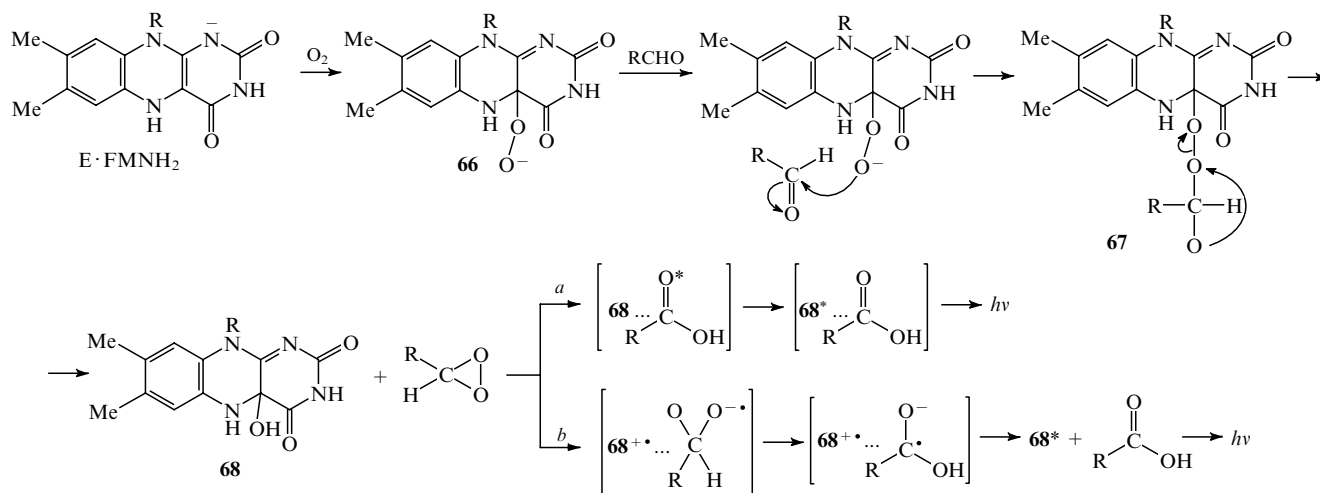
As many other peroxides, dioxiranes are sensitive to light; this was partially illustrated in Section III in relation to the dioxirane **1b** (see Schemes 3 and 4).¹¹⁴ A similar type of behaviour is displayed by the dioxirane **1a**. Thus the quantum yield of photodecomposition of the dioxirane **1a** at 23 °C proved to be much greater than unity ($\phi = 13.9 \pm 0.6$, 12.9 ± 1.7 and 13.1 ± 0.7 Einstein mol^{-1} at 340, 350 and 360 nm, respectively),¹⁴ indicating that decomposition occurs by a radical chain mechanism. More evidence in favour of this mechanism is provided by the detection of adducts formed from alkyl radicals during the photolysis ($\lambda = 300$ nm) of the dioxiranes **1a** and **1b** in the presence of the trap **10** (**1b** completely decomposes under these conditions over a period of 30 min).¹²⁰



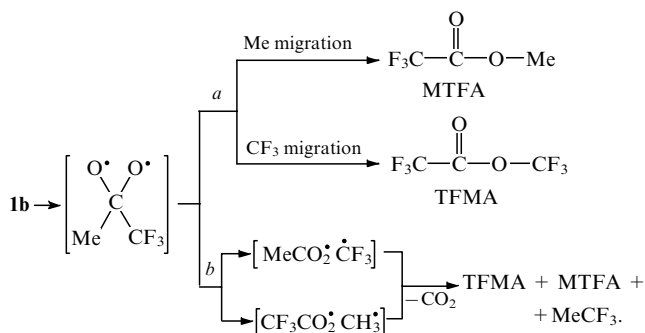
$\text{R}^1 = \text{Me}$ (**1a**), CF_3 (**1b**).

However, at 77 K in a matrix, radical chain processes are less significant, and decomposition of **1b** ($\lambda > 300$ nm) yields 1,1,1-trifluoroethane (41%) and MTFA (51%) as the major reaction products together with small amounts of trifluoromethyl acetate (TFMA, 8%). Thus, the photolysis of the dioxirane **1b** in a matrix occurs as either isomerisation (Scheme 16, pathway *a*) or β -cleavage followed by cage recombination of the resulting radical pair (Scheme 16, pathway *b*) or follows simultaneously both channels.¹¹⁴

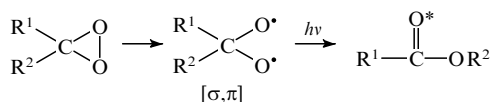
Scheme 15



Scheme 16



It should be noted that isomerisation to give the corresponding ester is the main route in the low-temperature photolysis of a whole series of other dioxiranes obtained in a matrix.^{33, 62, 65, 67, 69, 71, 72, 75, 80, 81} It has been suggested⁷ that the $[\sigma, \pi]$ -configuration of the dioxirane biradical should be responsible for the generation of an excited product.



Indeed, when the dioxirane **1a** in a matrix (77 K) is irradiated at a wavelength corresponding to its absorption band, phosphorescence of MA is observed (Fig. 11),¹⁴ which is evidently due to the following process:

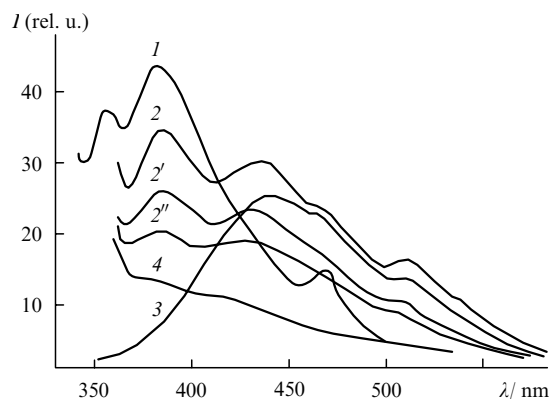
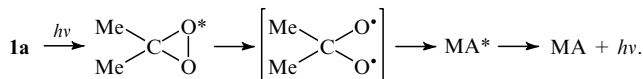
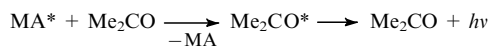


Figure 11. Phosphorescence spectra (77 K) of methyl acetate (**1**), dioxirane **1** (**2**, **2'**, **2''**) and acetone (**3**, **4**).

(**1**) $\lambda_{\text{excit}} = 260$ nm, $[\text{MA}]_0 = 0.09$ mol litre⁻¹, MeCN;
(**2**, **2'**, **2''**) $\lambda_{\text{excit}} = 350$ nm, $[\mathbf{1a}]_0 = 0.09$ mol litre⁻¹, acetone (spectra **2'** and **2''** were recorded at 25 min intervals under permanent irradiation);
(**3**) $\lambda_{\text{excit}} = 320$ nm; (**4**) $\lambda_{\text{excit}} = 350$ nm.

In addition to the triplet-excited MA*, photodecomposition of the dioxirane **1a** in a matrix affords triplet-excited acetone, probably, due to the transfer of energy from MA* to acetone.

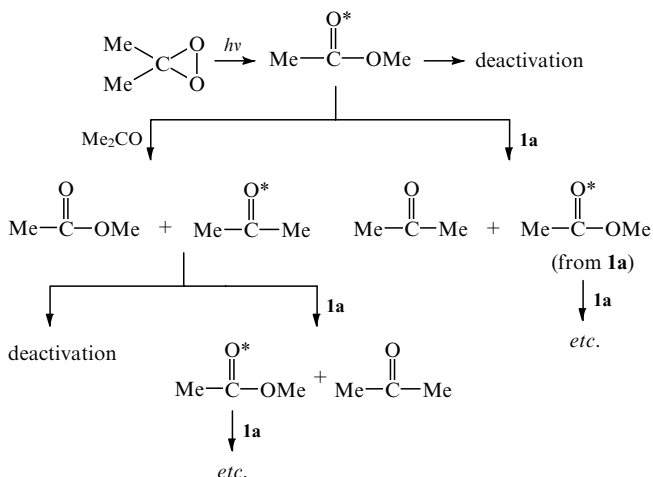


The formation of MA* and the fact of energy migration suggest the existence of one more channel of dioxirane consumption by a quantum chain (QC) mechanism. In the 1960s, Shilov and Vedenev³⁶⁶ discovered experimentally a new class of chain gas-phase reactions involving vibrationally excited states. Some-

what later, in the 1970s, taking decomposition of 1,2-dioxetanes in solution as an example, the occurrence of chain processes with participation of species existing already in electronically excited states was demonstrated.^{349, 367–369} In this case, a product of dioxetane decomposition — a triplet excited ketone — or an activator molecule is included in the chain propagation reactions.

Since decomposition of dioxiranes also gives a triplet-excited product (for example, decomposition of **1a** affords MA*), it can be expected that in the case of dioxiranes, QC processes are, in principle, quite probable (Scheme 17).

Scheme 17



Certainly, a solution of the dioxirane **1a** in acetone is far from being a perfect system for QC processes, first of all, due to the low efficiency of MA excitation and emission. In addition, the QC decomposition should be strongly hampered by the competing radical chain mechanism. However, other dioxiranes, in particular, those with chromophore-containing substituents, which give esters characterised by markedly larger emission yields, may prove to be prone to undergo photo and, perhaps, also thermal decomposition by the QC mechanism. Dimesityldioxirane **1j** seems quite promising in this respect.

VI. Conclusion

Dioxiranes remarkably combine two significant properties — the ability to act as strong oxidants and the ability to form products in the electronically excited states. It is these specific features that distinguish dioxiranes from other related compounds, in particular, 1,2-dioxetanes, the principal property of which is CL, or from a number of peroxy compounds, which have found application as oxidants in organic synthesis.

The high oxidative capacity of dioxiranes combined with the selectivity and mild conditions of reactions permitted researchers to perform a great number of oxidative transformations, which would have been impossible with other reagents. In addition, due to the availability of initial compounds and the ease of preparation of dioxiranes, these reagents can be used almost in any chemical laboratory.

Study of the CL of dioxiranes resulted in the discovery of a unique pathway to excited states. In fact, the rearrangement of dioxiranes into the corresponding esters initiated either thermally or photochemically is an exceptionally uncommon example of generation of an excited state directly upon an isomerisation event without fragmentation of the molecule (decomposition of 1,2-dioxetanes occurs *via* fragmentation of the molecule to give several products, one being in the excited state). A similar reaction route has been observed previously only for isomerisation of Dewar's benzene to excited Kekule's benzene.³⁷⁰

It can be conjectured that in the future, the chemistry of dioxiranes will develop along these lines. Without doubt, studies on the oxidative properties of dioxiranes and physicochemical

regularities of these reactions will be continued. Until now, the mechanism of decomposition of dioxiranes in the absence of oxidisable compounds has not been ultimately determined. The role of isomerisation in the set of other channels of dioxirane decomposition, which depend substantially not only on the external conditions but also on the structure of dioxiranes themselves, is still to be elucidated.

Despite the obvious difficulties, the search for the routes and conditions for the synthesis of new dioxiranes of various structures still remains a topical task. It is beyond doubt that success along this line (the first successful steps are being taken^{59, 80–83, 117}) would substantially extend the possibilities of studying the properties of this new class of peroxides. This refers both to oxidative transformations (in particular, with the outlook for the preparation of chiral dioxiranes suitable for attaining prochiral oxidation) and chemiluminescence. Thus decomposition of a dioxirane with chromophore-containing substituents, for example dimesityldioxirane **1j** already synthesised,^{80, 81} can be accompanied by CL comparable with the CL of dioxetanes. The presence of these dioxiranes including some bisdioxiranes would be useful for the study of energy migration paths in a matrix, in solution or on a sorbent surface and also for the study of quantum chain and energy coupled reactions.^{21, 371} However, we are sure that the study of CL of the dioxiranes **1a** and **1b** would provide not less impressive results. Apart from the CL of dioxiranes themselves, one should also expect luminescence during their oxidative reactions with various organic and organometallic substrates, oxidation of which by other oxidants (XeF₂, XeO₃, O₂, etc.) results in bright CL.^{372–374} This is equally true for inorganic compounds. It is known that in the recent decades, a large number of bright CL reactions accompanying oxidation of low-valence uranium species (e.g., by xenon compounds, XeF₂ or XeO₃) were discovered.^{375–386} If dioxiranes are included in the set of oxidants, high excitation yields can be expected in these systems.

A lot of interesting discoveries would result from combination of the chemistry of dioxiranes and 1,2-dioxetanes with the chemistry of complexes of *f*- and *d*-elements.^{387–401} A dioxirane–lanthanide complex system may prove to be the second system, after a similar dioxetane-containing system, in which a new class of chain processes — quantum-chain reactions with energy branching — can be observed.^{399–401}

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^e — *Radiochemistry (Engl. Transl.)*

^f — *High Energy Chem. (Engl. Transl.)*

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^h — *Opt. Spectrosc. (Engl. Transl.)*

Alkoxy(alkyl)silylalkyl derivatives of nitrogen-containing heterocycles

O M Trofimova, N F Chernov, M G Voronkov

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Abstract. The published data on the synthesis, properties and transformations of alkoxy(alkyl)silylalkyl derivatives of nitrogen-containing heterocycles of the general formula $\text{Het}(\text{CH}_2)_n\text{SiX}_3$ are surveyed and systematised. Data on the biological activities and applications of these compounds are presented. The bibliography includes 255 references.

I. Introduction

Considerable interest in organosilicon compounds containing a heterocyclic fragment in a hydrocarbon chain linked to the silicon atom is due to their valuable properties. These compounds served as the basis for the preparation of a large series of adsorbents, immobilised catalysts, synthetic intermediates, medicinal drugs, pesticides and other substances endowed with specific biological activities.

To date, a great number of publications are devoted to organosilicon derivatives in which the silicon atom is directly linked to a heterocyclic substituent (*e.g.*, see, Refs 1–7). However, the publications which describe carbofunctional organosilicon compounds with a silicon atom attached to the heterocyclic fragment through a hydrocarbon bridge are still few in number. Among those, special mention should be made of the review⁸ which describes the compounds containing a heterocyclic substituent with one nitrogen atom (the studies surveyed therein had been published before 1970) and two more recent reviews^{9,10} concerned with the synthesis of organosilicon derivatives of pyridine and quinoline.

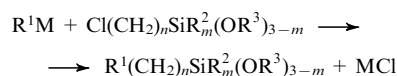
The present review gives a systematic and critical analysis of the data published after 1970 concerning heterylalkylsilanes containing at least one nitrogen atom in their heterocycles.

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II. Synthesis

1. Organometallic synthesis

One of the methods for preparing alkoxy(alkyl)silylalkyl derivatives of nitrogen-containing heterocycles in which the silicon atom is linked to the nitrogen or the carbon atom through a hydrocarbon bridge, $-(\text{CH}_2)_n-$, where $n = 1, 3$, is based on the reaction of organolithium, -sodium, -potassium or -magnesium derivatives of the corresponding heterocycles with silicon-substituted (chloroalkyl)silanes:^{11–70}

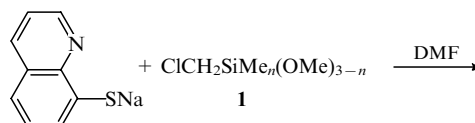


$\text{R}^1 = N\text{- or } C\text{-heteryl}; \text{R}^2, \text{R}^3 = \text{Me, Et}; \text{M} = \text{Li, Na, K, MgBr, ZnCl}; n = 1, 3; m = 0-3.$

Thus silicon-substituted *N*-heterylalkylsilanes were obtained from the corresponding alkoxy(alkyl)chloroalkylsilanes and *N*-potassium derivatives of phthalimide,¹¹ imidazole, 1,2,4-triazole,^{12,13} benzothiazinone,¹⁴ piperidine, perhydroazepine, morpholine¹⁵ and purine¹⁶ in boiling benzene or toluene. The use of Bu_4NBr as a phase transfer catalyst permits one to reduce the reaction time.¹²

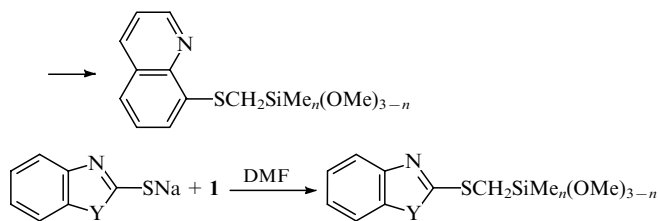
The reaction of *C*- or *N*-sodium derivatives of quinoline,^{17,18} 2-pyrrolidinone,¹⁹ substituted 1,2,4-triazole,^{20–31} imidazole,^{22,23,26,30–35} uracil, thymine and adenine,³⁶ pyridone,³⁷ pyrazine³⁸ and benzotriazole³⁹ with $\text{Cl}(\text{CH}_2)_n\text{SiR}_m^2(\text{OR}^3)_{3-m}$ (where $n = 1, 3$ and $m = 0-3$) in DMF gave the corresponding *C*- or *N*-substituted heterylalkylsilanes.

The silicon-substituted (heterylthiomethyl)silanes $\text{HetSCH}_2\cdot\text{SiMe}_n(\text{OMe})_{3-n}$, where $n = 0$ or 1, were synthesised in 65%–86% yields by the reaction of *S*-sodium derivatives of 8-mercaptoquinoline, 2-mercaptobenzoxazole, 2-mercaptobenzothiazole and 2-mercaptobenzimidazole with trimethoxy-(chloromethyl)- and dimethoxymethyl(chloromethyl)silanes (**1**) in a polar aprotic solvent (DMF, DMSO) for 2–3 h at 80–90 °C.^{40–42}



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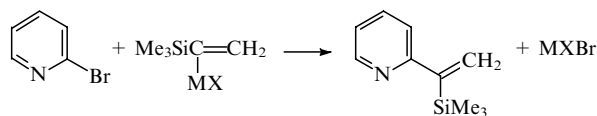
$n = 0, 1$; $Y = \text{NH}, \text{O}, \text{S}$.

The synthesis of trimethylsilylalkyl-substituted pyrrole,^{43, 44} piperidine,⁴⁵ pyridine,^{46–49} 2-pyridone,⁵⁰ pyrrolidine,^{51, 52} pyrazole, imidazole, benzoimidazole,⁵³ quinoline,^{54–56} 3,4-dimethylisoxazole,^{57, 58} 2-mercaptobenzothiazole,^{59, 60} benzothiazole,⁶¹ indole,⁶² tetrazole,⁶³ pyrimidine⁶⁴ and carbazole⁶⁵ makes wide use of *C*-, *N*- or *S*-lithium derivatives of these heterocycles. The latter are obtained by the reaction of the corresponding heterocyclic compounds with RLi ($\text{R} = \text{Me}, \text{Bu}^n, \text{Bu}^t, \text{Ph}, \text{NPr}_2$) in THF or hexane. Thus the 2-ethylpyridine carbanion prepared by the reaction of ethylpyridine with butyllithium (THF, -70°C) readily reacts with *tert*-butyldimethylchlorosilane. In this case, the silyl group enters into the α -position of the alkyl substituent.⁴⁷

The reactions of 2-, 3- and 4-methylquinoline⁵⁴ with lithium diisopropylamide and then with trimethylchlorosilane give rise to 2-, 3- and 4-trimethylsilylmethyl derivatives (in this case, 3-substituted derivatives are formed with the lowest yield). Metallation of 2-methyl-6-(2,5-dimethylpyrrolo)pyridine (THF–hexane, -25°C) with lithium diisopropylamide and subsequent reaction with trimethylchlorosilane gave 2-trimethylsilylmethyl-6-(2,5-dimethylpyrrolo)pyridine in 77% yield.⁴⁴ Lithium derivative of 2-methylbenzothiazole reacts with trimethylchlorosilane analogously.^{59, 60}

The reaction of halogen-substituted pyridines and quinolines with trimethylsilylmethylmagnesium chloride or -zinc chloride in ether in the presence of a catalytic amount of $\text{Cl}_2\text{Ni}[\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2]$ afforded 2- and 3-trimethylsilylmethylpyridines (72% and 35% yields, respectively), 2,6-bis(trimethylsilylmethyl)pyridine (yield 69%) and trimethylsilylmethylquinoline (yield 44%).⁶⁶

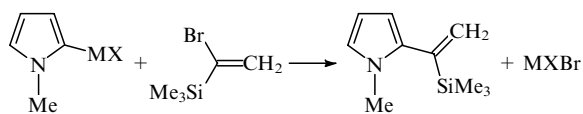
The reaction of 2-bromopyridine with (1-trimethylsilylvinyl)zinc chloride or -magnesium bromide in the presence of a palladium–phosphine complex results in 2-(1-trimethylsilylvinyl)pyridine.^{67, 68}



$\text{MX} = \text{MgBr}, \text{ZnCl}$.

2-(3-Trimethylsilylbut-3-enyl)pyridine was obtained unexpectedly when a fourfold excess of 2-bromopyridine was used.

(2-Trimethylsilylvinyl)magnesium bromide or -zinc chloride was used in the synthesis of the corresponding organosilicon derivatives of pyrrole and indole.⁶⁷ Thus trimethyl(α -bromovinyl)silane reacts with 1-methyl-2-pyrrolyl- and 1-methyl-2-indolylmagnesium bromide or -zinc chloride in the presence of a catalytic amount of $\text{Cl}_2\text{Pd}[\text{Ph}_2\text{P}(\text{CH}_2)_4\text{PPh}_2]$ to give the corresponding 1-methyl-2-trimethylsilylvinyl derivatives of these heterocycles in 74%–87% yields.⁶⁷ For example:



$\text{MX} = \text{MgBr}, \text{ZnCl}$.

The reaction of 6-methylpyridine with methyl chloroformate and trimethylsilyl ethynylmagnesium bromide gives exclusively 2-trimethylsilyl ethynyl-6-methyl-*N*-methoxycarbonyl-1,2-dihydropyridine (yield 79%).⁶⁹

The reaction of 7-chloro-4-(4-iodopyrazolo)quinoline with CuI and $\text{Me}_3\text{SiC}\equiv\text{CH}$ in the presence of $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$ gives 7-chloro-4-(4-trimethylsilyl ethynylpyrazolo)quinoline.⁷⁰

2. Amination reactions

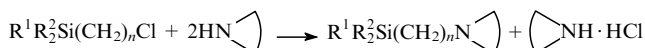
The following methods are also used in the synthesis of alkoxy(alkyl)silylalkyl derivatives of nitrogen-containing heterocycles:

1. Reaction of the corresponding derivatives of (halogenoalkyl)silanes $\text{X}(\text{CH}_2)_m\text{SiR}_m^1(\text{OR}^2)_{3-m}$ with compounds containing an endocyclic (>NH) group.

2. Reaction of halogen-substituted nitrogenous heterocycles with organosilicon derivatives containing a $(\text{CH}_2)_n\text{NH}_2$ group at the Si atom.

3. Attachment of substituted nitrogenous heterocycles containing endocyclic (>NH) groups with an active hydrogen atom to unsaturated organosilicon compounds.

Organosilicon derivatives of morpholine,⁷¹ perhydroazepine,^{71–73} piperazine,^{71, 73, 74} piperidine,^{71, 72, 74, 75} pyrrolidine^{71–73, 76} and imidazole^{77, 78} were obtained by heating trialkyl(chloroalkyl)- or trialkoxy(chloroalkyl)-silanes with an excess of the corresponding N-heterocycle which acts simultaneously as an acceptor of hydrogen chloride:



$\text{R}^1\text{R}^2\text{Si} = \text{Me}_3\text{Si}, \text{Et}_3\text{Si}, \text{Me}(\text{EtO})_2\text{Si}, (\text{EtO})_3\text{Si}, \text{Me}(\text{Me}_3\text{SiO})_2\text{Si}, (\text{Me}_3\text{SiO})_3\text{Si}; n = 1, 3;$

Hereinafter HN is a nitrogen-containing heterocyclic base.

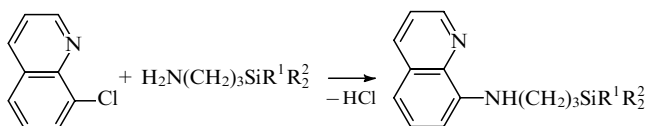
This reaction is carried out in a boiling non-polar solvent (benzene, hexane, toluene). Trialkoxy(chloromethyl)silanes react faster than the corresponding trialkyl derivatives.

The synthesis of silicon-substituted *N*-silylmethylacetams,^{79–81} 1-trialkylsilylmethyl(propyl)piperazine⁸² and 1-trimethylsilylmethyl-1,2,4-triazole^{83–85} was carried out in the presence of anhydrous potassium carbonate or sodium carbonate.

Siliconalkylation of pyrrole, carbazole, pyrazole, imidazole, benzoimidazole, 1,2,4-triazole, 1,2,3-benzotriazole and tetrazole with trialkyl(3-halogenopropyl)silanes gave the corresponding *N*-(3-trialkylsilylpropyl)azoles in 80%–90% yields.^{86, 87} The reaction was carried out in a biphasic system (benzene–60% aqueous KOH) with boiling for 4–6 h in the presence of 5 mol. % of tetrabutylammonium hydrogen sulfate as a phase transfer catalyst. Attempts to obtain these compounds by hydrosilylation of *N*-allyl derivatives of the corresponding azoles failed.⁸⁶ The reaction of 4-amino-1,2,4-triazole with trimethyl(halogenomethyl)silanes in DMSO (8 h, 80°C) afforded 4-amino-1-trimethylsilylmethyl-1,2,4-triazolium halides. 4-Amino-3-trimethylsilylmethyl-1,2,4-triazole is formed when boiling nitromethane is used as a solvent.⁸⁸

Triethylamine was used as a hydrogen chloride acceptor in the synthesis of *N*-(trialkylsilylalkyl)- and *N*-(trialkoxysilylalkyl) derivatives of piperazine,⁸⁹ 3,5-dimethylpyrazole,⁹⁰ 1,2,3,4-tetrahydro(iso)quinoline,^{91–93} pyrrolidone⁹⁴ and other lactams.⁹⁵ This reaction is carried out in boiling toluene or xylene. *N,N'*-Bis(triethoxysilylalkyl)piperazines were obtained by heating triethoxy(chloroalkyl)silane with piperazine in a 2 : 1 molar ratio.⁸⁹

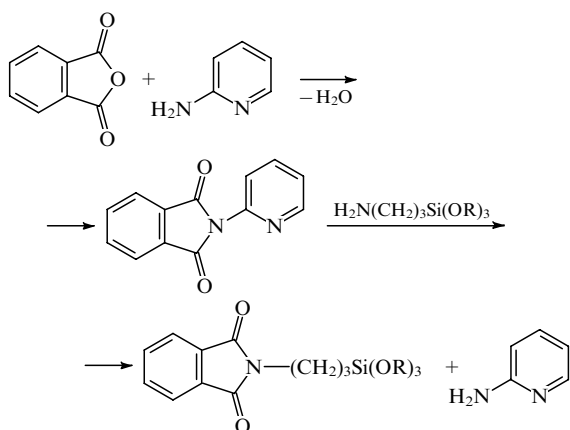
Heating of quinoline-2- and -4-carbonyl chlorides,⁹² 9-chloroacridine⁹⁶ and chloroquinolines^{91, 97–99} with (3-aminopropyl)-trialkylsilanes gives the corresponding 3-(trialkylsilyl)propyl-amino derivatives of these heterocycles.



$\text{R}^1\text{R}^2\text{Si} = \text{Et}_3\text{Si}, \text{MeBu}_2\text{Si}, \text{Bu}^t\text{Me}_2\text{Si}.$

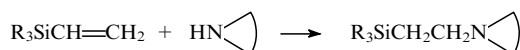
Their isolation is usually simplified when diglyme is used as a solvent and triethylamine is used as a hydrogen chloride acceptor.

A two-step procedure for the synthesis of *N*-[3-(trialkoxysilyl)propyl]phthalimide has been developed. The first step consisted in condensation of phthalic anhydride with 2-aminopyridine to give the corresponding imide; its interaction with (3-aminopropyl)trialkoxysilane (toluene, 10–15 h) resulted in 3-(trialkoxysilyl)propylphthalimide with good yield.¹⁰⁰



R = Me, Et.

Heterocycles containing an endocyclic NH group are smoothly and regioselectively added to unsaturated organosilicon compounds containing a SiCH=CH₂ or SiCH₂CH=CH₂ fragment in the presence of alkali metals (Li, Na, K or their amides). In both cases, the adducts formed contain a nitrogen atom in the β-position relative to the silicon atom. The addition of pyrrolidine,⁷¹ perhydroazepine,⁷¹ piperazine,⁸² 3,5-dimethylpyrazole, imidazole, benzoimidazole,^{90, 101} 3(5)-methylpyrazole,¹⁰² aziridine,¹⁰³ piperidine^{71, 104, 105} and azetidine¹⁰⁶ to vinyltrialkyl- and vinyltrialkoxysilanes proceeds rather easily even at 20–75 °C. The adducts are formed in 70%–85% yields.



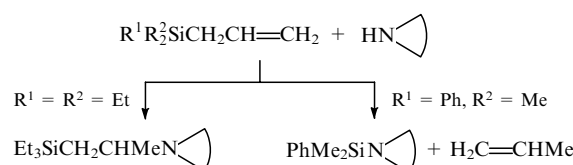
R = Alk, Alko.

The rate of addition of nitrogenous heterocycles to silicon-substituted vinylsilanes depends substantially on the nature of the solvent. Thus the yields of the addition products of aziridine and piperidine to triethylvinylsilane in 2 h under identical conditions were 39% and 72% in the absence of a solvent, 20% and 15% in *n*-heptane and 55% and 92% in THF.¹⁰³

The nature of the substituents at the silicon atom has also a profound effect on the reactivity of the original silicon-substituted vinylsilanes. Thus the yield of 2-(aziridinoethyl)triethylsilane formed in the reaction of triethylvinylsilane with aziridine is 90% (7 h, 100 °C). 2-(Aziridinoethyl)triethoxysilane, the addition product of aziridine to triethoxyvinylsilane, was obtained in 69% yield in 10 h at 100 °C. The rate of catalysed addition of *N*-heterocycles to silicon-substituted vinylsilanes R¹R²SiCH=CH₂ increases in the following order depending on the substituents R¹ and R² at the silicon atom: (OEt)Me₂ < Et₃ < Me₃ < Me₂Ph < -MePh₂. This was ascribed to an increase in the *p*_π–*d*_π interaction of the vinyl group with the silicon atom which resulted in electron density displacement toward the α-carbon.¹⁰³ At present, this effect is interpreted as σ–π conjugation, *i.e.*, the interaction of the C=C bond π-orbital with the Si–C bond σ-orbitals. The decrease in the rate of addition of *N*-heterocycles to triethoxyvinylsilane was attributed to the consumption of the catalyst upon cleavage of the Si–OR bond.¹⁰³

As the double bond in compounds of the R¹R²Si(CH₂)_{*n*}CH=CH₂ series, where *n* = 0, 1 and 2 becomes more distant from the silicon atom, the rate of addition of

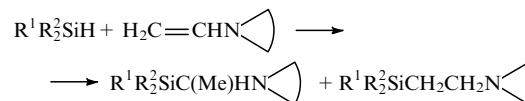
N-heterocycles decreases. In the case of *n* = 1, β-elimination often accompanies the addition reaction.



The yield of the addition product of aziridine to allyltriethylsilane is 35%. However, aziridine is not added to allyldimethylphenylsilane, the β-degradation product, *viz.*, aziridinyl-dimethylphenylsilane (10% yield), and propene are formed instead.¹⁰⁵

3. Hydrosilylation reactions

Hydrosilylation of heteroalkenes usually gives a mixture of two isomers the yields and ratio of which depend on the structure of each of the reagents and the catalyst as well as on reaction conditions (solvent, temperature).



R¹, R² = Alk, Alko, Cl.

Trichlorosilane is added to 2-vinyl-, 4-vinyl- and 2,6-dimethyl-4-vinylpyridines in the absence of a catalyst to give the corresponding pyridylethyltrichlorosilanes.⁸ It is assumed that the role of a catalyst is played by the heterocyclic base itself. Labile yellow complexes Cl₃SiH·*n*B (*n* = 3 for 4-vinylpyridine; *n* = 4 for 2-vinylpyridine) are intermediate products of this reaction.

Triorganyl- and diorganyl-chlorosilanes are added to the same vinylpyridines only in the presence of catalysts. Thus the corresponding β-adducts are formed in the presence of an Me₂NCH₂CH₂NMe₂–Cu₂Cl₂ complex, while a mixture of α- and β-adducts with the predominance of the former is formed in H₂PtCl₆-catalysed hydrosilylation of 2-vinylpyridine.¹⁰⁷ In the absence of a catalyst, triethylsilane does not react with 2- and 4-vinylpyridines, whereas in the presence of H₂PtCl₆ it is added to 4-vinylpyridine and 2-methyl-5-vinylpyridine to give solely β-adducts (in 46% and 36% yields, respectively).

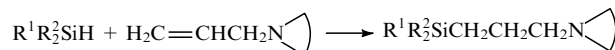
Hydrosilylation of 2-vinylquinoline catalysed by H₂PtCl₆ also results in a mixture of α- and β-adducts. Thus ethyldichlorosilane is added to 2-vinylquinoline to give predominantly the β-adduct (75% yield); trialkylsilanes give a mixture of regioisomers with the predominance of the α-adduct (10 h, 120–160 °C, overall yield 65%), while triethoxysilane gives a mixture of α- and β-adducts in a 1:1 ratio. The use of non-polar aprotic solvents (xylene, dioxane, diglyme) has no effect on the ratio of isomeric adducts but permits one to increase the total yield from 55% to 70%.¹⁰⁸ As for polar solvents (pyridine, quinoline), these favour the formation of the β-isomer; the total yield of the adducts decreases to 40% under these conditions. No hydrosilylation takes place in DMF.

2-(1-Triethoxysilylethyl)pyrrolidone^{109–111} and 2-(1-triethoxysilylethoxy)perhydroazepine^{112, 113} were obtained by the reaction of *N*-vinylpyrrolidone and *N*-vinylcaprolactam with triethoxysilane. This reaction was catalysed by rhodium or palladium complexes, rhodium dicarbonyl acetylacetonate being the most efficient catalyst.^{111, 112} With this catalyst, the reaction was selective and gave only the α-adduct in 73% yield.

Hydrosilylation of 2- and 2,3-substituted 1-vinylpyrroles and 1-vinyl-4,5,6,7-tetrahydroindole with triethylsilane catalysed by H₂PtCl₆ and ClRh(PPh₃)₃ (4–10 h, 80–100 °C) was highly regioselective and resulted exclusively in the β-adducts in 55%–80% yields.^{114–118} The use of polar aprotic solvents (THF, acetone) and increase in the reaction time allow one to increase the yield of the adduct up to 90%. No hydrosilylation of

these 1-vinylpyrroles with alkyldichloro-, trichloro- and trialkoxy-silanes occurred.

Hydrosilylation of *N*-allyl pyrrolidine, -piperidine,^{71, 119} -*N*'-methylpiperazine,¹²⁰ -morpholine^{120, 121} and -benzotriazole¹²² with triorganylsilanes catalysed by 0.1 M H₂PtCl₆ resulted in *N*-(3-triorganylsilylpropyl)derivatives of the corresponding heterocycles.



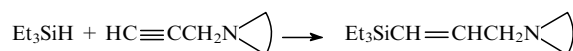
R¹ = Me, R² = Et, Pr, Bu, C₅H₁₁, Ph, Cl;

R¹ = Et, R² = Et, Pr, Bu;

R¹ = R² = Pr, Bu, EtO.

No individual reaction products could be obtained upon hydrosilylation of *N*-allylcarbazole with ethyldichlorosilane.¹²³

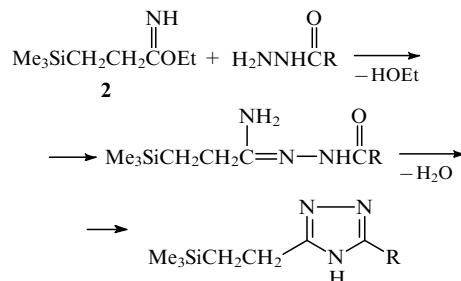
Hydrosilylation of *N*-propargyl-substituted pyrrolidine, piperidine, perhydroazepine and morpholine with triethylsilane in the presence of H₂PtCl₆ gives the γ -adducts with a *trans*-structure.^{71, 124, 125}



The yields of the hydrosilylation products formed upon 10-h boiling of the reaction mixture vary from 25% to 53%. Substitution of silanes with more electronegative substituents for triethylsilane favours the formation of the α -adduct.

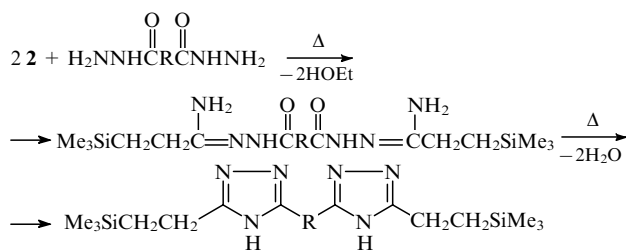
4. Cyclisation reactions

The reaction of carbohydrazides with ethyl β -trimethylsilylpropionimide (**2**) yields 3-alkyl-5-(2-trimethylsilylethyl)-1,2,4-triazoles.¹²⁶ Trimethylsilylethylamidrazones are the primary products of this reaction; their intramolecular cyclisation results in the corresponding organosilicon derivatives of 1,2,4-triazole upon heating *in vacuo*.



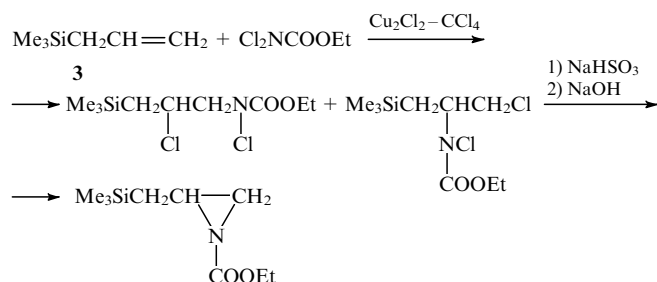
R = H, Me.

Dicarboxylic acid dihydrazides are converted into 3,3'-Di[5-(2-trimethylsilyl)ethyl]-1,2,4-triazoles less easily (only upon heating to 200 °C).

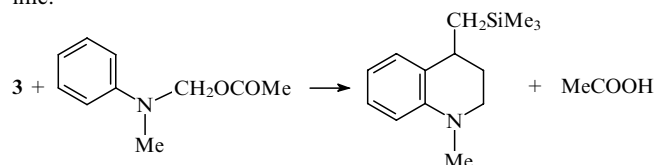


R = CH₂, (CH₂)₄, C₆H₄.

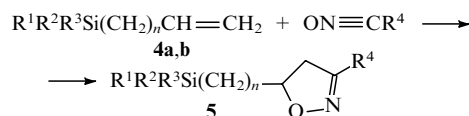
The addition of ethyl *N,N*-dichlorocarbamate to allyltrimethylsilane (**3**) with subsequent reduction with sodium hydrogen-sulfite and dehydrochlorination affords ethyl-*N*-chloro-*N*-(2-chloro-3-trimethylsilylpropyl)carbamate and ethyl-*N*-chloro-*N*-(1-chloromethyl-2-trimethylsilylethyl)carbamate. Intramolecular alkylation of the latter results in ethyl 2-(trimethylsilylmethyl)aziridine-2-carboxylate in 20% yield.¹²⁷



The reaction of allyltrimethylsilane with PhMeNCH₂O.*C*(O)Me in dichloromethane results ultimately in the corresponding 4-trimethylsilylmethyl derivative of 1,2,3,4-tetrahydroquinoline.¹²⁸



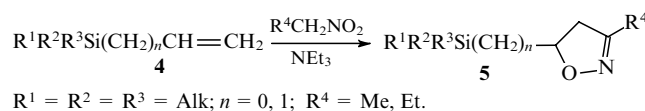
The addition of nitrile oxides to vinyl- and allyltrialkylsilanes **4** gave the corresponding organosilicon derivatives of 4,5-dihydroisoxazole **5** in 50%–70% yields.^{129, 130}



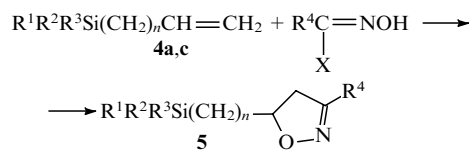
R¹ = R² = R³ = Me (**a**), Et (**b**); *n* = 0, 1; R⁴ = Br, Ph, 4-C₆H₄NO₂.

The rate of this reaction decreased upon substitution of phenyl or methoxy groups, having a negative inductive effect for methyl or ethyl groups at the silicon atom.

Vinyl- and allyltrialkylsilanes **4** react with nitroethane or 1-nitropropane in the presence of phenyl isocyanate and catalytic amounts of Et₃N in benzene to give the corresponding 3-alkyl-5-trialkylsilylisoxazolines **5** in 64%–88% yields.¹³¹

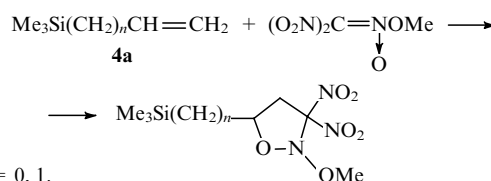


The reaction of vinyl- and allyltrialkyl(aryl)silanes [R¹ = R² = R³ = Me (**4a**), Ph (**4c**)] with hydroxyamoyl halides proceeds regioselectively and yields only one isomer.



R¹ = R² = R³ = Me (**a**), Ph (**c**); *n* = 0, 1; R⁴ = Ph, COOEt, Br; X = Cl, Br.

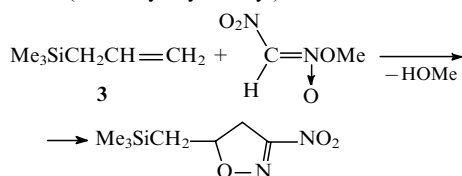
The reaction of trinitromethane *O*-methyl ester with vinyl- and allyltrimethylsilanes (**4a**) results in *N*-methoxy-3,3-dinitro-5-(trimethylsilyl)- and -5-(trimethylsilylmethyl)isoxazolidine.¹³⁰



n = 0, 1.

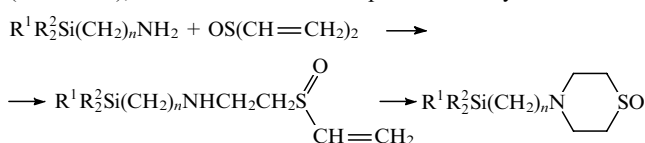
The reaction of these silanes with diethyl nitromalonate *O*-methyl ester proceeds in a similar way.¹³²

The reaction of dinitromethane *O*-methyl ester with allyl(trimethyl)silane is also accompanied by the formation of a cyclic adduct. However, 3-nitro-5-(trimethylsilylmethyl)isox-azoline is formed in high yield instead of the expected product, *N*-methoxy-3-nitro-5-(trimethylsilylmethyl)isoxazolidine.



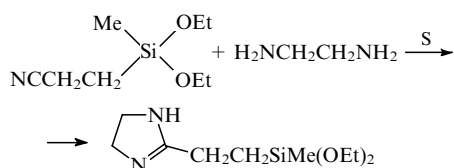
It can be inferred from these data that the cyclisation is regiospecific, *viz.*, the oxygen atom always attacks the least hydrogenated carbon atom.

At 50–75 °C, triorganylsilylalkylamines react with divinyl sulfoxide to give 4-(triorganylsilylalkyl)tetrahydro-1,4-thiazine oxides (in 62%–80% yields).¹³³ At lower temperatures (30–50 °C), a linear monoadduct is predominantly formed.



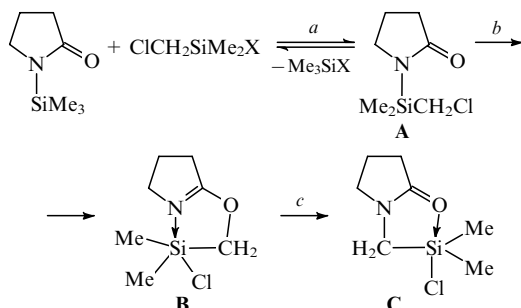
$\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{Me, Et, Bu}$; $\text{R}^1 = \text{R}^2 = \text{Et, EtO}$; $n = 1, 3$.

Cyclisation of methyl(2-cyanoethyl)diethoxysilane with ethylenediamine in the presence of sulfur as a catalyst gives 2-(2-methyldiethoxysilylethyl)-4,5-dihydroimidazole.¹³⁴



5. Transsilylation reactions

The reactions of halogeno- and alkoxydimethyl(chloro-methyl)silanes $\text{ClCH}_2\text{SiMe}_2\text{X}$ with *N*-trimethylsilyl derivatives of 2-piperidone,^{135–144} pyrrolidone,^{81, 136, 138–148} caprolactam,^{81, 138, 139, 141–144, 148} butyrolactam¹³⁹ and morpholinone¹⁴⁹ occur in three steps: (a) transsilylation (substitution of $\text{CH}_2\text{SiMe}_2\text{Cl}$ for SiMe_3); (b) intramolecular silylmethylation of the oxygen with migration of the chlorine atom from the carbon atom to silicon and (c) *O,N*-migration of the silylmethyl group. For instance:

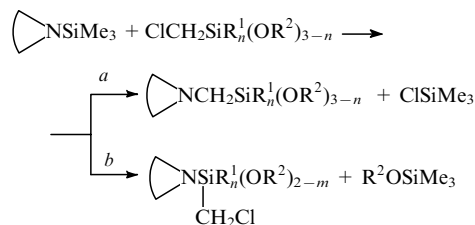


$\text{X} = \text{F, Cl, Br, I, OR}$.

Data from X-ray analysis¹⁴⁸ confirmed the conclusion that the silicon atom in *O*- (compound **B**) and *N*-alkylation (compound **C**) products is five-coordinate. It should be noted that *N*-trimethylsilyl derivatives of piperidone and caprolactam react with $\text{ClCH}_2\text{SiMe}_2\text{X}$ at room temperature, whereas the *N*-trimethylsilyl derivative of butyrolactam reacts with these silanes at 110–130 °C.¹³⁹ This reaction is catalysed by AlCl_3 , $\text{Me}_3\text{SiOSO}_2\text{CF}_3$ or PhNEt_2 . In this case, the reaction time decreases

from 3 to 0.5 h but the yield of the final product does not change (32%–71%).¹⁴²

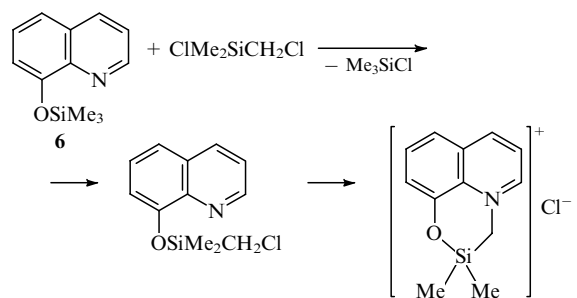
In the reaction of $\text{ClCH}_2\text{SiR}_n^1(\text{OR}^2)_{3-n}$ with *N*-trimethylsilyl-substituted 3,5-dimethylpyrazole, imidazole, benzimidazole^{90, 150, 151} and 2,2'-dipyridylamine,¹⁵² the main *N*-silylmethylation reaction (reaction *a*) is accompanied by transsilylation (reaction *b*):



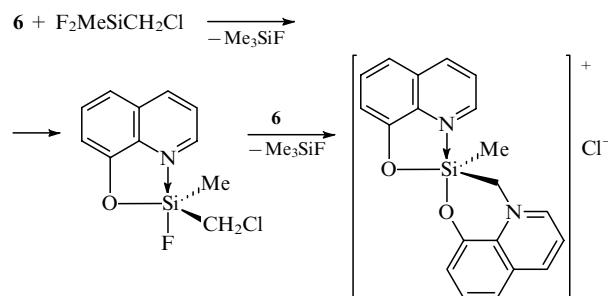
$\text{R}^1, \text{R}^2 = \text{Me, Et}$; $n = 0–3$; $m = 0, 2$.

Thus in the case of 3(5)-methylpyrazole, the ratio of silylmethylation and transsilylation products is 85 : 15.¹⁰²

The reaction of 8-trimethylsiloxyquinoline (**6**) with dimethyl(chloromethyl)chlorosilane proceeds according to the following scheme:^{153, 154}



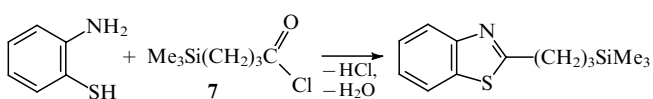
Methyl(chloromethyl)dihalogenosilanes react with 8-trimethylsiloxyquinoline to give a spirocyclic ionic derivative of five-coordinate silicon.



This review provides only a superficial description of transsilylation reactions resulting in heterocyclic derivatives of hypervalent silicon, because they have been surveyed in other reviews.^{141, 142, 146, 148}

6. Miscellaneous reactions

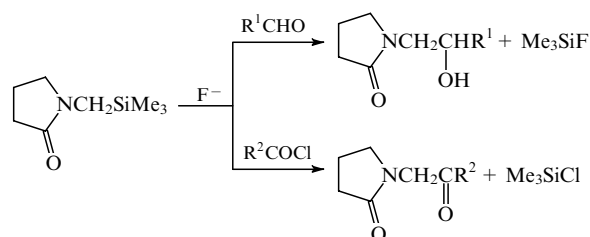
2-(3'-Trimethylsilylpropyl)benzothiazole was obtained by the reaction of 2-aminobenzenethiol with 3-trimethylsilylbutyryl chloride (**7**) in a polar solvent and in the presence of triethylamine (50–150 °C).¹⁵⁵



1,2,3,4-Tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline and *N*-methylpiperazine are more reactive than 8-hydroxyquinoline with respect to the acid chloride **7** in inert solvents (ether, hexane) at 0–10 °C.¹⁵⁶

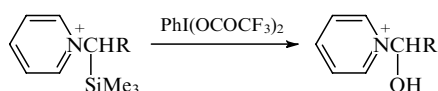
Depending on the position of the substituent (CH_2SiMe_3) in the heterocycle, the reactivity decreases in the following order (the relative reaction rates are given in parentheses): 2-Q CH_2SiMe_3 (41) > 4-Q CH_2SiMe_3 (37) > 4-Py CH_2SiMe_3 (8.9) > 2-Py CH_2SiMe_3 (1.0) > 3-Q CH_2SiMe_3 (0.161) > 3-Py CH_2SiMe_3 (0.03).⁵⁴ These data suggest that quinoline derivatives are desilylated faster than the corresponding pyridine derivatives.

In the presence of tetrabutylammonium fluoride in DMF or CsF in HMPA, *N*-trimethylsilylmethyl-substituted phthalimide,¹¹ 2-piperidone,³⁷ 2-mercaptobenzothiazole,⁶⁰ 2-benzothiazole,⁶¹ 1,2,4-triazole^{83,85,169} and 4-methylpyridine¹⁷⁰ are smoothly desilylated with aldehydes in THF (20–25 °C) to give the corresponding heterocyclic alcohols. Similar reactions of acid chlorides give the corresponding heterocyclic ketones.³⁷ For example:

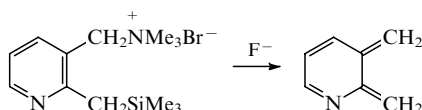


$\text{R}^1 = \text{Pr}^n, \text{Pr}^i, \text{Ph}$; $\text{R}^2 = \text{Pr}^n, 4\text{-MeC}_6\text{H}_4, \text{PhO}$.

Oxidative desilylation of trimethylsilylmethyl derivatives of pyridine and quinoline with $\text{PhI}(\text{OCOCF}_3)_2$ yields the corresponding alcohols in good yields.¹⁷¹



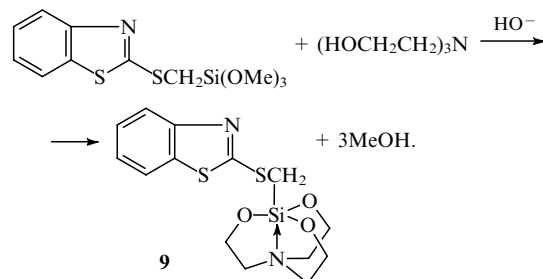
CsF-Induced desilylation of trimethyl[3-(2-trimethylsilylmethylpyridyl)methyl]ammonium bromide in acetonitrile (55 °C) affords a pyridinium analogue of *o*-quinodimethane.^{172,173}



The reaction of 2-(trimethylsilylmethyl)pyridine with perfluoro(2-methylprop-1-enyl)methyl ether and perfluoro(2-methylpent-2-ene) gave 2-[2-methoxy-3-(trifluoromethyl)but-1-enyl]pyridine (yield 50%) and 2-pentafluoroethyl-3-trifluoromethyl-4*H*-quinolizin-4-one, respectively.¹⁷⁴

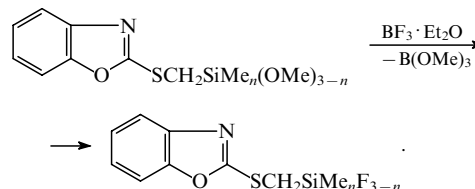
3. Reactions with functional substituents at the silicon atom

KOH-Catalysed transesterification of (heterylmethyl)trialkoxysilanes with triethanolamine results in the corresponding heterylmethylsilatrane.^{40–42,72,89,91,117,118,133,142,175–178} For example:

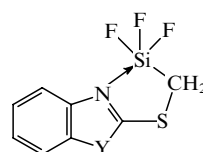


The molecular and crystal structures of 1-(2-benzothiazolylthiomethyl)silatrane was established by high-resolution X-ray analysis.¹⁷⁸

The reactions of trimethoxysilylmethyl- and methyltrimethoxysilylmethyl derivatives of pyridine, 8-mercaptoquinoline, 8-hydroxyquinoline, 2-mercaptobenzoxazole, 2-mercaptobenzothiazole, pyrrolidine and pyridine with HF , $\text{BF}_3 \cdot \text{Et}_2\text{O}$ or SbF_3 give the corresponding heterylalkyltrifluoro- and methyl(heterylalkyl)difluorosilanes in 61%–72% yields.^{117,118,179–183} For example:

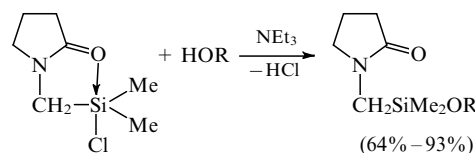


According to X-ray analysis data, the molecules of (2-benzoxazolylthiomethyl)- and (2-benzothiazolylthiomethyl)-trifluorosilanes contain an intramolecular $\text{N} \rightarrow \text{Si}$ coordination bond, which closes the five-membered ring.^{117,181}



$\text{Y} = \text{O}, \text{S}$.

Etherification of the corresponding chlorides in the presence of triethylamine as the HCl acceptor is the most versatile method for the synthesis of *N*-(dimethylalkoxysilylmethyl)lactams.^{184,185}

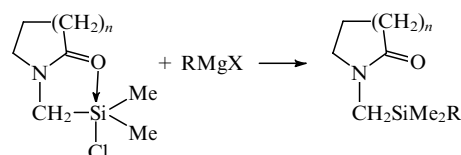


$\text{R} = \text{Me}, \text{Pr}^i, \text{C}_{10}\text{H}_{21}, \text{CH}_2\text{Ph}$.

The $\text{O} \rightarrow \text{Si}$ coordination bond is destroyed in the synthesis of alkoxy derivatives. With substitution of an $\text{RONa} - \text{PhMe}$ for an $\text{ROH} - \text{Et}_3\text{N}$ system, the yields of *N*-(dimethylalkoxysilylmethyl)lactams ($\text{R} = \text{Me}$ and Pr^i) are only 46% and 38%, respectively. This is due to the cleavage of the $\text{Si}-\text{CH}_2$ bond, which occurs simultaneously with the formation of *N*-methyl-lactams.

Trialkylalkoxystannanes can also be used instead of sodium alkoxides. This method was used to prepare *N*-(dimethylalkoxysilylmethyl)-substituted pyrrolidones and 2-azepinones in 79%–96% yields.¹⁸⁶

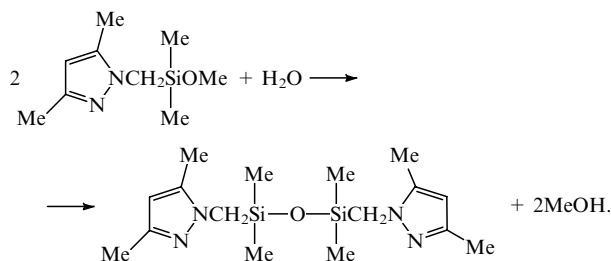
N-Chlorodimethylsilyllactams react with the Grignard reagents (MeMgI , PhCH_2MgCl) at the $\text{Si}-\text{Cl}$ bond with high chemoselectivity to give the corresponding *N*-(trimethylsilylmethyl)- and *N*-(benzyltrimethylsilylmethyl)-lactam derivatives.¹⁸⁷



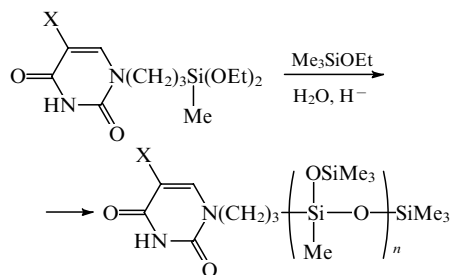
$\text{R} = \text{Me}, \text{CH}_2\text{Ph}$; $\text{X} = \text{Cl}, \text{I}$; $n = 1-3$.

4. Hydrolytic reactions

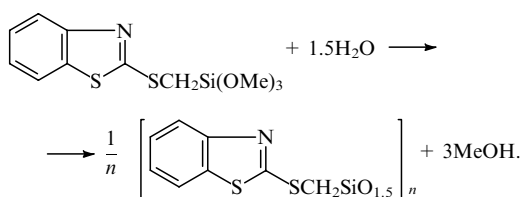
The hydrolysis of *N*-(methoxydiphenylsilylmethyl)-1,2,4-triazole,²⁸ *N*-(methoxydimethylsilylmethyl)-3,5-dimethylpyrazole,⁹⁰ *N*-(chlorodimethylsilylmethyl)-¹⁸⁸ and *N*-(alkoxydimethylsilylmethyl)lactams¹⁸⁹ gives the corresponding linear 1,3-bis(*N*-heterylmethyl)tetraorganylsiloxanes in 60%–82% yields. For example:



The hydrolytic polycondensation of *N*-[3-(diethoxy)methylsilylpropyl] derivatives of uracil, thymine and adenine gives rise to the corresponding polyorganylsiloxanes.³⁶

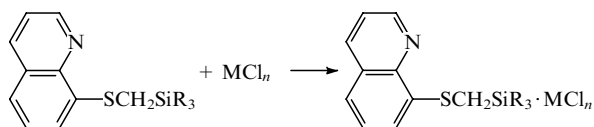


The hydrolysis of 4-(trialkoxysilylalkyl)tetrahydro-1,4-thiazine oxide,¹³³ 2-(2-trimethoxysilylmethylthio)benzimidazole, -benzoxazole and -benzothiazole,^{40–42, 190} as well as of (*N*-trialkoxysilylpropyl)morpholine¹⁹¹ proceeds with the formation of the corresponding polyheterylalkylsiloxanes in 10%–63% yields. For example:



5. Complex formation

2-[3-(Triethylsilylpropyl)methyl]quinoline,⁹¹ *N*-trimethylsilylmethyl-1,2,3,4-tetrahydroisoquinoline,^{75, 93, 192} *N*-[3-(diphenylmethylsilyl)propyl]morpholine and piperazine¹¹⁰ and *N*-[3-(trialkylsilyl)propargyl]pyrrolidine and -piperidine¹²⁴ react with a saturated solution of hydrogen chloride in ether to yield the corresponding hydrochlorides. The reaction of (8-quinolythiomethyl)trimethylsilanes, -trimethoxysilanes and -silatrane with CuCl₂, ZnCl₂, PtCl₂ and SnCl₄^{193–195} gave various types of coordination compounds the structure of which depended on the nature of the metal and substituents at the silicon atom. Thus the reaction of (8-quinolythiomethyl)trimethylsilane with potassium tetrachloroplatinate results in a planar-tetragonal chelate complex with PtCl₂.



R = Me, OMe; R₃ = (OCH₂CH₂)₃N; MCl_n = CuCl₂, ZnCl₂, PtCl₂, SnCl₄, HCl.

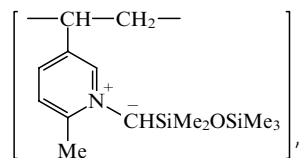
IV. Biological activities and practical applications

Many of the compounds considered in this review possess highly specific biological activities which are determined by both the presence of a heterocyclic system and the silicon atom flanked with the corresponding substituents. Therefore, such compounds

have attracted considerable attention in the past decade. *N*-(Triorganylsilylalkyl)imidazoles,^{12, 13, 20, 22, 23, 26, 30, 31, 196, 197} and -1,2,4-triazoles,^{12, 13, 20–24, 26–31, 84, 85, 196–206} 8-(trimethoxysilylpropylamino)quinoline and -5,7-dibromoquinoline,²⁰⁷ as well as 2-(trimethylsilyl)methylpyridines²⁰⁸ possess a broad spectrum of bactericidal and fungicidal activities. Used as fungicides (20–100 g hectare^{−1}), these compounds inhibit the growth of *Puccinia recondita*, *Sphaerotheca fuliginea*, *Erysiphe graminis* and *Podosphaera leucotricha*. Thus 1-[2-(4-bromophenyl)ethyldimethylsilylmethyl]imidazole (50–200 mg litre^{−1}) exhibits a fungicidal activity against *Erysiphe cichoracearum*, *Erysiphe graminis*, *Puccinia recondita*, *Puccinia coronata* and *Phalosophaeria nodorum*.²⁶

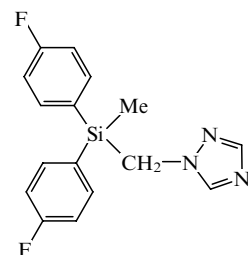
Substituted (trimethylsilyl)-3,5-bisaminomethyl-1,2,4-triazole and 2-(trimethylsilylmethoxy)pyrrolidone manifest high insecticidal activity.⁹⁴ *N*-[3-(4-Chlorophenyl)dimethylsilylpropyl]piperidine (2 and 5 g kg^{−1}) inhibits the growth of tobacco sucking discs.¹⁵

(4-Halogenophenyl)methyl-bis(1,2,4-triazol-1-ylmethyl)silane (Hal = F, Cl),²⁴ 3-[bis-(4-fluorophenyl)methylsilyl]imidazole³⁴ and 7-chloro-4-(4-trimethylsilylethynylpyrazolo)quinoline⁷⁰ used at a concentration of 500 mg litre^{−1} exert catalytic systemic effects against various diseases of wheat, rice, barley, oats, maize, cotton, soybean, coffee, sugar cane, apple trees, etc. *N*-Trialkylsilylmethyl-2-pyrrolidones and -caprolactams inhibit the growth of certain bacteria inducing diseases in vine and cucurbitaceous plants.⁸⁰ *N*-Trimethylsilylmethylbenzoxazine is an active and non-phytotoxic (for culture plants) component of herbicidal preparations which are commonly used in doses of 0.06–1.00 kg hectare^{−1} (see Ref. 209). 3,5-Diamino-6-(trimethylsilylethyl)-1,2,4-triazine is used for elimination of organisms attacking cabbage, beetroot and tobacco seedlings.²¹⁰ Poly-[2-methyl-5-vinylpyridinium 1-pentamethylsilyloxymethylide] possesses high pesticidal and growth-regulating activities.^{211, 212}



4-[3-(Trimethylsilyl)propylamino]quinolines manifest not only herbicidal but also selective antimicrobial activities,^{97, 99} viz., they efficiently suppress pathogenic fungi and exhibit moderate inhibiting action on the growth of gram-positive bacteria without any effect on gram-negative bacteria. 4-[3-(Trialkylsilyl)propylamino]-7-chloroquinolines exhibit high fungistatic activity. Incorporation of a methoxy group at position 6 of these compounds markedly increases their bacteriostatic activity.^{98, 99}

Flusilazole, 1-[bis(4-fluorophenyl)methylsilylmethyl]-1,2,4-triazole, is an efficient organosilicon ergosterol-like fungicide able to suppress various biosynthetic reactions.^{25, 213–231}



At present, flusilazole is one of the most widely used broad-spectrum agricultural fungicides. It is used against a complex of diseases in cereals, vine, seed fruits, sugar beet and peanut induced by asco-, basidio- and deuteromycetes (also in combination with other fungicides) in the doses of 80–240 g hectare^{−1}.

(*N*-Methylpiperazinylmethyl)phenylcyclohexylsilanol sulfomethylate exerts a potent and highly selective antimuscarinic effect and is used in experimental pharmacology for classification of various subtypes of muscarine receptors.⁷⁴

N-(Triethylsilylpropargyl)piperidine and -pyrrolidine hydrochlorides have a neurotropic effect on animals.¹²⁴ 6-[4-(Trimethylsilyl)butylamino]quinoline hydrochloride manifests an antiviral activity against influenza A virus.⁹² 1-(2-Chlorophenyldiphenyl)methyl-3-(dimethylphenylsilyl)methylimidazolium chloride,⁷⁷ *N*-[3-(trialkylsilyl)propyl]imidazole,^{86, 87} *N*-[3-(triorganylsilyl)propyl]piperazine and -morpholine,¹¹⁰ *N*-[1-(trimethylsilylmethyl)]-1,2,4-triazole,²⁰⁹ as well as 4-trialkylsilylpropylaminoquinoline^{91, 93, 156} and -pyridine²³² possess high antimicrobial activities. These compounds display high fungistatic and cytotoxic activities.

4-(Triorganylsilylalkyl)tetrahydro-1,4-thiazine 1-oxides produce a potent effect on the central and peripheral nervous systems and possess a bacteriostatic activity.¹³³

Weakly toxic [1-(2-oxopyrrolidino)ethyl]triethoxysilane exerts antishock and tranquillising effects.¹¹⁶ Methyl-2-butyl-(3-piperidinopropyl)silane and 2-(3-trimethylsilylpropargyloxy)-pyrazine-6-thiocarboxamide hydrochlorides and *N*-(triethylpropargylsilylmethyl)piperidine manifest a tuberculostatic activity *in vitro* against *M. tuberculosis* and a bacteriostatic activity against *Staphylococcus aureus haemolyticus* 209.^{38, 233}

4-[3-(Trialkylsilyl)propylamino]quinolines, 1-(trialkylsilylpropyl)fluorouracil,²³⁴ *N*-trimethylsilylmethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride,⁹³ 4-quinolylaminoalkyl-, 1-(1-tetrahydroquinolylmethyl)- and 1-[1-(4-quinolylamino)propyl]-silatrane²³⁵ manifest an antitumour activity, Ehrlich ascites tumour and leukemia L_D 5178 cells being especially sensitive to the cancerostatic effects of these compounds. (Heterylalkyl)trialkylsilanes are less active than the corresponding silatrane derivatives.

1-(3-Trialkylsilylpropyl)piperidine is used as an active component of a disinfectant used for the treatment of textiles.²³⁶ 4-(2-Trimethoxysilyl)ethyl-*N*-alkylpyridinium bromide, which has the property to increase the volume and softness of textile fibres, also manifests an antimicrobial activity.²³⁷

(Triorganylsilyl)benzotriazole derivatives are used as additives to sun protection lotions.¹¹²

N-(Trimethoxysilylpropyl)maleimide²³⁸ and 3-(triorganylsilylalkyl)-2-pyrrolidone²³⁹ are added to polymer-based pharmaceuticals in order to improve their mechanical properties.

5-[(Trimethylsilyl)methylthio]- and 5-[(diethylmethylsilyl)methylthio]-8-mercaptoquinolines are used as organic analytical reagents.^{18, 240, 241}

2-(2'-Trimethoxysilyl)pyridine is used for the preparation of rhodium carbonyl complexes. The latter are immobilised on silica gel and used as catalysts.²⁴²

1-(Trialkoxysilylalkyl)-3,5-diaminotriazine,²⁴³ -piperidine²⁴⁴ and -2-(4-triazolyl)benzoimidazole²⁴⁵ derivatives are used for treatment of fibre glass fabrics in order to improve their coupling with the polymeric binders. *N*-Substituted organosilicon derivatives of imidazole,²⁴⁶ benzoimidazole²⁴⁷ and triazine²⁴⁸ are used to protect metal surfaces owing to their ability to form highly thermostable films that withstand 100 heating cycles.

2-(Trialkylsilylalkyl)benzothiazole has been patented as a binder in the production of siliceous fillers for rubber tyres.^{78, 249–253}

Polysilanes containing *N*-alkylpyrrole groups²⁵⁴ and *N*-trimethoxysilylpropyl imidazole derivatives²⁵⁵ are used in the production of conducting materials.

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Electron density and traditional structural chemistry of silicates

E L Belokoneva

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Abstract. New results of studies on the electron density of silicates are considered in accordance with the traditional structural classification. Precision X-ray diffraction data and results of structure refinement based on high-angle and multipole models are discussed. Bonded radii, charges on atoms and bond ionicities in Si, Al, B and Be tetrahedra are estimated from the deformation electron density maps in relation to the electronic structures of the atoms and their electronegativities. New possibilities for the solution of problems of isomorphism, for investigations on hydrogen bonds and for the classification are demonstrated. It is noted that the electron density distributions allow one to consider fundamentals of traditional structural chemistry of silicates on the electronic level. For selected compounds, the results of experimental studies of the electron density and of quantum-chemical calculations are compared. The bibliography includes 97 references.

I. Introduction

Silicates are substances whose structures contain different combinations of silicon-oxygen tetrahedra as the major anionic components. Their negative charges are compensated for by charges of cations bulkier than silicon (for example, by magnesium, iron, calcium, sodium or potassium cations). Silicates belong to rock-forming minerals, which account for 90% of the Earth's crust. Virtually all elements of the Periodic table ranging from hydrogen to uranium and transuranium elements are the components of these minerals. Many silicates are mined and used as sources of raw materials.

The discovery of X-ray diffraction and the development of a fundamentally new method for studying compounds, *viz.*, X-ray diffraction analysis, have had a crucial effect on the studies of silicate structures. Before this method had been developed, numerous 'salts of polysilicic acids,' which are virtually insoluble in strong acids, had presented a puzzle for chemists. In the first

studies performed in the mid-1920s, the structures of garnet (the first silicate), quartz, olivine, sphene, zircon, diopside, topaz, phenakite, willemite, beryl, vesuvianite, benitoite, hypersthene, staurolite, hemimorphite and thortveitite were solved.^{1,2} Abundant data on silicate structures have now been accumulated. Russian scientists, namely, Academician N V Belov and his followers, have contributed significantly to the development of the notion of silicate structures.³

The advent of automated diffractometers and programme packages for special data processing marked the beginning of precision X-ray diffraction studies. The review by Tsirelson⁴ was the first Russian publication in which the current state of precision X-ray diffraction investigations and the modern notion of the electron density distribution in crystals have been covered most comprehensively. Examples of structural studies of organic and inorganic compounds, including silicates, were also reported in the cited review. Presently, studies on the electron density are among intensively developing lines of investigation in the structural chemistry. The principles and methods of investigations of the electron density are considered in detail in the monographs.^{4–7}

Classical (traditional) investigations in the field of structural chemistry of silicates were most completely surveyed in the monograph by Liebau.⁸ In this monograph, precision X-ray diffraction studies of silicates were briefly considered and the deformation electron density maps for orthoenstatite and coesite were presented. However, the currently available factual data are substantially more abundant.

The publications by Tsirelson *et al.*,^{9,10} can be considered as the first reviews devoted to the studies on the electron density of silicates. In the latter review, the major concepts, including principles of interpretation of electron density maps, were reported. A total of about 20 structures were discussed in these publications.

The present review surveys the results of studies on the electron density distribution in silicates published in recent years. Taking into account new data, crystal-chemical notions, such as the bond ionicity, the effective radius and the charge on the atom, as well as principles of the classification of silicate structures, which are compared with the classical views, are considered.⁸ For selected structures, the results of experimental studies on the electron density are compared with the results of quantum-chemical calculations.

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In the analysis of the results of investigations of silicate structures by the precision X-ray diffraction method, particular attention is given to the chemical bonds (especially, to those in silicon–oxygen tetrahedra). The data on these bonds can be obtained from electron density maps. The experimental electron density maps constructed with the use of the known procedures^{4–7} revealed regions of concentration of the electron density which were identified with overlapping orbitals. The silicon atom in the [SiO₄] tetrahedron possesses four equivalent *sp*³-hybrid orbitals corresponding to single covalent σ -bonds.^{11,12} In silicates, the experimental average SiO distance is shorter than that calculated with the use of Shomaker–Stevenson's equation taking into account the covalent radii of the silicon and oxygen atoms for the single bond. Cruickshank suggested¹¹ that the remaining *p*-orbitals of the oxygen atoms overlap with the *d*-orbitals of the silicon atoms to form additional π -bonds, which impart a somewhat double character to Si–O interactions. This fact was noted by Liebau⁸ and Tsirelson *et al.*¹⁰

Most studies on the chemical bonds in silicates involved calculations of deformation electron density distribution maps on the basis of an independent spherical-atom model (IAM), which is refined based on high-angle reflections (high-angle refinement), and the determination of the deformation component of the density ($\delta\rho$) responsible for the chemical bond with the use of difference Fourier series^{4–7}

$$\delta\rho(\mathbf{r}) = \frac{1}{V} \sum [F_{\text{exp}}(\mathbf{s}) - F_{\text{IAM}}(\mathbf{s})] \exp(-2\pi i \mathbf{s} \cdot \mathbf{r}),$$

where *V* is the unit cell volume, *F*_{exp} is the experimental structure amplitude, *F*_{IAM} is the calculated structure amplitude of the independent spherical model, *s* is the scattering vector of the reciprocal lattice, which describes the reflection of the *hkl* node, and *r* is the radius vector.

Therefore, the deformation electron density $\delta\rho$ characterises the electron density redistribution upon the involvement of atoms in chemical bonding.

The method of the multipole analysis of the electron density differs fundamentally from that of the high-angle refinement.^{4–7,10,13,14} The atomic scattering factor can be calculated from the following formula:

$$f(q) = P_c f_c(q) + P_v f_v\left(\frac{q}{\alpha}\right),$$

where *P*_c and *P*_v are population coefficients of the core and valence shells, respectively, and *f*_c(*q*) and *f*_v(*q*/α) are their scattering factors. The parameter α accounts for contraction or expansion of the valence shell of the atom. Chemical bonding leads to deviation from the spherical symmetry of the valence shell. However, this deviation is relatively small and can be described by the low-order expansion of the electron density in terms of nucleus-centred angular harmonics. For this purpose, different models are used, those suggested by Hansen and Coppens¹³ and by Stewart and Spackman¹⁴ are most generally employed. As an example let us consider the equation for the electron density suggested by Hansen and Coppens

$$\rho_a(\mathbf{r}) = P_c \rho_c(r) + P_v \alpha'^3 \rho_v(\alpha' r) + \sum_{l=0}^4 \alpha''^3 R_l(\alpha'' r) \sum_{lm} P_{lm} y_{lm}\left(\frac{\mathbf{r}}{r}\right),$$
 where *r* is the radius vector, *P*_c, *P*_v and *P*_{lm} are the population coefficients of the core, valence and deformation components, respectively, α' and α'' are the expansion–contraction parameters of the valence and multipole shells, respectively, *R*_{*l*} are the radial functions and *y*_{*lm*} are spherical harmonics (up to the fourth order); *r* = |*r*|.

The atom is represented as the sum of the core, valence and deformation (multipole) electron densities. The population coefficients of the valence and multipole terms, the parameters of the radial functions *P*_{*lm*} and the α' and α'' parameters are refined by the least-squares method. The refinement is performed until the

closest agreement between the calculated and experimental structure factors is achieved.

Precision calculations of silicate structures are carried out with the use of different programme packages, which allow one to process experimental data, to perform the refinement within the framework of a particular model and to construct sections of the electron density distribution passing through the interacting atoms. The following programmes can serve as examples: LINUS and its modified version EARTH,¹⁵ RADIEL,¹⁶ CRYLSQ,¹⁷ FOURR,¹⁸ SADIAN90,¹⁹ MINEXTL,²⁰ *etc.* The improved programme packages MOLLY¹³ and VALRAY¹⁴ are most generally used for the multipole refinement. Presently, the XD programme package,²¹ which involves modern investigation techniques, including topological analysis of the electron density, provides the greatest scope.

In the present review, most attention is concentrated on the results of high-angle refinement because only five examples of multipole refinement are known for silicates. The structures are considered in accordance with the degree of condensation of tetrahedra in the [Si_{*n*}O_{*m*}]^{*q*–} anionic silicon–oxygen motif. In crystal chemistry, this motif is also referred to as a radical. This consideration corresponds to the classical mineralogical classification.^{22–25}

II. Orthosilicates

Orthosilicates involve structures consisting of isolated (island) silicon-oxygen *ortho* groups. Natural and synthetic orthosilicates, *viz.*, Mg-, Fe-, Ni-, Co- and Mn-olivines,^{26–30} Fe-, Co- and Nispinel,^{31,32} phenakite,^{33,34} euclase,³⁵ eulytine,³⁶ topaz³⁷ and sphene,³⁸ were studied by precision methods.

1. Topaz

A specimen of natural topaz from the Volyn' deposit (Ukraine) was studied.³⁷ Intensities of reflection were measured within four octants of the reciprocal space related by a $\bar{4}$ axis. The principal crystallographic characteristics and conditions of the X-ray diffraction study are given in Table 1. Calculations were carried out using the MINEXTL programme. The extraordinarily high extinction was taken properly into account using the Zachariasen algorithm. An independent atomic model was obtained in the high-angle refinement, the *c* coefficient in the weighting scheme being varied:

$$w_s = [\sigma^2 + (cF^2)]^{-1},$$

where σ is the standard deviation and *F* is the structure factor. The correctness of the choice of the weighting scheme and of the determination of the scale factor was checked using Abrahams –

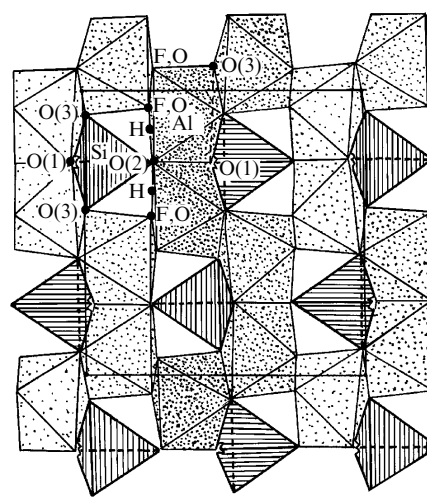


Figure 1. Structure of topaz.

Table 1. Crystallographic characteristics and conditions of X-ray diffraction studies of silicates.

Mineral	Space group	Unit cell parameters				<i>A</i>	<i>B</i>	<i>C</i>	Refinement parameters		
		<i>a</i> /Å	<i>b</i> /Å	<i>c</i> /Å	β /deg				<i>R</i> (%)	<i>R_w</i> (%)	<i>S</i>
Topaz $\text{Al}_2[\text{SiO}_4]\text{F}_2$	<i>Pbnm</i>	4.6511(8)	8.802(1)	8.402(1)	—	4694	1356	715	0.99	1.16	1.03
Sphene $\text{CaTiO}[\text{SiO}_4]$	<i>P2₁/a</i>	7.061(1)	8.7165(9)	6.5603(9)	113.84(1)	6924	3043	2445	1.63	2.81	1.18
Beryl $\text{Be}_3\text{Al}_2[\text{Si}_6\text{O}_{18}] \cdot \text{H}_2\text{O}$	<i>P6/mcc</i>	9.222(3)	—	9.204(1)	—	4671	752	338	0.73	0.79	1.02
Cordierite $\text{Mg}_2\text{Al}_3\text{Al}[\text{Si}_5\text{O}_{18}] \cdot \text{H}_2\text{O}$	<i>Cccm</i>	17.155(5)	9.777(4)	9.339(4)	—	6324	1982	1058	1.18	1.19	1.02
Diopside $\text{Ca}[\text{Si}_2\text{O}_6] \cdot 6\text{H}_2\text{O}$	<i>R3</i>	14.597(2)	—	7.796(1)	—	3878	1593	625	1.90	2.00	0.87
Tourmaline $\text{NaMg}_3\text{B}_3\text{Al}_6\text{Si}_6\text{O}_{27}(\text{OH})_4$	<i>R3m</i>	15.890(8)	—	7.129(3)	—	7383	1389	458	2.36	3.48	1.19
Datolite $\text{CaBSiO}_4(\text{OH})$	<i>P2₁/a</i>	9.646(6)	7.620(4)	4.839(3)	90.14(5)	6018	2584	1250	1.28	1.33	1.00
Coesite SiO_2	<i>C2/c</i>	7.1367(4)	12.369(1)	7.1742(5)	—	7253	1716	1716	1.25	1.23	1.35
Danburite $\text{CaB}_2\text{Si}_2\text{O}_8$	<i>Pnam</i>	8.0456(7)	8.7629(4)	7.7341(7)	—	16243	3315	3315	3.46	5.80	0.87
Natrolite $\text{Na}_2\text{Al}_2\text{Si}_3\text{O}_{10} \cdot 2\text{H}_2\text{O}$	<i>Fdd2</i>	18.293(1)	18.641(1)	6.5871(6)	—	13920	3471	1856	0.9	0.8	1.40
Phenakite Be_2SiO_4	<i>R3</i>	18.288(2)	18.631(2)	6.583(1)	—	8250	5191	1961	2.16	2.20	1.27
		12.485(3)	—	8.264(3)	—	3935	1270	324	1.52	1.62	0.978
		12.472(2)	—	8.251(1)	—	11700	1053	1053	1.84	1.77	1.834

Note. Notation adopted: *A* is the number of measured reflections; *B* is the number of independent reflections; *C* is the number of reflections used in the high-angle or multipole refinement.

Keve's test.³⁹ The refined real structural formula of the specimen is $\text{Al}_2[\text{SiO}_4](\text{F}_{0.95}\text{OH}_{0.05})$; its structure is shown in Fig. 1.

The deformation density distribution in the sections of the $[\text{SiO}_4]$ tetrahedron is in agreement with the concept of the presence of sp^3 -hybridisation and σ -bonds. The map calculated for the $\text{O}(1) - \text{Si} - \text{O}(3)$ section in topaz based on the experimental results and the map calculated for $\text{O} - \text{Si} - \text{O}$ in the H_4SiO_4 molecule by the quantum-chemical method⁴⁰ are similar. Thus the $\delta\rho$ maxima have close values (0.40 and 0.35 $\text{e} \text{ \AA}^{-3}$ for topaz and $\text{O} - \text{Si} - \text{O}$, respectively) and these maxima in both maps are shifted toward the more negative oxygen atom (Fig. 2*a, b*).[†] In other orthosilicates (olivine, spinel, euclase and phenakite), the values of the corresponding maxima are in the range of 0.2–0.4 $\text{e} \text{ \AA}^{-3}$. Calculations of the error maps demonstrated that these errors in the chemical bond region were 0.05 $\text{e} \text{ \AA}^{-3}$. A comparison of the electron density distributions at the faces of the tetrahedra in topaz and olivine also demonstrates that they are basically similar. However, a slight spread in values of the maxima in the σ -bonds is

observed. Note that topaz is characterised by a four-layer close packing, while olivine is described by a two-layer close packing.

The average $\text{Si} - \text{O}$ distances in the tetrahedra are diminished as the degree of their condensation increases.^{8, 25, 41} This is associated with the electrostatic interactions of the atoms. In the cases that electropositive cations (potassium, sodium, magnesium or calcium) in the structure dominate over electronegative silicon ions, simple anionic motifs, in which oxygen atoms adopt high coordination numbers and the $\text{Si} - \text{O}$ bonds are elongated, are realised.²⁵ The potassium, sodium, magnesium and calcium cations rather readily donate electrons to the oxygen atoms, thus increasing their effective charges upon chemical bonding so that the ability of oxygen atoms to ionise silicon atoms decreases.⁴² Hence, the second coordination sphere of the silicon atom has a determining effect on the electron density distribution in the silicon–oxygen tetrahedra in orthosilicates. In topaz and olivine, this sphere is formed by the Al atoms or by the Fe and Mg atoms, respectively. These atoms occupy octahedral cavities of the close packings in different fashions. The influence of the cations of the second coordination sphere is most clearly manifested in the electron density map as the splitting of the peak at the oxygen atom due to interactions between the oxygen atom and two aluminium atoms located to its right and left above the closely

[†] In the figures, which present the electron density distributions, the maps are contoured as follows: the solid lines indicate positive values of $\delta\rho$; the dash-and-dot lines indicate the zero level; the dashed lines indicate negative values of $\delta\rho$.

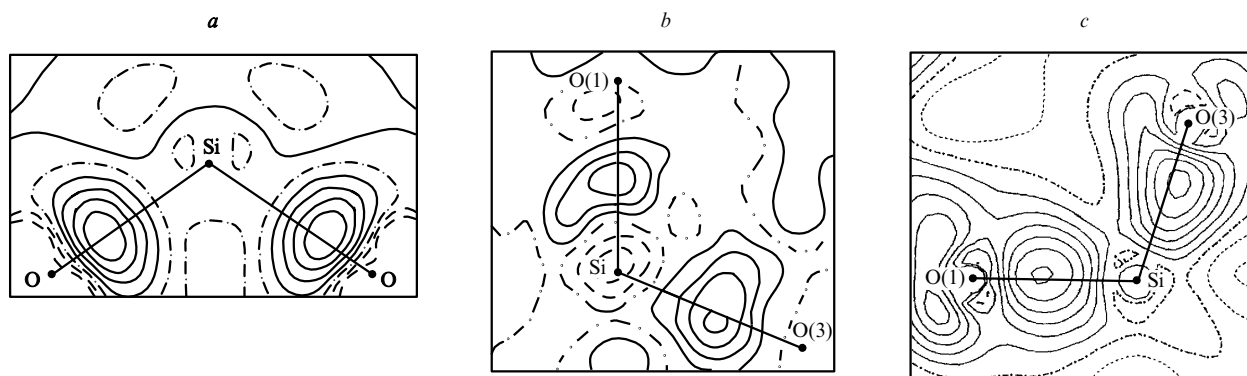


Figure 2. The electron density distribution in the H_2SiO_4 molecule (*a*) and in topaz (*b, c*); (*a*) the deformation density calculated for the SiO_2 group in the H_4SiO_4 molecule, the map is contoured at intervals of 0.07 $\text{e} \text{ \AA}^{-3}$ (see Ref. 40); (*b*) the experimental deformation density in the $\text{O}(1) - \text{Si} - \text{O}(3)$ section; (*c*) the static deformation density in the $\text{O}(1) - \text{Si} - \text{O}(3)$ section, the maps are contoured at intervals of 0.1 $\text{e} \text{ \AA}^{-3}$.

packed layer. The sections through the layers of the close packing indicate that the electron density of the oxygen atoms is shifted along the bond toward the occupied octahedral (Al) and tetrahedral (Si) holes.

The multipole refinement of the $\rho(\mathbf{r})$ function⁴³ based on the same experimental results as those used in another study,³⁷ confirmed the principal characteristic features of the electron density distribution and the crystal-chemical conclusions made previously. Calculations were carried out with the use of the MOLDOS96 and SALDOS97 programmes.⁴⁴ The characteristics of the refinement ($R = 0.91\%$, $R_w = 1.1\%$, $S = 1.13$) were improved compared to the data given in Table 1.

The calculated and experimental deformation density maps for the silicon–oxygen tetrahedron are virtually identical (see Fig. 2*a,c*). Analysis of the static deformation density maps calculated based on the results of multipole refinement most clearly revealed the shift of the electron density of the oxygen atoms in the close packed layer toward the occupied holes (Fig. 3). The splitting of the maximum at the O(2) atom toward two aluminium atoms was also reproduced.

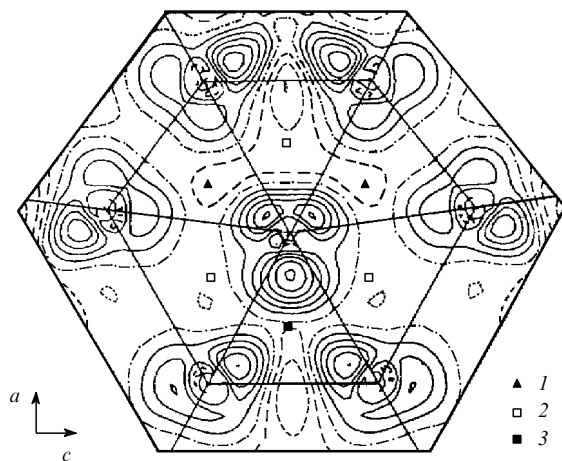


Figure 3. The static deformation density distribution in the section of topaz passing through close packed layers of O(1) (in the centre) and O(3) atoms (at the vertices of the internal hexagon); the map is contoured at intervals of $0.1 \text{ e } \text{\AA}^{-3}$. The positions of the atoms: (1) Al in octahedral holes above the close packed layer; (2) unoccupied octahedral holes below the close packed layer; (3) Si in tetrahedral holes.

The charges on the atoms in topaz were estimated on the basis of the results of determination of population coefficients of valence shells.⁴³ In this work, considerable attention has been given to the topological analysis of the electron density, which is an intensively developing modern method^{6,7} (this method is not considered in the present review). Note however that according to

Bader's theory^{4,6} chemical interactions in the silicon–oxygen tetrahedron are interpreted to a greater degree as ionic (*i.e.*, as interactions of atoms with closed electron shells) rather than as covalent interactions. This is inconsistent with the experimental and theoretical data obtained to date.

2. Sphene

A synthetic crystal of sphene $\text{CaTiO}[\text{SiO}_4]$ grown by Czochralski's method (Fig. 4) was investigated.³⁸ This mineral possesses antiferroelectric properties. The investigators attempted to relate these properties to the electronic structure. The conditions of the X-ray diffraction study are given in Table 1. Calculations were carried out with the use of the MINEXTL programme package.

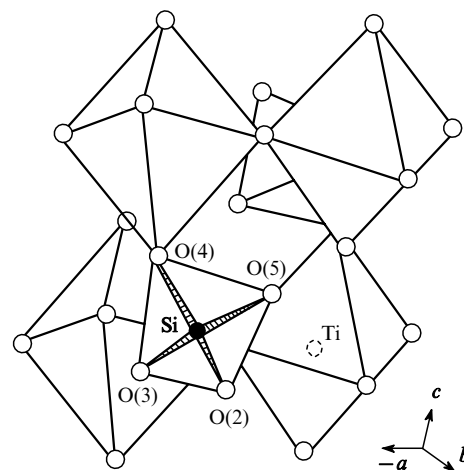


Figure 4. Structure of sphene.³⁸

The distances in the silicon–oxygen tetrahedra in sphene and topaz (Table 2) are close to each other and are larger than those in other silicates containing condensed anionic groups. The deformation electron density distribution corresponds to four σ -bonds (sp^3-p) with maxima of $0.2-0.4 \text{ e } \text{\AA}^{-3}$. The effect of the second coordination sphere on the electron density in the isolated $[\text{SiO}_4]$ tetrahedron can be judged from the difference in the values of peaks in the bonds between the silicon atom and the oxygen atoms belonging to the edge shared by Ti octahedra in a column and to the edge shared by Ti octahedra of two different columns (Fig. 5*a*). An electron-density 'bridge' ($0.2 \text{ e } \text{\AA}^{-3}$) is clearly seen on the edge. This bridge can be interpreted as the manifestation of a somewhat double character of the bridging Si–O bonds in this structure. The error of $\delta\rho$ in the chemical-bond region was $0.2 \text{ e } \text{\AA}^{-3}$.

The asymmetrical deformation density distribution was observed in the Ti octahedron, the density being concentrated at the shortened titanyl Ti–O(1) bond [$1.7594(7) \text{ \AA}$; Fig. 5*b*], which

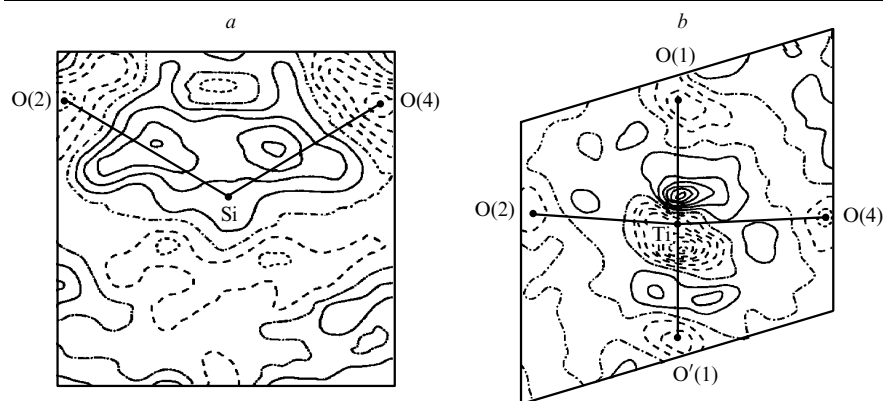


Figure 5. The experimental deformation density distribution in the section of the Si tetrahedron (*a*) and Ti octahedron (*b*) in sphene;³⁸ (*a*) the O(2)–Si–O(4) section, the map is contoured at intervals of $0.05 \text{ e } \text{\AA}^{-3}$; (*b*) the O(2)–Ti–O(4)–O'(1) section, the map is contoured at intervals of $0.1 \text{ e } \text{\AA}^{-3}$.

Table 2. Interatomic distances in the tetrahedra of silicate structures determined in precision X-ray diffraction studies.

Tetrahedron	Atoms	Distance /Å	Tetrahedron	Atoms	Distance /Å	Tetrahedron	Atoms	Distance /Å
Topaz			Diopside			Danburite		
[SiO ₄]	Si—O(1)	1.636(1)		Si—O(2)	1.596(2)	[BeO ₄]	B—O(1)	1.479(1)
	Si—O(2)	1.646(1)		Si—O(3)	1.528(2)		B—O(2)	1.500(1)
	Si—O(3)	1.641(1)×2			1.598		B—O(3)	1.463(1)
		1.641					B—O(5)	1.454(1)
Sphene			Tourmaline					1.474
[SiO ₄]	Si—O(2)	1.6410(5)	[SiO ₄]	Si—O(4)	1.626(3)	Natrolite		
	Si—O(3)	1.6418(5)		Si—O(5)	1.639(3)	[Si(1)O ₄]	Si(1)—O(1)	1.6056(8)×2
	Si—O(4)	1.6401(7)		Si—O(6)	1.607(2)		Si(1)—O(5)	1.6310(9)×2
	Si—O(5)	1.6429(6)		Si—O(7)	1.615(2)			1.616
		1.6415			1.622			
Beryl			Datolite			[Si(2)O ₄]	Si(2)—O(2)	1.6193(6)
[SiO ₄]	Si—O(1)	1.623(1)	[SiO ₄]	Si—O(1)	1.575(4)		Si(2)—O(3)	1.6121(7)
	Si—O(1')	1.595(1)		Si—O(2)	1.649(5)		Si(2)—O(4)	1.6133(8)
	Si—O(2)	1.600(1)×2		Si—O(3)	1.656(5)		Si(2)—O(5)	1.6368(9)
		1.610		Si—O(4)	1.660(4)			1.6204
[BeO ₄]	Be—O	1.657×4			1.635	[Al(1)O ₄]	Al(1)—O(1)	1.7371(9)
Cordierite			[BO ₄]	B—O(2)	1.484(5)		Al(1)—O(2)	1.7457(6)
[Si(1)O ₄]	Si(1)—O(2)	1.630×4		B—O(3)	1.479(6)		Al(1)—O(3)	1.7344(6)
[Si(2)O ₄]	Si(2)—O(1)	1.638(0)×2		B—O(4)	1.470(4)		Al(1)—O(4)	1.7430(8)
	Si(2)—O(5)	1.587(1)		B—O(5)	1.497(3)			1.7400
	Si(2)—O(6)	1.609(1)			1.483			
		1.618	Coesite			Phenakite		
[Si(3)O ₄]	Si(3)—O(3)	1.640(0)×2	[Si(1)O ₄]	Si(1)—O(1)	1.595(1)	[Si(1)O ₄]	Si(1)—O(1)	1.631(2)
	Si(3)—O(4)	1.574(1)		Si(1)—O(3)	1.613(2)		Si(1)—O(2)	1.630(2)
	Si(3)—O(6)	1.616(1)		Si(1)—O(4)	1.611(4)		Si(1)—O(3)	1.631(1)
		1.618		Si(1)—O(5)	1.621(1)		Si(1)—O(4)	1.637(1)
		1.618			1.610			1.632
[Al(1)O ₄]	Al(1)—O(2)	1.766(0)×2	[Si(2)O ₄]	Si(2)—O(2)	1.6118(3)	[Be(1)O ₄]	Be(1)—O(1)	1.638(2)
	Al(1)—O(4)	1.710(1)		Si(2)—O(3)	1.6140(6)		Be(1)—O(2)	1.641(2)
	Al(1)—O(5)	1.713(1)		Si(2)—O(4)	1.605(4)		Be(1)—O(4)	1.659(2)
		1.741		Si(2)—O(5)	1.6186(7)		Be(1)—O(4')	1.650(3)
		1.756			1.6124			1.647
[Al(2)O ₄]	Al(2)—O(1)	1.758(0)×2	Danburite			[Be(2)O ₄]	Be(2)—O(1)	1.647(2)
	Al(2)—O(3)	1.755(0)×2	[SiO ₄]	Si—O(1)	1.6187(8)		Be(2)—O(2)	1.645(2)
		1.756		Si—O(2)	1.6238(8)		Be(2)—O(3)	1.659(2)
Diopside				Si—O(3)	1.6150(8)		Be(2)—O(3')	1.643(3)
[SiO ₄]	Si—O(1)	1.615(2)		Si—O(4)	1.6158(8)			1.649
	Si—O(1')	1.651(2)			1.618			

Note. Average values are given in boldface type.

is apparently responsible for the appearance of the electric moment in the structure. The difference in the bond lengths and, correspondingly, in the charges on these bonds is typical of many compounds containing titanium atoms. For example, the titanyl bond in KTiOPO_4 , which exhibits nonlinear-optical properties, is often considered as a double bond. This conclusion was made on the basis of calculations of the valence forces of the bond. The antiferromagnetic properties of sphene may result from the antiparallel distribution of the anisotropy of Ti—O interactions.

The radii of the best separation or the bonding radii were estimated from the full electron density maps.⁴⁵ It was noted that these radii were distributed over two pairs of the bonds of the silicon atom (0.85 and 0.49 Å; the average value is 0.67 Å). The estimation of the radius of the oxygen atom from the corresponding bonds in sphene gave the values 0.78 and 1.17 Å (the average value is 0.98 Å). The latter value differs only slightly from the corresponding values reported for coesite and stishovite⁴¹ (0.95 and 1.05 Å, respectively).

III. Ring silicates

Ring silicates are minerals the structures of which consist of silicon—oxygen tetrahedra arranged in rings. This group of silicates considered previously^{9, 10} was supplemented with a large number of new subjects.

1. Beryl

A specimen of natural beryl which was virtually free of impurities with the real structural formula $\text{Na}_{0.04}\text{Be}_{2.98}\text{Al}_2[\text{Si}_6\text{O}_{18}] \cdot 0.3\text{H}_2\text{O}$ (Fig. 6) was studied.^{9, 10} Investigation of the electron density

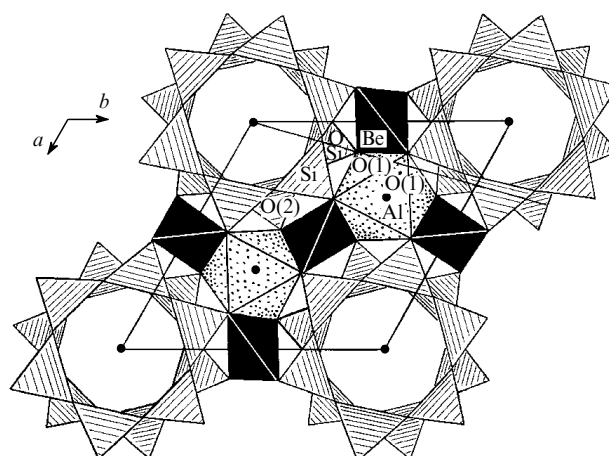


Figure 6. Structure of beryl.⁴⁶

distribution made it possible to characterise chemical bonds in the six-membered $[\text{Si}_6\text{O}_{18}]$ ring, the Be tetrahedron, the Al octahedron and in the structure as a whole.^{46,47} Actually, a group of beryls (exhibiting microisomorphism) containing various impurities of 3d elements (Fe, Co, Cu and Cr) which impart a typical colour to the crystals (*viz.*, aquamarine is pale-blue, emerald is green, *etc.*) was studied. The results of studies of microisomorphism were considered in detail.⁴⁸ Chromophore impurity ions occupy the positions of Al in octahedra (Fe, Co or Cr) or Be in tetrahedra (Cu) rather than interstitial sites as suggested previously. In addition to 3d elements, beryl structures contain small impurities of sodium atoms and water molecules. Their positions were determined as $2(b)$ (0 0 0) for the Na atom and $2(a)$ (0 0 1/4) for the oxygen atom of the water molecule. On the basis of the arrangement of the $\delta\rho$ maxima ($0.4 \text{ e } \text{\AA}^{-3}$) in the electron density maps, the planes of the water molecules were found to be oriented horizontally (parallel to the ab plane), their own twofold axes being perpendicular to the principal sixfold axis (Fig. 7a). This distribution was characterised on the assumption that molecules are statistically disordered about the sixfold axis. The electron density distributions in all horizontal and vertical (parallel to the c axis) sections for isomorphous modifications of beryls steadily reproduced the hydrogen bond pattern. The errors of the maps were $0.02\text{--}0.05 \text{ e } \text{\AA}^{-3}$.

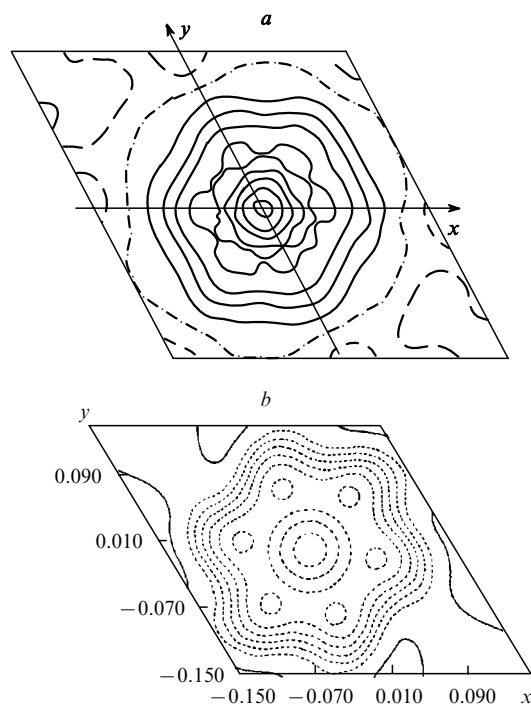


Figure 7. The experimental deformation density distribution in the section of beryl passing through the oxygen atom of the water molecule, $z = 0.25$ (a) and the difference Fourier map (neutron diffraction data, 30 K), $z = 0.317$ (b).⁴⁹

The horizontal orientation of the water molecules corresponds to one of two models of beryl structures proposed for interpreting their IR spectra. The model that assumes the vertical orientation of the planes of the water molecules was not confirmed by our investigations. Neutron diffraction studies^{49,50} of the structure of beryl confirmed the horizontal orientation of the water molecules established previously^{46,47} (Fig. 7b). The statistical disorder was assumed. However, the peaks around the position $2(a)$ (0 0 1/4) were misinterpreted as those possessing the mirror symmetry: in the space group of beryl (see Table 1) this position has the point symmetry 622, while the point symmetry $6/m$ is typical of position $2(b)$ (0 0 0) (Na atoms). The maxima on the sixfold axis in the

vicinity of the site (0 0 1/4) are apparently due to lone electron pairs of the water molecules. Other orientations of the water molecules in beryls are also not ruled out.^{49,50} Unfortunately, the vertical sections in which the positions of the hydrogen atom under consideration could be clearly seen were not presented.

2. Cordierite

The mineral cordierite $\text{Mg}_2\text{Al}_3\text{AlSi}_5\text{O}_{18}$ is structurally similar to beryl although its symmetry is lower (see Table 1).⁵¹ The high-temperature modification of cordierite with the beryl structure has long been known.⁵² Both minerals consist of six-membered rings of tetrahedra occupied by silicon atoms in beryl and by silicon and aluminium atoms in cordierite. Additional Be tetrahedra in beryl and Si and Al tetrahedra in cordierite are linked with the tetrahedra of rings *via* shared vertices to form open-work tetrahedral frameworks with bulky cavities filled by Na atoms and H_2O and CO_2 molecules (Fig. 8). Currently, cordierite in the form of ceramics is considered as an adsorbent of harmful Zn-containing exhausts of motor transport.⁵³ In this connection, the problem of incorporation of impurities into this zeolite-type framework is under investigation. In addition to studies on microisomorphism of 3d elements in beryls,⁴⁸ incorporation of Cu^+ and Cu^{2+} ions into cordierites was examined by the Rietveld method.⁵⁴ The electron density maximum at the site (0 0 0), which is analogous to that observed in beryl, was attributed to the incorporation of copper atoms.

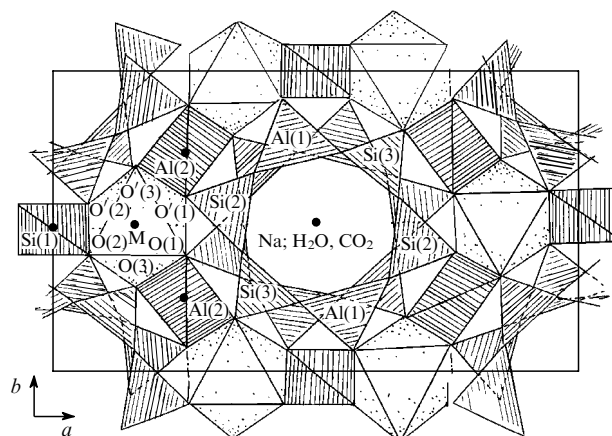


Figure 8. Structure of cordierite.⁵¹ M is the (Mg, Fe, Mn) octahedron.

Precision investigation of a single crystal of cordierite (a natural specimen from the Tuva deposit) demonstrated that the crystal-chemical formula of the mineral taking into account microisomorphism was $\text{Na}_{0.04}(\text{Mg}_{1.13}\text{Fe}_{0.78}\text{Mn}_{0.05})\text{Al}_2\text{Si} \cdot [\text{Al}_2\text{Si}_4\text{O}_{18}] \cdot 0.02\text{H}_2\text{O} \cdot 0.06\text{CO}_2$. X-ray diffraction data were collected within a hemisphere of the reciprocal space. Calculations were carried out with the use of the MINEXTL programme. An iron impurity in Mg octahedra was detected. The site (0 0 0) of the Na atoms is identical with that in beryl. It is worthy of note that this position is too 'bulky' for copper atoms, which should cause the impurity atom to displace from the centre of the cavity. It seems more likely that copper and zinc impurity atoms in the structure of cordierite occupy positions of 'non-ring' tetrahedra or Mn octahedra. Water molecules together with CO_2 occupy the position (0 0 1/4) in a channel identical with that in the above-considered structure of beryl.

It is of most interest to compare the electron density distributions and to reveal the difference in the chemical bonds when different atoms fill the same structural units. The deformation density distributions in the $[\text{Si}_6\text{O}_{18}]$ and $[\text{Al}_2\text{Si}_4\text{O}_{18}]$ rings in beryl and cordierite, respectively, are shown in Fig. 9a,b. In the low-temperature modification of cordierite, Al and Si atoms are distributed over tetrahedral positions in an orderly fashion (see

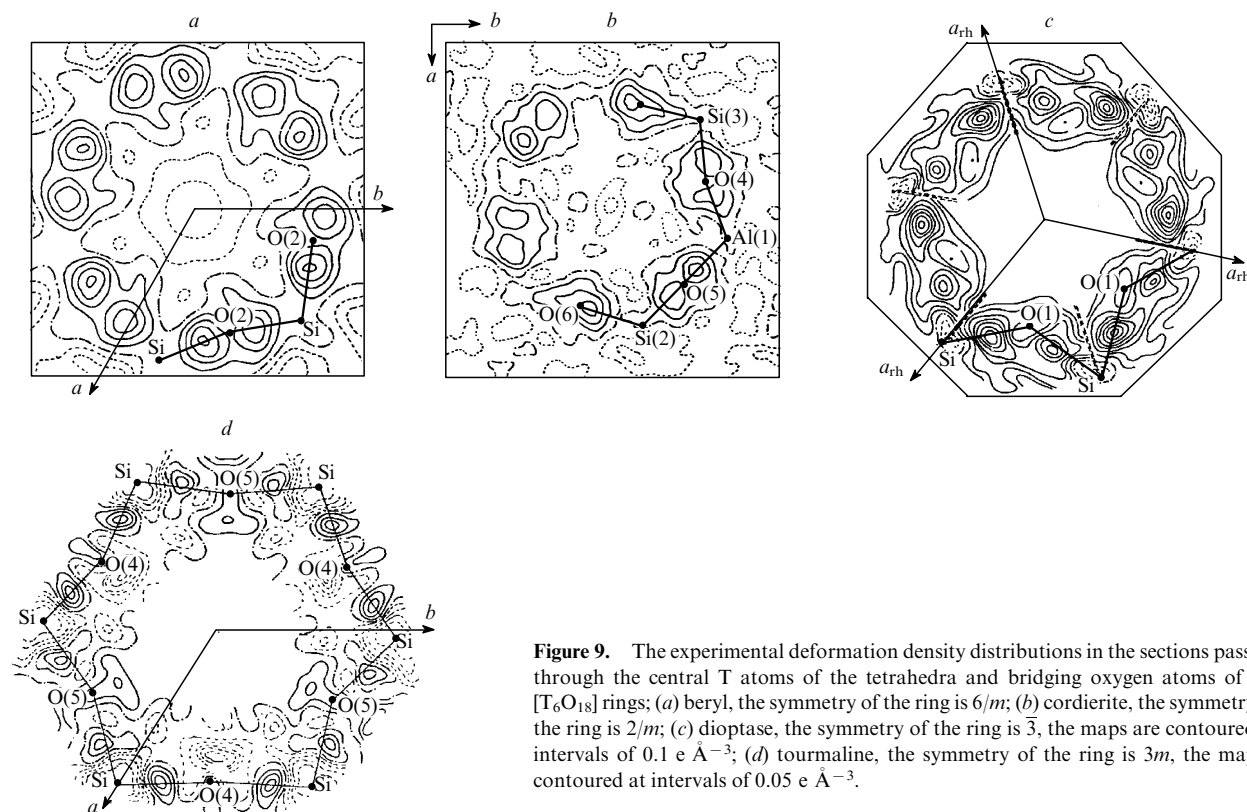


Figure 9. The experimental deformation density distributions in the sections passing through the central T atoms of the tetrahedra and bridging oxygen atoms of the $[T_6O_{18}]$ rings; (a) beryl, the symmetry of the ring is $6/m$; (b) cordierite, the symmetry of the ring is $2/m$; (c) diopside, the symmetry of the ring is $\bar{3}$, the maps are contoured at intervals of $0.1 \text{ e } \text{\AA}^{-3}$; (d) tourmaline, the symmetry of the ring is $3m$, the map is contoured at intervals of $0.05 \text{ e } \text{\AA}^{-3}$.

Table 2). At high temperature, these atoms are disordered, which leads to a phase transition. The interatomic Si—O distances in the tetrahedra of these minerals consisting of linked tetrahedra are shorter than those in orthosilicates. According to the rules of electrostatics, the distance between two silicon atoms interacting *via* the bridging oxygen atom is increased due to their repulsion. However, both in beryl and cordierite, all oxygen atoms act as bridges, minerals have the framework structures, the tetrahedral positions are occupied by Be, Si and Al atoms and the above-described effect is not manifested.

For both structures, the deformation electron density maps (see Fig. 9 *a, b*) reveal accumulation of the density at the bridging oxygen atoms. The maxima in the Si—O and Al—O bonds are $0.30\text{--}0.40 \text{ e } \text{\AA}^{-3}$ and $0.20\text{--}0.25 \text{ e } \text{\AA}^{-3}$, respectively, which correspond to different electronic structures of the atoms. However, this difference in the Si, Al ring in cordierite is smoothed. Calculations of the error maps demonstrated that these errors were $0.02\text{--}0.05 \text{ e } \text{\AA}^{-3}$ in the chemical-bond region and 0.05 and $0.04 \text{ e } \text{\AA}^{-3}$ at the silicon and aluminium atoms, respectively. As in the case of beryl, no difference between the bridging and terminal

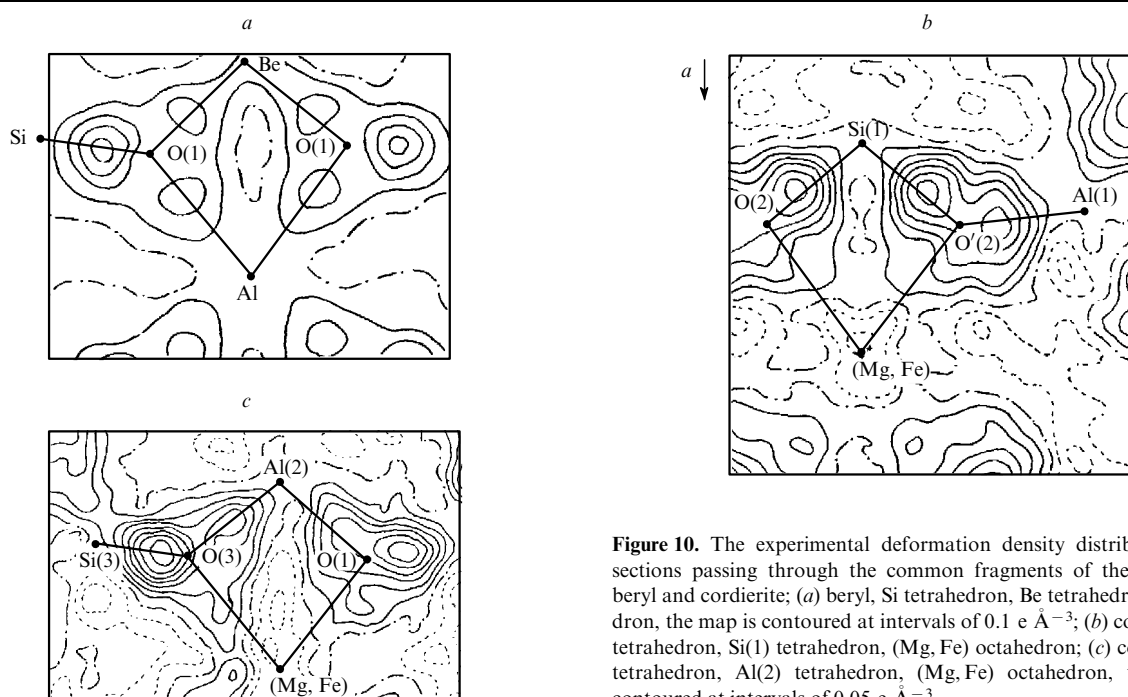


Figure 10. The experimental deformation density distributions in the sections passing through the common fragments of the structures of beryl and cordierite; (a) beryl, Si tetrahedron, Be tetrahedron, Al octahedron, the map is contoured at intervals of $0.1 \text{ e } \text{\AA}^{-3}$; (b) cordierite, Al(1) tetrahedron, Si(1) tetrahedron, (Mg, Fe) octahedron; (c) cordierite, Si(3) tetrahedron, Al(2) tetrahedron, (Mg, Fe) octahedron, the maps are contoured at intervals of $0.05 \text{ e } \text{\AA}^{-3}$.

oxygen atoms was observed as regards the values of the maxima in the σ -bonds.

In the framework structure, virtually all oxygen atoms are shared by two tetrahedra. Therefore, the assignment of beryl and cordierite to framework beryllsilicates⁵⁵ and framework aluminosilicates, respectively, is valid from the viewpoint of the electronic structure and chemical bonds in these compounds.

The structural fragment common to beryl and cordierite consists of the octahedron (Al or Mg, Fe) and the tetrahedra (Be, Al and Si tetrahedra) linked to the octahedron *via* shared edges or vertices. The differences in the electron density redistribution which occur if the centres of the corresponding polyhedra are occupied by atoms with different electronic structures and electronegativities (Be, Al or Si)^{8,56} are in complete agreement with those expected (Fig. 10): 0.2, 0.2–0.25 and 0.3–0.4 e Å⁻³ for the Be–O, Al–O and Si–O distances, respectively. An increase in the shift of the $\delta\rho$ maxima toward the more electronegative oxygen atom with increasing difference in the electronegativities of the Si–O, Al–O and Be–O pairs of elements allows one to estimate the bond ionicity. In agreement with the traditional crystal-chemical criteria, an increase in the bond ionicity is also observed for the M–O bond in the octahedron where Al is replaced by (Mg, Fe) (see Fig. 10). Note that even a small impurity of iron atoms in the case of hexagonal distortion of the octahedron is manifested in the map as an additional maximum directed toward the threefold axis of the coordination polyhedron, which corresponds to 3d-electrons of the iron atom located on the d_{z^2} -orbital (a_g level).

3. Diopase

The mineral diopase has the formula Cu₆[Si₆O₁₈]·6H₂O. A specimen of natural diopase from Kazakstan was studied by the same methods as described above for the specimens of beryl and cordierite.⁵⁷ The reflections within a hemisphere of the reciprocal space were reindexed from the hexagonal to the trigonal setting. The rings in silicates under consideration have different symmetry, *viz.*, 6/*m*, 2/*m*, $\bar{3}$ and 3*m* in beryl, cordierite, diopase and tourmaline (discussed below), respectively.

By virtue of the absence of the horizontal mirror plane and corrugation of the [Si₆O₁₈] ring in the case of the symmetry $\bar{3}$, the electron density map for this ring was constructed from fragments (see Fig. 9 *c*). The difference in the Si–O bond lengths in diopase is consistent with the classical concepts.⁸ As in the case of cordierite, the deformation density is accumulated at the bridging oxygen atoms. Of particular interest is the difference in the maxima in the bonds with the participation of the bridging and terminal oxygen atoms (see Fig. 9 *c,d*): 0.6–0.8 and 0.2–0.3 e Å⁻³, respectively (the error in the chemical-bond region is 0.1 e Å⁻³). These data are indicative of the nonequivalence of the bonds in the silicon–oxygen tetrahedron in diopase (unlike beryl and cordierite) and underline the role of the bridging oxygen atoms that fasten the corrugated ring as the structural unit in the overall three-dimensional construction. Hence, the characteristic features of the chemical bonds in this mineral confirm the assignment of diopase to ring silicates.

The structure of diopase (Fig. 11) is characterised by the presence of corrugated six-membered rings of silicon–oxygen tetrahedra that alternate with analogous six-membered rings of water molecules, which can be considered as the fragments of the ice structure. The positions of the protons in diopase were determined by neutron diffraction analysis.⁵⁸ The electron density distribution in the section passing through the water molecules (Fig. 12 *a*) is similar to the calculated distribution (Fig. 12 *b*)⁵⁹ and other experimental distributions. The observed decrease in the electron density on the lone electron pairs is associated with interactions of water molecules with other atoms (in particular, with copper atoms).⁶⁰ The calculated geometrical characteristics (bonds and angles) of the hydrogen bonds correspond to the standard values. The hydrogen bonds are directed toward the water molecules within the ring as well as upward and downward

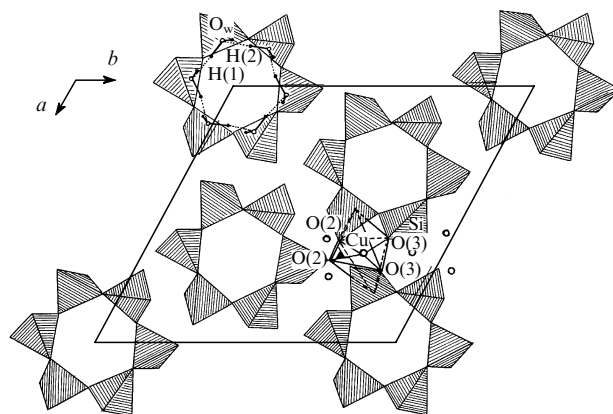


Figure 11. Structure of diopase.⁵⁷

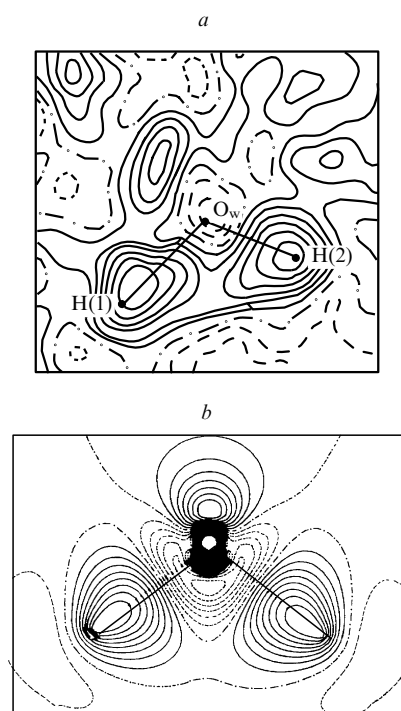


Figure 12. The deformation electron density distributions in the sections passing through water molecules; (a) the H(1)–O_w–H(2) section (experiment) in diopase; (b) the H–O–H section (calculation) for the isolated water molecule.⁵⁹

(toward the silicon–oxygen rings) thus holding the ring of water molecules in the structure. The experimental and calculated electron densities for the hydrogen bond between two water molecules in the ring are in satisfactory agreement.⁶¹ In the structure of diopase, unlike the structure of ice (Pauling's model), all lone electron pairs are oriented outward the ring.

In the structure of diopase, all divalent copper atoms occupy Jahn–Teller-distorted octahedra. The effect of the ligand crystal field on the distribution of the 3d-electrons of the copper atom ([d⁹] configuration) can be described assuming the symmetry D_{4h} (the true symmetry C_1) of a distorted octahedron. The 3d-level splits into 4 sublevels, *viz.*, $e_g(d_{xz}, d_{yz})$, $b_{2g}(d_{xy})$, $b_{1g}(d_{x^2-y^2})$ and $a_{1g}(d_{z^2})$.⁶² When the axes of coordinates are directed along the Cu–ligand bonds with the z axis directed toward the apical water molecules, depletion of the $b_{1g}(d_{x^2-y^2})$ orbitals in electron density is observed, all other orbitals being occupied. Hence, in accordance with the Jahn–Teller removal of degeneration, the $a_{1g}(d_{z^2})$ level is stabilised, while the $b_{1g}(d_{x^2-y^2})$ level is destabilised. In

chalcantite,⁶³ in which the Cu octahedron possesses a symmetry centre, this pattern is more pronounced.

4. Tourmaline (elbaite)

A specimen of natural tourmaline from Afghanistan was studied by Belokoneva and Tsirelson⁶⁴ (see Table 1). Intensities of reflections were measured within a hemisphere of the reciprocal space in the hexagonal setting and, as in the case of diopase, the reflections were reindexed to the trigonal setting.

The tourmaline family is characterised by a broad spectrum of isomorphism. Five major modifications are distinguished according to the composition and colour of the minerals, *viz.*, dravite, elbaite, buergerite, schorl and ulvite.²³ Based on the results of investigations on isomorphism in this specimen and on the results of X-ray microspectral analysis, the formula of tourmaline (elbaite) was established to be $(\text{Na}_{0.85}\text{Ca}_{0.05}) \cdot (\text{Al}_{1.10}\text{Li}_{1.15}\text{Fe}_{0.41}\text{Mn}_{0.22}\text{Mg}_{0.12}) \cdot \text{Al}_6\text{B}_3\text{Si}_6\text{O}_{27}(\text{OH})_{3.92}$. The structure of the mineral is shown in Fig. 13.

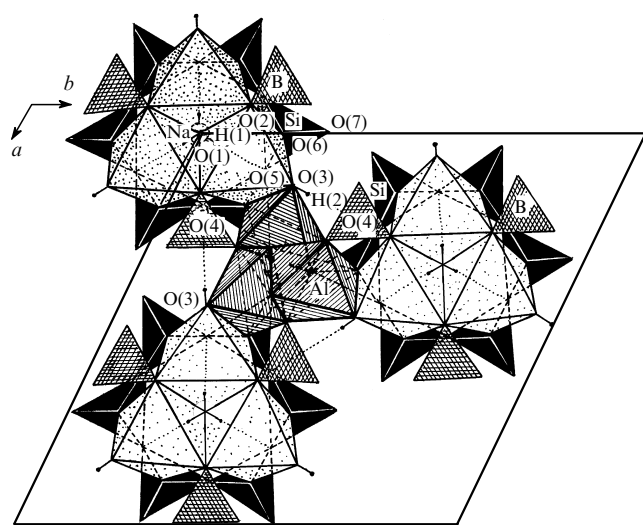


Figure 13. Structure of tourmaline.⁶⁴ Dotted hatching indicates (Al, Li, -Fe, Mn, Mg) octahedra.

Unlike all the above-considered ring anionic groups which possess a symmetry centre, the ring of silicon–oxygen tetrahedra in tourmaline is polar and corresponds to the symmetry $3m$. Tourmaline is a pyroelectric mineral.[‡] The structural prerequisites for this phenomenon still remain unclear. Hence, analysis of the electron density distribution in the crystal of tourmaline is a topical problem.

The triangular O(4)–O(5)–O(7) faces in the ring of the silicon–oxygen tetrahedra of tourmaline are nearly parallel to the *a* and *b* axes of the unit cell and the polar vertices of the O(6) tetrahedra are located directly above the silicon atoms exactly along the *c* axis. In the silicon–oxygen ring (unlike the analogous rings in the three above-considered minerals), weak $\delta\rho$ maxima are observed in the vicinity of the bridging oxygen atoms (see Fig. 9*d*), *viz.*, outside the ring close to the O(4) atom and within the ring close to the O(5) atom. These maxima correspond to O(H)···O hydrogen bonds. The most remarkable characteristic feature of the deformation density maps is the displacement of the electrons toward the base of the silicon–oxygen tetrahedron with the maximum located directly below the silicon atom (Fig. 14*a*). In this case, the apical oxygen atom is depleted in electrons in the bond and the $\delta\rho$ maximum is displaced from the bond line

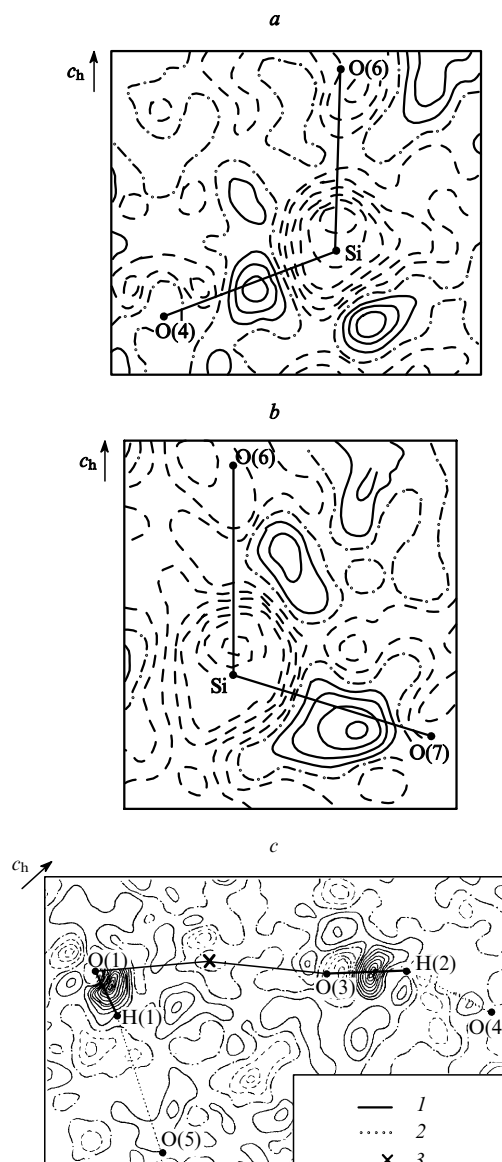


Figure 14. The experimental deformation density distributions in the sections of tourmaline; (a) the O(6)–Si–O(4) section with the maximum under the Si atom; (b) the O(6)–Si–O(7) section, the maps are contoured at intervals of $0.05 \text{ e } \text{\AA}^{-3}$; (c) O(3)–H(2)···O(4) and O(1)–H(1)···O(5) hydrogen bonds, the map is contoured at intervals of $0.1 \text{ e } \text{\AA}^{-3}$; (1) hydrogen donor, (2) hydrogen acceptor; (3) the position of the (Al, Li, Fe, Mn, Mg) octahedron.

(Fig. 14*a,b*). The interatomic distance to the apical oxygen atom is shortened, while the distances to the bridging oxygen atoms are elongated (see Table 2). The experimental errors of the determination of the $\delta\rho$ maps in the bond region were $0.06 \text{ e } \text{\AA}^{-3}$. An asymmetrical charge distribution within the tetrahedron and within the ring as a whole may be responsible for the appearance of an electric dipole moment in the structure and the pyroelectric properties.

The maximum of the deformation electron density was experimentally detected in the $[\text{VOCl}_3]$ tetrahedron on the opposite side of the metal–ligand bond,⁶⁵ as is the case in the silicon–oxygen tetrahedron in tourmaline. The phenomenon of deformation of the inner electronic shell of the vanadium atom under the action of the polarisation ligand field to produce the local concentration of the charge exterior to the bond was predicted by Bader and co-workers^{66,67} on the basis of the results of quantum-chemical calculations. Apparently, the polarisation field of the oxygen ligands in the ring of tourmaline is responsible

‡ It was in crystals of tourmaline that the phenomenon of pyroelectricity was discovered.

for the unusual deformation electron density distribution and pyroelectric properties.

Tourmaline is a borosilicate the boron atoms of which have a triangular coordination. The electron density distribution in the section passing through the $[\text{BO}_3]$ triangle is indicative of the bonds described by the sp^2 -hybrid state of the orbitals of the boron atom, which overlap (to form σ -bonds) with the p -orbitals of the oxygen atoms.

In the structure of tourmaline, the hydrogen bonds directed from one of the so-called antigorite fragment to another were studied.³ Figure 14c shows maxima ($\sim 1 \text{ e } \text{\AA}^{-3}$) corresponding to the electron density of the hydrogen atoms involved in the O–H bonds. The hydrogen bonds are directed from the O(3) and O(1) donor atoms to the O(4) and O(5) acceptor atoms of the silicon–oxygen ring.

Note that studies of the above-described ring silicates were preceded by only one publication devoted to the investigation of the synthetic analogue of wadeite, $\text{K}_2\text{Si}[\text{Si}_3\text{O}_9]$, which contains three-membered rings of Si tetrahedra and silicon atoms in octahedra.⁶⁸

IV. Chain and band silicates

The group of chain and band silicates includes three orthopyroxenes containing a two-membered $[\text{Si}_2\text{O}_6]$ chain (enstatite, ferrosilite and its cobalt analogue),⁶⁹ three clinopyroxenes (diopside, $\text{Mg}_2\text{Si}_2\text{O}_6$ and α -spodumene $\text{LiAlSi}_2\text{O}_6$)²⁹ and pectolite containing a three-membered chain.⁷⁰

Andalusite, which has been considered by Tsirelson *et al.*¹⁰ in the section devoted to orthosilicates, should be assigned to band aluminosilicates.⁷¹

The electron density distributions in structures of chain and band silicates have been investigated.^{9, 10} Since these publications, this group of silicates has not been supplemented with new members.

V. Sheet silicates

In sheet silicates, bonds between the layers (sheets) are weakened owing to which virtually all these minerals exhibit perfect cleavage. Sheet silicates very rarely occur as faceted crystals. If these crystals do occur, they are strongly flattened along the $[0001]$ direction. When ground to spheres, these crystals either collapse into plates or the spheres obtained give a large diffuse scattering component. For these samples, it is difficult to take proper account of absorption as well as to apply other corrections, which does not allow one to achieve a required precision of experimental data.

A specimen of natural datolite from the Tetuyche deposit (Far East) was studied.⁷² The mineral has the layered structure. The configuration of the layer is analogous to that in apophyllite $\text{KCa}_4[(\text{Si}_4\text{O}_{10})_2] \cdot 8\text{H}_2\text{O}$. Attempts to prepare a spherical sample of the latter mineral, which could give sharp reflections, have failed. In contrast, high-quality spherical samples of datolite crystals were prepared and precision investigation was performed. Intensities of reflections were measured within a hemisphere of the reciprocal space and within an additional hemisphere with $2\theta_{\text{max}} = 50^\circ$. The preliminary data processing was carried out with the use of the profile analysis procedure on the basis of Lehmann–Larsen's algorithm. This procedure allows one to obtain more reliable estimations of integrated intensities, particularly, those of weak reflections. Calculations were carried out using the CSD programme.

Microisomorphous relations were studied in the specimen and microimpurities of sodium and iron were detected. The content of the latter correlated with the hydrogen content. The formula of datolite was established to be $(\text{Ca}_{0.986}\text{Na}_{0.014})\text{Fe}_{0.012} \cdot \text{H}_{0.988}[\text{BSiO}_5]$; its structure is shown in Fig. 15. The incorporation of the iron atoms into the datolite structure indicates that it is related to minerals such as gadolinite and homilite.²³

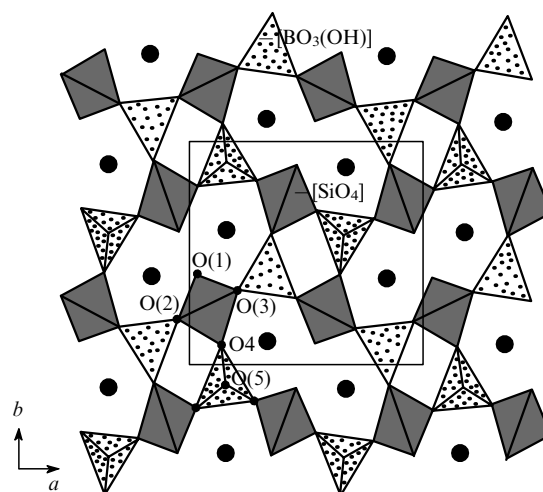


Figure 15. Structure of datolite.⁷²

The structure of datolite is built up of silicon–boron–oxygen $[\text{BSiO}_5]_\infty$ layers, which consist of tetrahedra linked *via* shared vertices. A characteristic feature of these layers is that the apical vertices of the B tetrahedra occupied by the OH groups are oriented upward and downward with respect to the layer, while the silicon–oxygen tetrahedra are oriented so that their edges are parallel to the layer surface.

Hydrogen bonds were examined on the basis of the electron density maps (Fig. 16) and characterised as bifurcated bonds exhibiting the typical geometrical characteristics. Their crystal-chemical function is to link free vertices of the B tetrahedra and the oxygen atoms in the layer, thus strengthening the boron–oxygen layer.

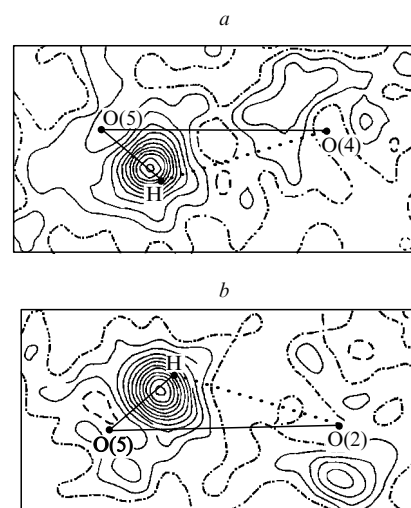


Figure 16. The experimental deformation density distributions in the sections of datolite passing through bifurcated O(5)–H···O(4) (a) and O(5)–H···O(2) (b) hydrogen bonds, the maps are contoured at intervals of $0.1 \text{ e } \text{\AA}^{-3}$.

The deformation electron density distribution in the silicon–oxygen tetrahedron corresponds to the above-described quantum-chemical concepts. The values of the maxima in the bonds vary from 0.25 to $0.40 \text{ e } \text{\AA}^{-3}$ (the average value is $0.35 \text{ e } \text{\AA}^{-3}$). The $\delta\rho$ distribution is characterised by the presence of electron-density bridges ($0.2 \text{ e } \text{\AA}^{-3}$) between the maxima corresponding to the Si–O bonds [the bridges are parallel to the edges of the tetrahedra and to the layer (Fig. 17a)] and by the absence of such bridges at

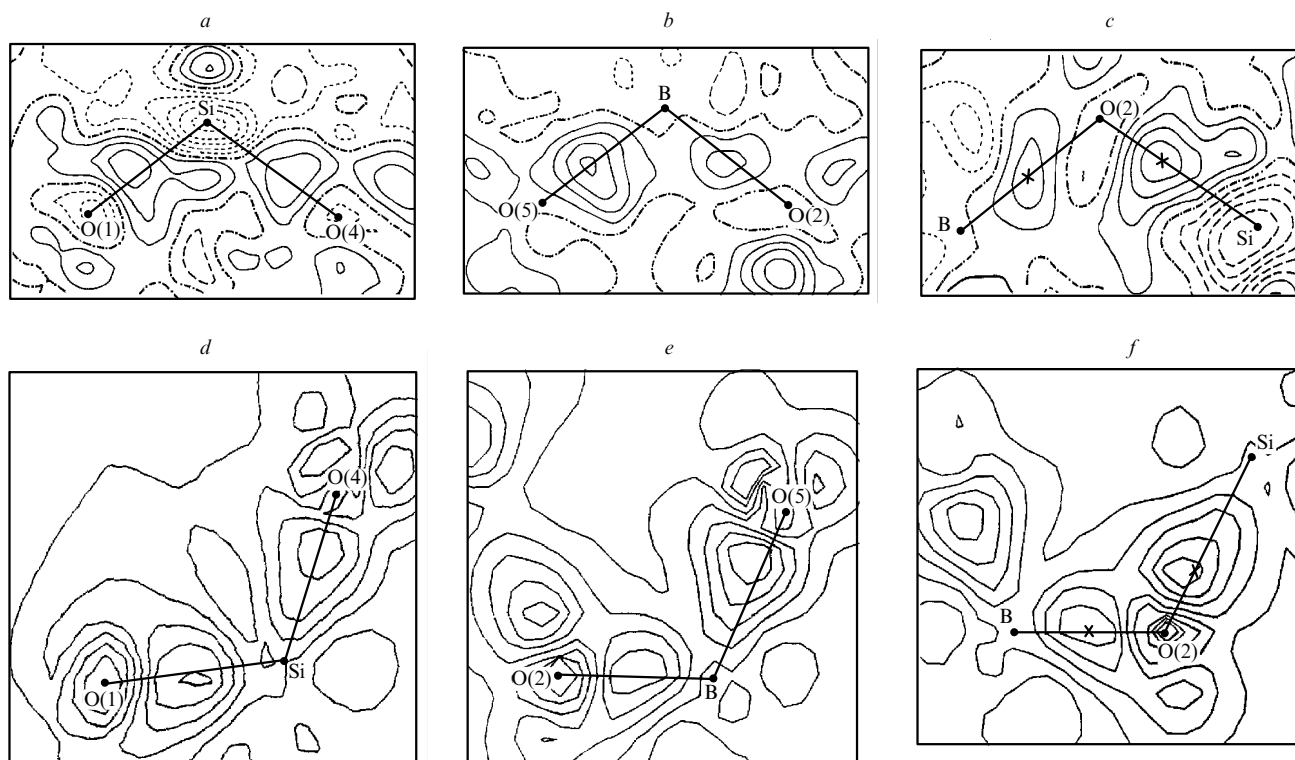


Figure 17. The experimental high-angle (*a–c*) and multipole (*d–f*) deformation density distributions in the O(1)–Si–O(4) (*a, d*), O(2)–B–O(5) (*b, e*) and B–O(2)–Si (*c, f*) sections of datolite, the maps are contoured at intervals of $0.1 \text{ e } \text{\AA}^{-3}$. The central points of the peaks are marked with asterisks.

the inclined edges. The electron density distribution in the B tetrahedron (Fig. 17*b*) is similar to that in the silicon–oxygen tetrahedron. The peak heights corresponding to the B–O bonds (on the average, $0.29 \text{ e } \text{\AA}^{-3}$) are smaller than those corresponding to the Si–O bonds. The difference in the electronegativities of the B–O and Si–O pairs is readily followed from the shifts of the $\delta\rho$ maxima, which are located approximately at the midpoints of the $R(\text{B–O})$ distances and displaced by $\sim 0.38 R(\text{Si–O})$ toward the oxygen atoms (Fig. 17*c*).

The multipole refinement of the datolite structure was performed based on the experimental data reported previously⁷² with the use of the MOLDOS96 and SALDOS97 programmes.⁴⁴ The refinement characteristics remained virtually unchanged. The calcium atoms were described by monopoles with the wave functions for the Ca^{2+} ion. The calculated static deformation electron density maps agree well with those based on the high-angle model and confirm the principal characteristic features of the electron density distribution in the mineral as well as the crystal-chemical conclusions drawn previously. Thus the static electron density maps for the silicon–oxygen and B tetrahedra have maxima ($0.5 \text{ e } \text{\AA}^{-3}$) corresponding to σ -bonds (Fig. 17*d,e*). For the silicon–oxygen tetrahedron, the electron-density bridge ($0.1 \text{ e } \text{\AA}^{-3}$) is clearly seen. The distances from the oxygen atoms to the peaks in the bonds between the bridging oxygen atoms and the silicon and boron atoms are different, *viz.*, $0.38 R(\text{Si–O})$ and $0.50 R(\text{B–O})$ (Fig. 17*f*), respectively. The bond ionicity can be estimated from the displacement of the peak from the midpoint toward the oxygen atom

$$1 - i = 100 \frac{r_i/R}{1/2},$$

where i is the ionicity, r_i is the distance from the maximum to the oxygen atom and R is the interatomic distance. For the Si tetrahedron in datolite, the ionicity and covalence calculated by this formula are 24% and 76%, respectively. Note that the static

electron density maps match better the theoretical maps than those calculated based on the high-angle model.

The charge on the silicon atom $q = +0.75 \text{ e}$, estimated in the determination of the population coefficients of valence shells, was lower than that estimated with the use of alternative modern multipole refinement procedures for the structures of silicates.⁴³ This fact is attributable to the involvement of the d -orbitals of the silicon atom in bonding and the presence of the π -component as was suggested by Cruickshank.¹¹ As a result, the electrons of the d -orbital decrease the charge on the silicon atom thus increasing its radius.

As demonstrated above (see Fig. 9*c*), the ‘force’ (tightening) function of the bridging oxygen atom is manifested in the corrugated silicon–oxygen ring in diopside. Similarly, chemical bonds in the layer in datolite are also strengthened to retain the layer as a structural unit. In the structure of datolite, layers are linked to each other only *via* bulky polyhedra (Thomson’s cubes) about calcium atoms.

For layered silicates, such as kaolinite⁷⁴ and lizardite,^{75–77} a series of quantum-chemical calculations was performed with the use of the CRYSTAL programme.⁷⁸ For kaolinite, the deformation electron density maps were calculated and the characteristics of the oxygen atoms that differ in their crystal-chemical function in the layer were obtained. It was concluded that contributions of the $2s$ - and $2p$ -orbitals of the oxygen atoms to the valence state density dominate over those of the $3s$ - and $3p$ -orbitals of the silicon atoms. The results of calculations of the electron density in the tetrahedral layer of lizardite⁷⁵ allowed conclusions to be drawn that both the $3d$ -orbitals of the silicon atoms and the d -orbitals of the oxygen atoms play a significant role in bonding. The population coefficient of the d -orbital of the silicon atom with the charge of 0.6 e was determined. The charges on the silicon and oxygen atoms calculated with account of the d -orbitals agree more closely with the most probable values than those calculated without considering these orbitals.

VI. Framework silicates

1. Coesite

The minerals α - and β -quartz^{79,80} and a high-pressure modification of SiO_2 , viz., coesite,^{81,82} belonging to framework silicates were studied by precision methods. The structure of coesite is shown in Fig. 18. In the classical crystal chemistry of silicates, considerable attention is given to the analysis of the Si—O bonds and the Si—O—Si bond angles. Histograms of angles for different structural types were reported, the typical value of the Si—O—Si bond angle was determined (140° ; the experimental values are in the range of 120 – 180°) and the correlations between the bond angles and thermal parameters of the bridging oxygen atoms were treated in the monograph.⁸ Coesite is an advantageous subject for

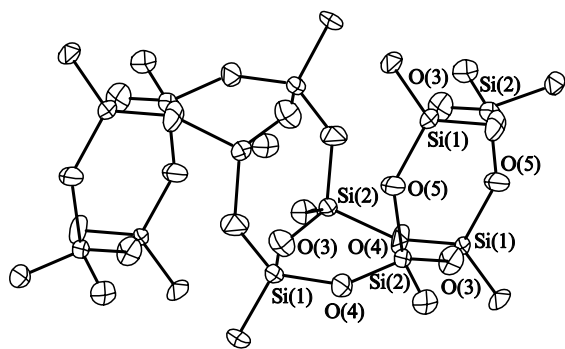


Figure 18. Structure of coesite.⁸¹

precision investigations because it contains crystal-chemically nonequivalent Si—O—Si groups with different geometry (viz., the geometry varies from linear with the angle of 180° to bent with angles of up to 137°).⁸¹ The chemical bonds in these groups were studied with the use of the multipole refinement based on Stewart's model. The following deformation electron density distributions were obtained: static (thermal vibrations of atoms were ignored) and dynamic (thermal vibrations were taken into account). For the Si—O—Si groups characterised by the smallest angles (142° and 137°), the electron density bridges between the maxima in the bonds were observed; these bridges were located within the bent Si—O—Si fragment (Fig. 19a,b).

A diversity of crystal-chemically different Si—O—Si groups in the structure of coesite made it possible to reveal the regularities relating the bond lengths to the bond angles in these groups. The results of precision investigations demonstrated that the linear group is characterised by the shortest Si—O distances, the electron

density symmetrically 'enveloping' the bridging oxygen atoms. The Si—O bond length increases and a bond bridge appears within the angle as this angle decreases. The transfer of the electron density and formation of a bond bridge within the Si—O—Si angle are manifested in the electron density distribution map of diopside (see Fig. 9c). In diopside, the Si—O—Si angle in the ring (132.77°) is smaller and the average bridging Si—O distance ($1.609 \text{ \AA}$) is larger than the corresponding values in beryl (167.99° and $1.633 \text{ \AA}$, respectively; see Table 2). In beryl, the electron density almost uniformly envelopes the bridging oxygen atom (see Fig. 9a).

In the dependence of $R(\text{Si—O})$ on $1/[1 - \sec(\text{Si—O—Si})]$, all points determined in calculations^{8,11} for different angles lie along a straight line which runs parallel and below the experimental straight lines constructed on the basis of the results of multipole refinement. This fact is indicative of the possible participation of the $3d$ -orbitals of the silicon atom in bonding. A comparison of the dynamic and static experimental and calculated $\delta\rho$ maps demonstrated that they are basically alike.

The structure of coesite was reinvestigated by Downs in more detail.⁸² This investigation was also performed with the use of Stewart's model (VALRAY programme) but another monopole was specified and a different number of parameters were finally refined. Maps of the experimental full electron density and of the total and deformation electrostatic potentials were calculated in addition to static maps $\delta\rho$. The radii of best separation (bonded radii) were estimated from the full electron density distributions analogously to that described in Refs 38,45. The silicon and oxygen radii were found to be 0.68 and $0.94 \text{ \AA}$, respectively. These values are close to those determined previously and differ from Shannon–Prewitt's radii⁸³ estimated for an ionic model. Analysis of the $\delta\rho$ distributions in the static maps for different Si—O—Si angles revealed (as in Ref. 81) that the density accumulated as bridges at the Si—O(2) and Si—O(5) bonds (the smaller Si—O—Si angles) and its transfer inward the angle. For the O(5) atom, which is characterised by the minimum bond angle, the maximum is also observed in the nonbonding region (Fig. 19c). The perpendicular section was not reported by Downs.⁸² However, it was suggested that the O(5) atom is sp^2 -hybridised, which invokes an additional reasoning.

The electrostatic potential maps in the vicinity of different bridging oxygen atoms are not the same. This confirms the general conclusion that long-range interactions should be taken into account in calculations of catalytic properties. These interactions affect substantially the local density and, consequently, the probability of localisation of an impurity. Using coesite as an example, let us note that dynamic models which include the monopole term of the multipole function as a subtrahend⁸¹ are close to models used in high-angle refinement. From the viewpoint

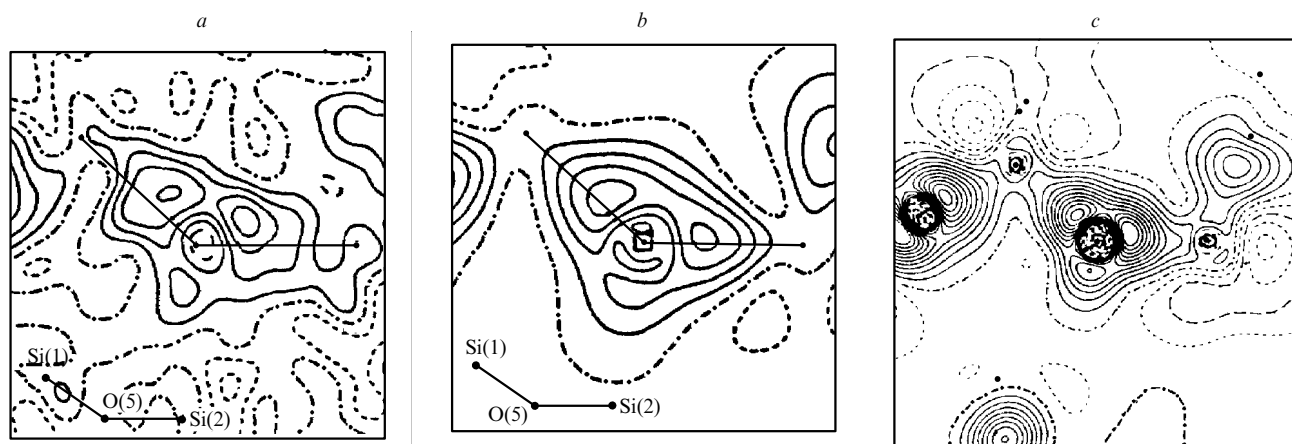


Figure 19. The experimental deformation density distributions in the Si(1)–O(5)–Si(2) section of coesite; (a) dynamic density; (b) static density,⁸¹ (c) static density (multipole refinement);⁸² the maps are contoured at intervals of $0.1 \text{ e \AA}^{-3}$.

of characteristic features of chemical bonds, dynamic models are as informative as static multipole models.

2. Danburite

A natural specimen of danburite from Japan was studied.⁸⁴ The structure of danburite $\text{CaB}_2\text{Si}_2\text{O}_8$ is shown in Fig. 20. The investigation of the tetrahedral borosilicate framework was of prime interest. The calcium atoms were described by a monopole with the wave functions for the Ca^{2+} ion. The complete and difference electron density distributions as well as their topological characteristics and the electrostatic potential were calculated and examined. Unfortunately, the complete three-dimensional and, particularly, difference maps contained numerous small split peaks and hence, their quality was poorer compared to those reported, for example, by Geisinger *et al.*⁸¹ Downs and Swope⁸⁴ noted this fact and gave preference to the multipole model because it can serve as a 'filter' for experimental results of poor quality. The main aim of the cited work was to determine the topological characteristics. For borosilicate, these characteristics were determined for the first time. However, the conclusion, which was drawn on the basis of these data according to Bader's theory, that the ionic component prevails in the bonds (closed shell interactions) in danburite (as in topaz) is inconsistent on the whole with the commonly accepted view of the predominantly covalent character of these bonds. Possibly, new investigations as well as a deeper insight into the essence and interpretation of the topology of chemical bonds in complex structures of silicates will help in explaining this disagreement.

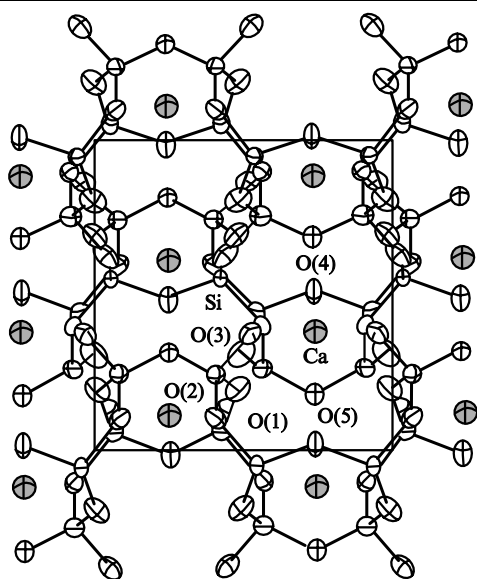


Figure 20. Structure of danburite.⁸⁴

3. Natrolite

Natrolite $\text{Na}_2\text{Al}_2\text{Si}_3\text{O}_{10} \cdot 2\text{H}_2\text{O}$ is a framework silicate belonging to zeolites. Specimens from the Czech Republic were studied.^{85–87} The mineral was originally investigated with the use of the high-angle refinement^{85, 86} (see §) and then studied with the use of the multipole analysis procedure.⁸⁷ Zeolites are characterised by a high degree of disorder, which precludes precision investigations of these minerals. However, natrolite is characterised by the ordered distribution of the silicon and aluminium atoms in the framework as well as of the sodium atoms and water molecules within the channels. The deformation electron density distributions were calculated with the use of the CRYLSQ, FOURR and

SADIAN90 programme packages. Stuckenschmidt and co-workers⁸⁶ tested different modes of refinement and gave preference to atomic scattering curves for half-ionised atoms. All necessary corrections were applied and errors of the electron density maps were evaluated. Natrolite was described⁸⁶ as an aluminosilicate studied for the first time without considering the results of investigations reported previously.^{47, 51} However, the characteristic features of the chemical bonds under consideration as well as the conclusions made agree well with the results of other studies.^{47, 51} On the basis of the shift of the $\delta\rho$ maximum, it was established that the Al–O bond is more ionic than the Si–O bond in accordance with the electronic structures of the Al and Si atoms, and the height of this maximum is smaller (Fig. 21 *a, b*). The distances to the maxima in the bonds (M) in the tetrahedra are identified with the radii of the overlapping orbitals in the silicon–oxygen tetrahedra ($\langle\text{Si}M\rangle = 0.90 \text{ \AA}$ and $\langle\text{O}M\rangle = 0.73 \text{ \AA}$) and Al tetrahedra ($\langle\text{Al}M\rangle = 1.09 \text{ \AA}$ and $\langle\text{O}M\rangle = 0.70 \text{ \AA}$). The radii of

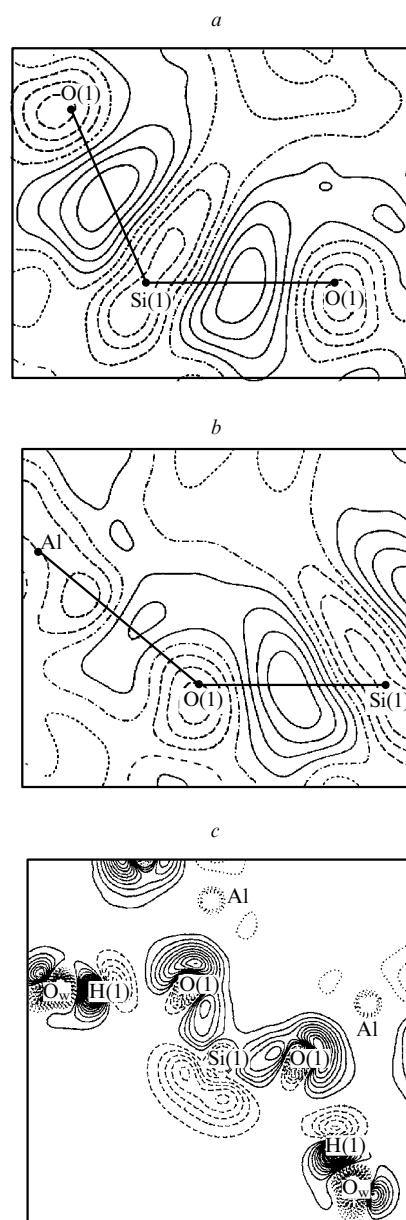


Figure 21. The experimental deformation density distributions in the O(1)–Si–O(1) (*a*) and Al–O(1)–Si(1) (*b*) sections (the maps are contoured at intervals of $0.1 \text{ e \AA}^{-3}$)⁸⁶ and the static deformation density distribution in the Si(1)–O(1)–Al section (*c*) (the map is contoured at intervals of $0.05 \text{ e \AA}^{-3}$)⁸⁷ in natrolite.

§ The experiment was detailed in the former study and the deformation density was examined in the latter study.

the silicon and aluminium atoms thus determined agree with the calculated maximum radii of the outer orbitals (0.904 and 1.044 Å for the 3s-orbitals of Si and Al, respectively). However, the radii for the 3p-orbitals have larger values (1.068 and 1.312 Å for Si and Al, respectively). It can be suggested that the values of the radii of overlapping hybrid orbitals are intermediate between the above values. It was concluded⁸⁶ that the maxima in the bonds are located at positions predicted for a covalent bond in tetrahedra.

The interest in studies of the electron density and electrostatic characteristics of zeolites stems from the fact that this group of silicates possesses ion-exchange properties. With the aim of relating the characteristics of natrolite to the ion-exchange properties, the multipole refinement of the structure of natrolite was carried out, the charges on the atoms were estimated and the electrostatic potential was examined.⁸⁷ General approaches and refinement procedures were detailed. All necessary corrections were applied to the experimental data (see Table 1). The multipole refinement was carried out using Hansen–Coppens's model and the MOLLY programme. The choice of the system of coordinates on atoms and the number of refinable multipole parameters were described in detail and the coefficients of radial functions were reported. The isotropic extinction, the scale factor, the positional and anisotropic thermal parameters of the atoms, the population coefficients of valence (P_v) and multipole (P_{lm}) orbitals and their contraction-expansion parameters (α and α' , respectively) were refined.

In the calculated static multipole maps (STATDENS programme), the deformation density is concentrated at more electronegative oxygen atoms (Fig. 21 c). The maxima in the Si–O and Al–O bonds are 0.25 and 0.45 e Å⁻³, respectively, although an inverse ratio, which is in better agreement with the electronic structures of the silicon and aluminium atoms, had been obtained previously. The shifts of the maxima toward the oxygen atoms correspond to the difference in the electronegativities of the oxygen and silicon atoms and of the oxygen and aluminium atoms and are consistent with a more covalent character of Si–O bond. The electrons of the silicon atoms occupy the sp^3 -bonding orbitals. Regions of localisation of the electron density of the hydrogen atoms and the lone electron pairs of the water molecules are clearly seen in the maps (see Fig. 21 c). Ghermany and co-workers⁸⁷ calculated the charges on the atoms, reported

the maps of the total potential and determined the electrostatic energy of the sodium atoms in the structure of natrolite. A comparison of the latter characteristic with an analogous value for dehydrogenated zeolite A demonstrated that the Na⁺ ion is more tightly held in the crystal structure of natrolite.

4. Phenakite

The results of studies of the electron density of phenakite Be₂SiO₄ were considered earlier¹⁰ in the section devoted to island silicates. However, investigations of the character of chemical bonds demonstrated^{33,34,88} that phenakite belongs to framework beryllosilicates (Fig. 22). In the studies^{33,34} published almost simul-

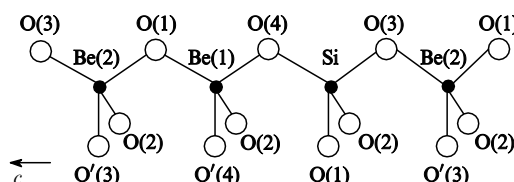


Figure 22. A fragment of the phenakite structure.

taneously, the deformation electron density distributions (Fig. 23 a,b) were calculated with the use of high-angle and multipole models. The dynamic and static maps were reported.³⁴ It was demonstrated that the Si–O and Be–O chemical bonds possess different ionicities (in accordance with the classical concepts of the electronegativities of pairs of interacting atoms). The difference in the maxima in the bonds (0.2 and 0.4 for Be–O and Si–O, respectively) and their substantial shifts toward the oxygen atom along the Be–O bond compared to the Si–O bond are clearly seen in the electron density distribution maps for the structure of phenakite (like beryl). The static density maps more closely resemble the calculated maps compared to the dynamic density maps.

The multipole refinement with the use of the α -technique allowed the determination of charges on atoms in silicates for the first time.³⁴ The deformation³³ and total electrostatic³⁴ potentials

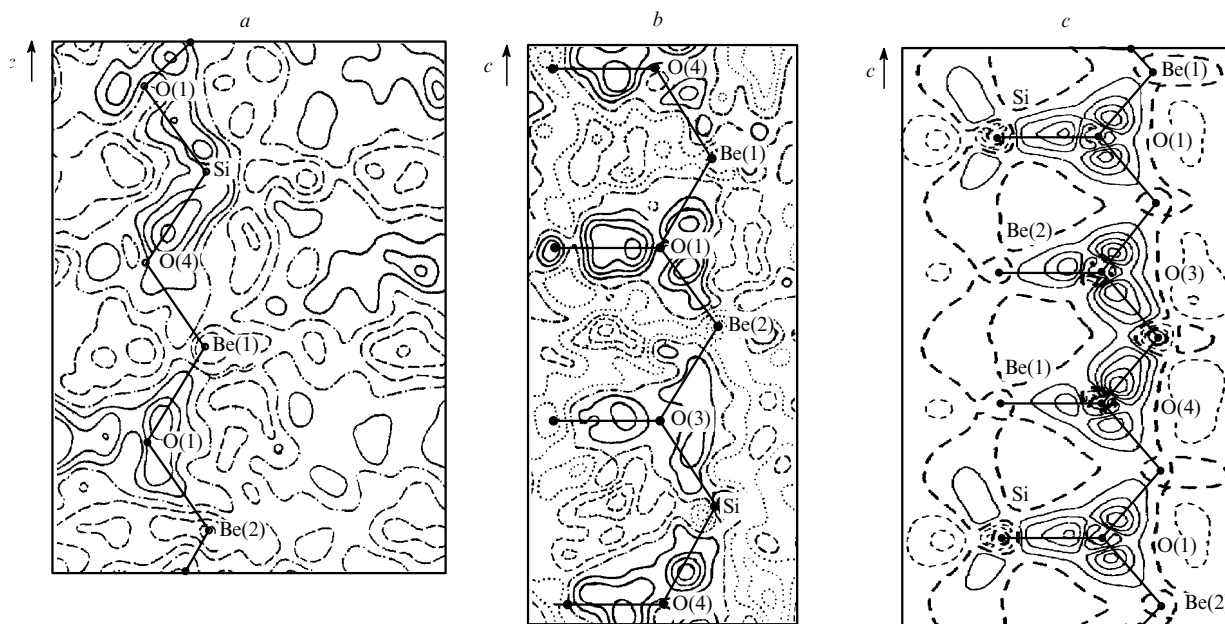


Figure 23. The experimental deformation density distributions in the sections of phenakite passing through ...Si–O(4)–Be(1)–O(1)–Be(2)–O(3)–Si... chains; (a) according to Ref. 33; (b) according to Ref. 34; (c) the static multipole refinement based on the experimental results.³³

were determined, which made it possible to reveal the electrostatic properties of beryllium and silicon.

Recalculations for phenakite were performed with the experimental results^{33, 34} using Hansen–Coppens's model with the use of the MOLDOS96 and SALDOS97 programme packages. The potential and topological characteristics of this mineral were also calculated. The static deformation maps (Fig. 23 c) as well as the charges on the atoms agree on the whole with the bonding pattern reported previously.^{33, 34}

VII. Quantum-chemical calculations of selected framework structures

The structure of neither danburite nor natrolite was calculated by the quantum-chemical methods, while the completely dealuminated form of zeolite $\text{Si}_{48}\text{O}_{96}$, viz., mordenite $(\text{Ca}, \text{Na}_2, \text{K}_2)[\text{Al-Si}_5\text{O}_{12}]_2 \cdot 6\text{H}_2\text{O}$, was investigated by these methods.⁸⁹ The results obtained in independent studies were used as the initial data in *ab initio* calculations (CRYSTAL programme). It was found that the bond strain increases as the bond angle decreases, which agrees with the results of studies of chemical bonding in coesite and diopside (the appearance of the above-described bridges). According to the results of calculations of the valence state density, the deformation and full density maps were constructed (Fig. 24). The results of determination of the sizes of cavities (chains) along the *c* axis with the use of isosurfaces of the complete density are intriguing. The diameter of the cavities (~ 7 Å) agrees well with the experimental values. Analysis of the characteristics of the potentials with the aim of predicting the behaviour of extraframework species (guests) demonstrated that the cations are preferentially located in the vicinity of the edges of large channels rather than in their centres.

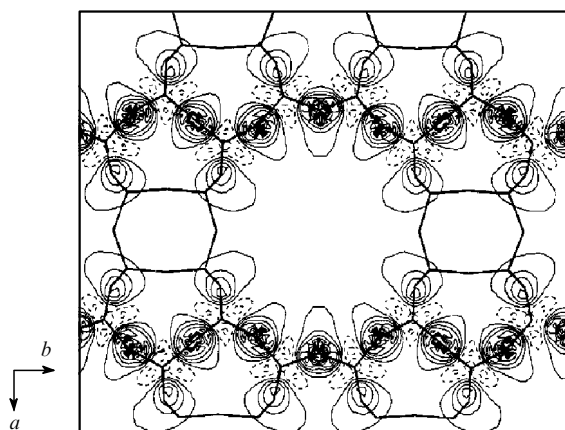


Figure 24. The deformation density distribution in the section of mordenite (calculation).⁸⁹

Quantum-chemical calculations of various frameworks were carried out for the $\text{H}_6\text{Si}_2\text{O}_7$ molecule.⁹⁰ Starting from four SiO_2 units, 23 tetrahedral framework structures characterised by different symmetry and different unit-cell dimensions were found from local energy minima. Initially, triclinic symmetry was assumed for these structures. However, only seven structures under study have this symmetry. The symmetry groups of other structures varied from monoclinic (*Pc*) to cubic (*I43d*).

Gibbs and co-workers⁹¹ carried out quantum-chemical (Hartree–Fock self-consistent field) calculations of electron densities and the topology of the electron density of the molecules of ‘polysilicic acids,’ viz., $\text{Si}^{\text{I}}\text{O}$, $\text{Si}^{\text{II}}\text{O}_2$, $\text{H}_4\text{Si}^{\text{IV}}\text{O}_4$, $\text{H}_6\text{Si}_2^{\text{IV}}\text{O}_7$, $\text{H}_8\text{Si}_3^{\text{IV}}\text{O}_{10}$, $\text{H}_{10}\text{Si}_5^{\text{IV}}\text{O}_{18}$ and $\text{H}_{12}\text{Si}_6^{\text{IV}}\text{O}_{24}$ (the coordination number of the silicon atom is designated by a Roman numeral). The effect of the bond length on the values of the maxima in the bonds as well

as the bond ionicity and atomic charges were examined. It was found that the bond ionicity increases as the coordination number of the silicon atom increases. On the contrary, the covalent character of the bond and the values of the bond maxima increase as its length decreases and the Si–O–Si angle increases. Thus the $\rho(r)$ value at the critical point in the bond as determined in topological analysis increases from $0.50 \text{ e } \text{\AA}^{-3}$ for the Si–O distance of $1.96 \text{ \AA}$ in the octahedron to 0.92 , 0.95 and $1.36 \text{ e } \text{\AA}^{-3}$ for the Si–O distances of 1.621 , 1.595 and $1.48 \text{ \AA}$, respectively, in the tetrahedron. The ionic (crystal) radius of the oxygen anion is not a constant and increases from $0.86 \text{ \AA}$ at $R(\text{Si–O}) = 1.48 \text{ \AA}$ to $1.20 \text{ \AA}$ at $R(\text{Si–O}) = 1.96 \text{ \AA}$. The atomic charge increases in accordance with an increase in the size of the ion because the atomic ‘reservoir’ and the bond ionicity increase. It was demonstrated that the bond ionicity could be estimated by determining the bonding radius of the anion from electron density maps using the Gibbs empirical formula

$$f_i(\text{XO}) = 1.0 - \exp \left\{ -\frac{1}{4} [-0.85 + 2.64r_b(\text{O})]^2 \right\},$$

where $r_b(\text{O})$ is the bonding radius. It was also concluded that weak π -bonds ($p-d$) are formed due to the involvement of the atomic $3d$ -orbital of the silicon atom the contribution of which increases as the angle decreases and the bond strain increases, as described for coesite, diopside and datolite.

Worthy of mention are also calculations of the structures of ilmenite MgSiO_3 ^{92, 93} and a high-pressure modification of stishovite.^{94, 95} The silicon atoms in these minerals occupy octahedra. Different computational methods were used, which supplemented investigations^{96, 97} on the electron density of this unusual modification of SiO_2 (stishovite) analogous to rutile.

VIII. Determination of charges on atoms in silicates

In structural chemistry, the notion of the charge on the atom is closely associated with the notion of the ionic radius and with the development of the concept of the bond ionicity. Liebau⁸ recalled that according to Pauling the ionicity of the Si–O bond was evaluated at 50%. In the work of Stewart and co-workers⁷⁹ cited in the monograph,⁸ the ionicity *i* was defined as the ratio of the residual (effective) charge to the formal charge expressed in percent. Thus if the residual charge on the silicon atom is equal to $+1$, then $i = 25\%$. Consequently, four very similar bonds are each 75% covalent.⁷⁹ The charges on the silicon and oxygen atoms can be independently determined from the data of direct precision X-ray diffraction studies or from the results of quantum-chemical calculations. The CRYSTAL programme package opens up possibilities of calculations for not only clusters but also periodical systems. Model charges on atoms can be also determined according to correlation formulas from the positions of lines in X-ray emission spectra.

For the purpose of evaluating charges in some silicates from precision X-ray diffraction data, Fujino and co-workers²⁷ proposed a procedure according to which the number of electrons was initially determined for cations within a sphere corresponding to the effective radius based on radial distributions of difference maps. Then, it was proposed to apply a procedure according to which the charge of the cation determined by the above procedure was fixed, the neutrality of the crystal was prescribed and atomic scattering factors of oxygen atoms were refined. In such a manner charges in a series of island and chain silicates were determined. For oxygen atoms, the values vary from -1.1 to -1.5 e and the charge for the silicon atom is $+1.4 \text{ e}$. For wadeite, these values were found to be higher (-1.43 and $+3.29 \text{ e}$ for oxygen and silicon, respectively).⁶⁸ The similar values (-1.8 and $+3.5 \text{ e}$, respectively) were obtained for diopside. The electron density was integrated within a sphere about the atom with the radius of the best separation found from valence density maps (with the use of

the MINEXTL programme package); however, the charges varied too sharply as the radii were changed.

The best procedure for the determination of the charges involves the multipole refinement of the population coefficient P_v simultaneously with the parameter α' , which characterises 'contraction' ($\alpha' > 1$) or 'expansion' ($\alpha' < 1$) of the atom. The values of the charges with the use of the α -technique and the VALRAY programme were calculated for the first time for phenakite.³⁴ For oxygen and silicon, these charges are, on the average, -1.01 and $+1.49$ e, respectively. Calculations for the layer in lizardite using the CRYSTAL programme gave the following charges on the silicon atom: $+2.39$ e when the d -orbitals of the silicon atom were ignored and $+1.66$ and $+1.58$ e when these orbitals were taken into account. For the structure of datolite, the values obtained from the experimental results were lower than those for other silicates:

Atom	Si	B	O(1)	O(2)	O(3)	O(4)	O(5)
Charge /e	+0.75	+0.84	-0.71	-0.66	-0.76	-0.72	-0.66

In this case, the charge on the calcium atom was taken to be equal to $+2$ (by analogy with danburite). In natrolite, the charge on the sodium atom was taken as equal to $+1$ and the charges on two independent silicon atoms were found to be $+1.84$ and $+1.65$ e, the charge on the aluminium atom was $+1.51$ e and the charges on the O(1), O(2) and O(3) atoms were -0.73 , -1.08 and -0.99 e, respectively, for the values of the α' parameter corresponding to a slight contraction of the shell of the silicon atom and expansion of the shell of the oxygen atom. Note that after the multipole refinement, the refinement of only P_v and α' was repeated, *i.e.*, the total multipole component that corresponds to the density in the bond was excluded. This procedure was not performed for danburite. As a consequence, the P_v values reported involve the multipole component and are unsuitable for the estimation of charges. For natrolite, the determined charges were compared with those calculated for α -quartz. In α -quartz, the charges on the silicon and oxygen atoms vary from $+2.4$ to $+1.6$ e and from -1.13 to -0.83 e, respectively. Calculations for topaz performed with the use of a procedure analogous to that used for natrolite gave the following effective charges:

Atom	Al	Si	O(1)	O(2)	O(3)	F
Charge /e	+1.53	+1.75	-0.76	-1.11	-1.03	-0.44

For phenakite, the charges were calculated using two experimental data sets (I and II):⁸⁸

Atom	Si	Be(1)	Be(2)	O(1)	O(2)	O(3)	O(4)
Charge (I) /e	+1.12	+1.19	+1.19	-0.87	-0.88	-0.87	-0.89
Charge (II) /e	+0.87	+1.53	+1.26	-0.90	-0.95	-0.91	-0.89

The charges obtained in the multipole refinement agree most closely with the real charges on atoms. A comparison of these values with each other as well with the results of quantum-chemical calculations demonstrated that the most typical values for the silicon and oxygen atoms are in the ranges of $+1.1$ to $+1.8$ e and of -0.7 to -1.1 e, respectively. Thus, in spite of the indefiniteness of the notion of the charge on the atom, it is applicable for semiquantitative estimations in structural chemistry. According to the new data on the charges, the Si—O bond ionicity determined with the use of equations given in Ref. 79 was $\sim 33\%$ with a correspondingly higher degree of covalence ($\sim 67\%$). Undoubtedly, this line of investigation is of interest.

IX. Conclusion

The data of precision X-ray diffraction studies allow one to take a new view of problems associated with investigations of structures and bonds in silicates and their classification. From the structural standpoint, positional and thermal parameters can be determined

with a better accuracy, isomorphous relations in silicates can be examined with the use of electron density distribution maps by determining structural positions of small amounts (less than 1 mass %) of impurities, in particular, of chromophore ions responsible for the colour of crystals, and hydrogen bonds can be reliably localised to the extent that positions of electrons of hydrogen atoms and lone electron pairs of oxygen atoms in water molecules can be revealed.

The experimental and calculated electron density distribution maps demonstrate that in the case of formation of a chemical bond in the silicon—oxygen tetrahedron as well as in the B, Al and Be tetrahedra, the electrons of these atoms occupy the sp^3 -bonding orbitals to form σ -bonds with the oxygen atoms, which corresponds to the classical concepts. In special cases, which require strengthening (strain) of the bond, in particular, in a silicon—oxygen layer, in a corrugated isolated ring of diopside or in strained bonds with a small Si—O—Si angle in the coesite framework, it was assumed that the $3d$ -orbitals of the silicon atom are involved in bonding with a contribution of the π -component to the bond. The presence of the π -component may account for the existence of electron-density 'bridges' in the silicon—oxygen tetrahedra in diopside, datolite and coesite (for the last-mentioned mineral, this fact is also confirmed by calculations).

The values of the $\delta\rho$ maxima correlate with the electronic structures of the elements. In most instances, the values of the maxima for the silicon atom vary within a rather narrow range (0.3 – 0.4 e $\text{\AA}^{-3}$) for various structures examined in different studies, which is indicative of the reliability of the results. The differences in the values may occur due to the characteristic features of the structures of compounds under study and chemical interactions in them.

The deformation density distribution maps for tetrahedra visualise the effect of the difference in the electronegativities of the elements involved in chemical bonding. In the B—O, Si—O, Al—O and Be—O series, an increase in the ionicity for these primarily covalent bonds can be quantitatively estimated. The effective radii of atoms, their effective charges (for the silicon and oxygen atoms, the most probable values are in the ranges from $+1.1$ to $+1.8$ e and from -0.7 to -1.1 e, respectively) and the Si—O bond ionicity can be quantitatively estimated from the $\rho(\mathbf{r})$ maps.

The traditional classification of silicates in accordance with the degree of condensation of anionic groups and the regularities of changes in the bond lengths and bond angles⁸ correlate with their electronic structures. Thus cations of the second coordination sphere play the major role in orthosilicates. These cations cause a change in the values of the $\delta\rho$ maxima and their shifts up to splitting. On condensation of tetrahedra, the electron density is accumulated at the bridging oxygen atoms. When all oxygen vertices are shared, the maxima in all four bonds are equal. This equality is disturbed in the case of formation of isolated tetrahedral groups, for example, rings.

Investigations of electron density distributions make it possible to consider the fundamentals of the traditional structural chemistry of silicates on the electronic level. Specifically, a particular classification of structures can be chosen taking into account the character of the electron density distribution.

Due to intensive development of computational quantum-chemical procedures in recent years, these procedures approach the accuracy of experimental methods and make it possible to perform a semiquantitative comparison of the results of two methods with the use of density maps and populations of orbitals. These combined investigations can provide most reliable data on structures of complex silicate systems on the electronic level.

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The effect of strong intermolecular and chemical interactions on the compatibility of polymers

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Abstract. The data on compatibility and on the properties of polymer blends are generalised. The emphasis is placed on the formation of strong intermolecular interactions (dipole–dipole interaction and hydrogen bonding) between the components of blends, as well as on the chemical reactions between them. A criterion for the prediction of compatibility of polymers is described in detail. Different cases of compatibility are considered and the dependences of the glass transition temperatures on the composition of blends are analysed. The published data on the effect of strong intermolecular interactions between the blend components on the glass transition temperature are considered. The preparation of interpolymers is described whose macromolecules are composed of incompatible polymers, which leads to the so-called ‘forced compatibility.’ The bibliography includes 80 references.

I. Introduction

In the studies of polymer blends much attention is currently given to the effect of strong intermolecular and chemical interactions between the polymer blend components on their compatibility.

Investigation of compatibility of polymers is of importance from both scientific and practical points of view.^{1–3} In one of the concepts, it is proposed to analyse compatibility of polymers using the solubility parameter (the density of cohesive energy). The equation used to assess the parameter of the polymer–polymer interaction (χ) includes the solubility parameters of each polymer

$$\chi = \frac{V}{RT}(\delta_1 - \delta_2)^2, \quad (1)$$

where V is the molar volume of the rubber-like phase per repeating unit of the polymer; δ_1 and δ_2 are the solubility parameters of the polymers 1 and 2, respectively; R is the universal gas constant and T is the absolute temperature.

According to this concept, polymers are compatible if the interaction parameter is positive and its value is close to zero. Limitations of this approach have been analysed.⁴ One of the limitations is associated with the necessity to calculate and measure the solubility parameter to a high accuracy. This is impossible for polymers since this parameter is assessed indirectly using determination of intrinsic viscosity of polymer solutions in various solvents followed by construction of the dependence of the intrinsic viscosity on the solubility parameter of the solvent in which the measurements have been carried out; construction of the dependence of the degree of swelling on the solubility parameter of the solvent in which swelling occurs, *etc.* The critical value of the parameter χ , *viz.*, the upper limit of solubility, is determined from the following relationship⁵

$$\chi_c = \frac{1}{2(N_1^{-1/2} + N_2^{-1/2})^2},$$

where N_1 and N_2 are the degrees of polymerisation of the components 1 and 2, respectively. Calculations or experimental measurements of the solubility parameters should be carried out with an accuracy of $0.1 \text{ (J cm}^{-3}\text{)}^{1/2}$.

A concept of compatibility of polymers using the solubility parameter has been developed in detail.⁴ In this study, individual contributions of the components into the solubility parameter were considered and the compatibility parameter (introduced previously⁶), which is the difference between the cohesive energy densities of the components, was used.

Let us consider other approaches to the prediction of the compatibility of polymers and the properties of blends obtained.

According to the reported data,^{7–11} the solubility of polymers occurs if the following inequality holds

$$\mu < 1.374\Phi(\Phi - \sqrt{\Phi^2 - 1 + a}). \quad (2)$$

Here $\mu = \delta_p^2/\delta_s^2$, where δ_p is the solubility parameter of the polymer, δ_s is the solubility parameter of the solvent; the Φ value is found from the relationship

$$\Phi = \frac{4(V_s V_p)^{1/3}}{(V_s^{1/3} + V_p^{1/3})^2}, \quad (3)$$

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where V_p and V_s are the molar volumes of the polymer and the solvent, respectively, and the a value is calculated using the formula

$$a = \frac{\gamma_{sp}}{\gamma_s}, \quad (4)$$

where γ_{sp} is the interface tension and γ_s is the surface tension of the solvent. The right part of the criterion (2) is represented in the

form $2\rho\beta$, where $\rho = 1.374/2$ and $\beta = \Phi(\Phi - \sqrt{\Phi^2 - 1 + a})$.

The interface tension is defined as follows:

$$\gamma_{sp} = \gamma_s + \gamma_p - 2\Phi(\gamma_s\gamma_p)^{1/2}, \quad (5)$$

where γ_p is the surface energy of the polymer.

An attempt to analyse the compatibility of polymers using the criterion for the polymer solubility in organic solvents, *viz.*, relationship (2), has been undertaken.¹¹ Let us consider this criterion in detail.

II. Criteria for the compatibility of polymers

If a small amount of a polymer 1 is introduced into a polymer 2, the polymer 1 and the polymer 2 are considered as the 'polymer' and the 'solvent', respectively. The following cases are possible when using criterion (2).

1. Polymers 1 and 2 are incompatible. A small amount of a polymer 1 is introduced into a polymer 2 and, *v.v.*, a small amount of a polymer 2 is introduced into a polymer 1. Then the compatibility criterion has the form

$$\mu_1 = \frac{\delta_{p1}^2}{\delta_{p2}^2} > 1.374\Phi(\Phi - \sqrt{\Phi^2 - 1 + a_1}) = 2\rho\beta_1, \quad (6)$$

$$\mu_2 = \frac{\delta_{p2}^2}{\delta_{p1}^2} > 1.374\Phi(\Phi - \sqrt{\Phi^2 - 1 + a_2}) = 2\rho\beta_2, \quad (7)$$

where δ_{p1} and δ_{p2} are the solubility parameters of the polymers 1 and 2, respectively;

$$\Phi = \frac{4(V_{p1}V_{p2})^{1/3}}{(V_{p1}^{1/3} + V_{p2}^{1/3})^2}, \quad (8)$$

where V_{p1} and V_{p2} are the molar volumes of repeating units of the polymers 1 and 2, respectively;

$$a_1 = \frac{\gamma_{p1,p2}}{\gamma_{p2}}, \quad (9)$$

$$a_2 = \frac{\gamma_{p1,p2}}{\gamma_{p1}}, \quad (10)$$

$$\gamma_{p1,p2} = \gamma_{p1} + \gamma_{p2} - 2\Phi(\gamma_{p1}\gamma_{p2})^{1/2}, \quad (11)$$

where $\gamma_{p1,p2}$ is the tension at the polymer 1–polymer 2 interface and γ_{p1} and γ_{p2} are the surface energies of the polymers 1 and 2, respectively.

Since the values of the left sides of the criteria (6) and (7) are larger than those of their right sides, polymers 1 and 2 are completely incompatible.

2. If a small amounts of a polymer 1 is introduced into a polymer 2, criterion (2) indicates that the 'solubility' of the first polymer in the second polymer occurs, *i.e.*,

$$\mu_1 = \frac{\delta_{p1}^2}{\delta_{p2}^2} < 1.374\Phi(\Phi - \sqrt{\Phi^2 - 1 + a_1}) = 2\rho\beta_1. \quad (12)$$

However, as indicated by calculations using the criterion (2), no 'solubility' of the second polymer in the first polymer should occur

on introduction of the polymer 2 into the polymer 1, *i.e.*, inequality (7) holds.

Usually, compatibility of two polymers is judged by the glass transition temperature of a blend. A blend of completely compatible polymers is characterised by one glass transition temperature, which is intermediate between those of the initial components. Blends of completely incompatible polymers are characterised by two glass transition temperatures corresponding to those of the initial components. In the case of partial compatibility, where both components are present in each microphase in different amounts, two glass transition temperatures are also observed; however, they are shifted 'towards each other' as compared to the glass transition temperatures of the initial components.

The dependence of the glass transition temperature on composition for the case where a polymer 1 is soluble in a polymer 2, whereas the polymer 2 is insoluble in the polymer 1, is shown in Fig. 1. As can be seen, initially the introduction of the polymer 2 into the polymer 1 affects slightly the glass transition temperature of the blend (curve 1). Such a shape of the curve will be rationalised below taking a particular system as an example. It should be noted that in this case one glass transition temperature is observed for each blend, which suggests that the components are compatible. This behaviour of the blend can be associated with the microphase separation, which is characteristic of even homogeneous systems.¹²

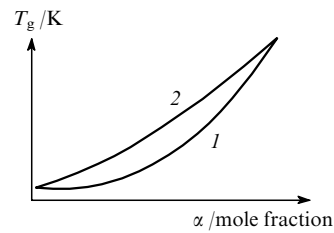


Figure 1. Dependences of the glass transition temperature on the composition for a system that meets criteria (7) and (12) (1) and for a blend of two completely compatible polymers (2).

3. Complete compatibility of the polymers occurs, *i.e.*, the polymer 1 is soluble in the polymer 2, which is soluble in the polymer 1. In this case, the blend prepared is completely homogeneous, no microphase separation occurs and the 'property–composition' dependences are analogous to those of random copolymers. The criteria for compatibility take the form:

$$\mu_1 = \frac{\delta_{p1}^2}{\delta_{p2}^2} < 1.374\Phi(\Phi - \sqrt{\Phi^2 - 1 + a_1}) = 2\rho\beta_1, \quad (13)$$

$$\mu_2 = \frac{\delta_{p2}^2}{\delta_{p1}^2} < 1.374\Phi(\Phi - \sqrt{\Phi^2 - 1 + a_2}) = 2\rho\beta_2. \quad (14)$$

Such a blend is characterised by one glass transition temperature. A typical dependence of T_g on the blend composition is shown in Fig. 1 (curve 2).

This dependence is described by the following relationship¹⁰

$$T_g^0 = \left[\alpha_1 \left(\sum_i \Delta V_i \right)_1 + \alpha_2 \left(\sum_i \Delta V_i \right)_2 \right] \times \left[\alpha_1 \frac{\left(\sum_i \Delta V_i \right)_1}{T_{g1}} + \alpha_2 \frac{\left(\sum_i \Delta V_i \right)_2}{T_{g2}} + 2\alpha_1(1 - \alpha_1) \times 0.03 \right]^{-1}, \quad (15)$$

where α_1 and α_2 are the mole fractions of the polymers 1 and 2, respectively; $\left(\sum_i \Delta V_i \right)_1$ and $\left(\sum_i \Delta V_i \right)_2$ are the van der Waals

volumes of repeating units of the polymers 1 and 2, respectively; and T_{g1} and T_{g2} are their glass transition temperatures (calculated or experimental), respectively.

Let us consider the behaviour of polymer blends taking a number of well studied polymer blends as examples. The first of them is a blend of polystyrene (PS) (polymer 1) with poly(vinyl methyl ether) (PVME) (polymer 2).

The characteristics of this blend of various compositions have been studied in detail.^{13–19} It is clearly seen in the plot of the dependence of the glass transition temperature on composition (Fig. 2, curve 2) that the T_g value changes only slightly and is virtually independent of the blend composition as the PS content increases from 0 to 0.4. This dependence is not described by Eqn (15), which can be applied to random copolymers and homogeneous polymer blends.

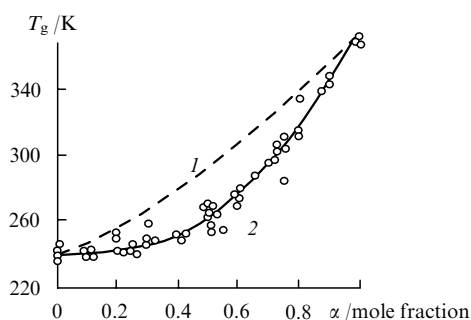


Figure 2. Dependence of the glass transition temperature of the PS–PVME blend on the PS content; (1) calculations using Eqn (15); (2) calculations using Eqns (22) and (23).

Let us analyse in detail the compatibility of PS and PVME using criterion (2). First, we assume that PS is the solvent for PVME. The initial characteristics [solubility parameters (δ), surface energies (γ), molar volumes (V_m), cohesive energies ($\sum_i \Delta E_i^*$), the van der Waals volumes ($\sum_i \Delta V_i$), and glass transition temperatures (T_g)] required to calculate the values of the left and right sides of the criterion (2), are listed in Table 1. By substituting the corresponding values into criterion (14) we obtain in this case

$$\mu_2 = 0.684 < 1.218 = 2\rho\beta_2.$$

The value of the left side of the criterion is smaller than that of the right side; hence PVME is readily soluble in PS.

Let us assume now that PVME is the solvent for PS. Using the compatibility criterion (6) and the data listed in Table 1, we get

$$\mu_1 = 1.462 > 1.175 = 2\rho\beta_1.$$

The value of the left side of the criterion is larger than that of its right side; hence PS is insoluble in PVME. Hence introduction of PS into PVME can lead to microphase separation and the blend

is expected to have one glass transition temperature. This is due to the fact that a portion of PVME will be compatible with PS. As a result, two microphases can be formed, one of which will contain only PVME, while the other will be a PVME–PS blend. The compatibility of the latter microphase with PVME will be improved as the PVME concentration in the second microphase is increased and at a certain PVME concentration, the second microphase will be completely compatible with PVME. Let us assess this critical PVME concentration. The relationship for calculating the solubility parameter of this polymer blend, which follows from the general relationship (see a monograph¹⁰), has the form

$$\delta^2 = \frac{\alpha \left(\sum_i \Delta E_i^* \right)_2 + 1(1-\alpha) \left(\sum_i \Delta E_i^* \right)_1}{N_A \left[\alpha \left(\sum_i \Delta V_i \right)_2 + (1-\alpha) \left(\sum_i \Delta V_i \right)_1 \right]}, \quad (16)$$

where α is the mole fraction of PVME in the blend; $\left(\sum_i \Delta E_i^* \right)_1$ and $\left(\sum_i \Delta E_i^* \right)_2$ are the molar cohesive energies of PS and PVME, respectively; N_A is the Avogadro constant; and $\left(\sum_i \Delta V_i \right)_1$ and $\left(\sum_i \Delta V_i \right)_2$ are the van der Waals volumes of repeating units of PS and PVME, respectively.

Substituting the characteristics of the polymers (see Table 1) into relationship (16), we get

$$\delta^2 = \frac{22988 - 14292\alpha}{66.13 - 29.57\alpha} 4.18 \text{ J cm}^{-3}. \quad (17)$$

It was proposed¹⁰ that the surface energy of a blend be assessed using the equation

$$\gamma = [\alpha C_1 + (1-\alpha)C_2] \left[\alpha \left(\sum_i \Delta E_i^* \right)_2 + (1-\alpha) \left(\sum_i \Delta E_i^* \right)_1 \right] \left\{ \left[\alpha \left(\sum_i \Delta V_i \right)_2 + (1-\alpha) \left(\sum_i \Delta V_i \right)_1 \right]^{2/3} [am_2 + (1-\alpha)m_1]^{1/3} \right\}^{-1}, \quad (18)$$

where C_1 and C_2 are the coefficients for PVME (nonpolar polymer) and PS, respectively, and m_1 and m_2 are the numbers of atoms in repeating units of PS and PVME, respectively.

After substituting the values of the parameters (see Table 1) into relationship (18) we obtain

$$\gamma = (0.0231\alpha + 0.1046) \frac{22988 - 14292\alpha}{(109.8 - 49.1\alpha)^{2/3} (16 - 6\alpha)^{1/3}}. \quad (19)$$

To perform further analysis, it is necessary to estimate the molar volume of the blend

$$V = \alpha \cdot 53.68 + (1-\alpha) \cdot 97.08. \quad (20)$$

To calculate the values of the left and right sides of the criterion (2), let us use expressions (17), (19) and (20). In this case, we will consider a two-component blend in which one of the components is PVME, while the second component is a PVME–PS blend (microphase) with various mole fractions of PVME (α). The results of calculations are shown in Fig. 3 in the form of two dependences of both parts of the criterion (2) on α . The intersection point of the dependences corresponds to the PVME content in the microphase at which PVME becomes compatible with this microphase. The threshold concentration (α_{cr}) is equal to 0.62. At this PVME concentration, the van der Waals volume of the blend is

$$\left(\sum_i \Delta V_i \right)_{cr} = 60.7 \times 0.62 + 109.8 \times 0.38 = 79.36 \text{ \AA}^3.$$

Table 1. Values of δ (J cm^{-3})^{1/2}, γ (mJ m^{-2}), V_m ($\text{cm}^3 \text{ mol}^{-1}$),

$\sum_i \Delta E_i^*$ (J mol^{-1}), $\sum_i \Delta V_i$ ($\text{\AA}^3$) and T_g (K) for PS, PVME and poly(2,6-dimethyl-1,4-phenylene oxide) (PPO).

Polymer	δ	γ	V_m	$\sum_i \Delta E_i^*$	$\sum_i \Delta V_i$	T_g
PS	18.6	41.6	97.1	22988	109.8	373
PVME	15.4	33.4	60.7	8696	60.7	245
PPO	18.2	44.4	103.8	23587	117.4	—

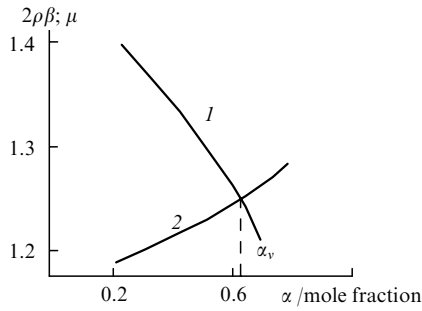


Figure 3. Dependence of μ and β on the PVME content in the micro-phase.

Now we can calculate the glass transition temperature of the blend with $\alpha_{cr} = 0.62$. To this end, let us use the following equation¹⁰

$$T_g = \left\{ \alpha_{cr} \left[\left(\sum_i \Delta V_i \right)_2 - \left(\sum_i \Delta V_i \right)_1 \right] + \left(\sum_i \Delta V_i \right)_1 \right\} \times \left\{ \alpha_{cr} \left[\left(\sum_i \Delta V_i \right)_2 / T_{g2} - \left(\sum_i \Delta V_i \right)_1 / T_{g1} \right] + \left(\sum_i \Delta V_i \right)_1 / T_{g1} + 2\alpha_{cr}(1 - \alpha_{cr}) \times 0.03 \right\}^{-1} \quad (21)$$

Substitution of the parameters for the components of the system (see Table 1) into relationship (21) gives $T_{gcr} = 284$ K. To find the dependence of T_g on composition of the blend formed by PVME and the critical blend, *i.e.*, by a blend composed of PS and PVME with $\alpha_{cr} = 0.62$, let us use Eqn (21). Finally, we get

$$T_g = \left\{ \alpha \left[\left(\sum_i \Delta V_i \right)_2 - \left(\sum_i \Delta V_i \right)_{cr} \right] + \left(\sum_i \Delta V_i \right)_{cr} \right\} \times \left\{ \alpha_{cr} \left[\left(\sum_i \Delta V_i \right)_2 / T_{g2} - \left(\sum_i \Delta V_i \right)_{cr} / T_{gcr} \right] + \left(\sum_i \Delta V_i \right)_{cr} / T_{gcr} + 2\alpha_{cr}(1 - \alpha_{cr}) \times 0.03 \right\}^{-1}, \quad (22)$$

where α is the mole fraction of PVME.

Relationship (22) is suitable only in the range $0.62 < \alpha < 1$. The dependence plotted using Eqn (22) is shown in Fig. 2 (curve 2). It can be seen that this dependence fits well the experimental points.

To describe the dependence of T_g on the composition of the PVME–PS blend on the interval $0 < \alpha < 0.62$, first of all it is necessary to calculate the van der Waals volume of the blend with $T_g = 284$ K. The corresponding formula has the form

$$\sum_i \Delta V_i = 0.62 \left(\sum_i V_i \right)_2 + 0.38 \left[0.62 \left(\sum_i \Delta V_i \right)_2 + 0.38 \left(\sum_i \Delta V_i \right)_1 \right].$$

Substituting the required values (see Table 1) into this equation, we get

$$\sum_i \Delta V_i = 67.8 \text{ \AA}^3.$$

The dependence of T_g on the composition of the blend, one of the components of which is PS and the second component is a microphase with $T_g = 248$ K, is as follows:

$$T_g = \left[\alpha' (109.8 - 67.8) + 67.8 \right] \times \left[\alpha' \left(\frac{109.8}{373} - \frac{67.8}{284} \right) + \frac{67.8}{284} + 2\alpha'(1 - \alpha') \times 0.03 \right]^{-1}, \quad (23)$$

where α' is the effective mole fraction of PS (from 1 to 0.38). Actual mole fraction of PS in the blend is found from the following equation

$$(1 - \alpha) = 0.38 + \alpha' 0.62,$$

where α is the mole fraction of PVME and $(1 - \alpha)$ is the mole fraction of PS in the combined blend.

Substituting the right part of the equality

$$\alpha' = \frac{(1 - \alpha) - 0.38}{0.62}$$

into relationship (25), one can find the dependences of T_g on the blend composition at high PS content, *i.e.*, on the interval $0 < \alpha < 0.62$ (see Fig. 2).

Thus, the solubility criterion (2) can be used to describe the dependence of the glass transition temperature of a polymer blend in which one of the components is a good solvent for the second component, but the second component is a poor solvent for the first component.

Let us consider a simpler case where two polymers are completely compatible with each other taking a well studied PS–PPO blend as an example. Let us assume that PS is the solvent for PPO. Using the solubility criterion (2) and the values of the physical characteristics of the blend components (see Table 1), we obtain: $\mu_2 = \delta_2^2 / \delta_1^2 = 0.959$; $\Phi = 1.0$; $\gamma_{1,2} = 0.0456$; $a = 0.001096$ and $2\rho\beta_2 = 1.328$ (δ_1 and δ_2 are the solubility parameters of PS and PPO, respectively). Since $\mu_2 < 2\rho\beta_2$, then, according to criterion (2), PS is a good solvent for PPO.

Let us assume now that PS is the solvent for PPO, then $\mu_1 = \delta_1^2 / \delta_2^2 = 1.043$, $\Phi = 1.0$, $\gamma_{1,2} = 0.0456$, $a = 0.00103$ and $2\rho\beta_1 = 1.33$. In this case, the value of the left side of the criterion (2) is smaller than its right side, *i.e.*, compatibility can also occur. Experiments confirm that this pair of polymers is completely compatible, therefore the dependence of the glass transition temperature on composition of the PS–PPO blend is the same as that for random copolymers [*i.e.*, it is described by relationship (21)]. The plot of this dependence is shown in Fig. 4. As can be seen, the calculated curve fits well the experimental points.

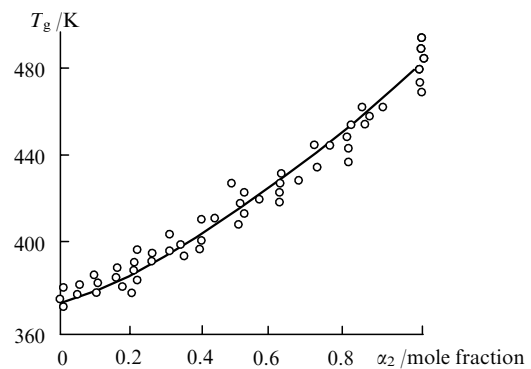


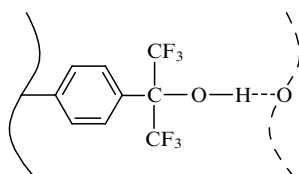
Figure 4. Dependence of the glass transition temperature of the PS–PPO blend on the content of the second component.

It should be noted that this approach used to predict compatibility of polymers has the advantage that no introduction of fitting parameters is required. In other words, to analyse compatibility of polymers using the approach considered, one needs to know only the chemical structure of the components, which makes it possible to calculate the necessary physical characteristics of the polymers.

III. The effect of strong intermolecular interaction on the compatibility of polymers

Mixing of two and more polymers can be accompanied by additional strong intermolecular interaction between their chains, e.g., by hydrogen bonding or strong dipole-dipole interactions, which does not occur between the macromolecules of individual polymers.

In studies concerned with the analysis of the compatibility of polymers and properties of the blends prepared, primary emphasis is placed on these specific interactions. The scheme below illustrates an example of such an interaction:



This interesting phenomenon is observed, e.g., in blends of poly[styrene-*co-p*-(hexafluoro-2-hydroxy-2-propyl)styrene] (STHFPS) with such polymers as a polycarbonate based on bisphenol A, poly(butyl methacrylate) and PPO.²⁵ Due to the presence of hydroxyl groups in this copolymer, hydrogen bonds between the copolymer and polycarbonate are formed, which determines substantial improvement of their compatibility. Two glass transition temperatures (which suggests incompatibility) are clearly seen in the thermograms obtained by the DSC method for PS–polycarbonate blends. The situation becomes quite different when the above copolymer is introduced into the blend instead of PS; in this case, one glass transition temperature (which suggests compatibility) is observed in the thermograms and the T_g value increases as the polycarbonate concentration increases.

This effect is also observed in a blend of STHFPS and crystalline poly(ethylene oxide) (PEO).²⁶ The degree of crystallinity of PEO in the blend changes in such a manner that the melting temperature of the blend decreases. The formation of hydrogen bonds between PEO and the copolymer was studied as a function of temperature. Hydrogen bonds dissociate as temperature increases; however, they reform on cooling. Even in the case of crystalline polymer such as PEO, hydrogen bonding between chains of polymers mixed leads to the improvement of their compatibility, the suppression of crystallisation and to the formation of a homogeneous system.

The behaviour of blends of STHFPS with such polymers as poly(vinyl acetate), poly(methyl methacrylate) (PMMA), poly(ethyl methacrylate), poly(*n*-butyl methacrylate) (PBMA), PVME, PPO, polycarbonate based on bisphenol A, poly(styrene-*co*-acrylonitrile), as well as with amorphous and crystalline esters and polyamides has been studied.²⁷ The effect of intermolecular interaction between macromolecules of the blend components on their compatibility was confirmed by measurements of the glass transition temperatures and by FT-IR spectroscopy.

Compatibility of STHFPS with a number of aliphatic polyamides such as nylon-6,12 and *N,N'*-dimethyl-nylon-6,12 was studied in detail.²⁸ Observation of one glass transition temperature for a blend was considered as the compatibility criterion. Polymers with glass transition temperatures that differ appreciably from T_g of PS and the copolymer were used. For instance, nylon-6,12 has a T_g of 46 °C, whereas its melting temperature lies in the interval 206–215 °C. To estimate the effect of crystallinity on the compatibility, nylon-6,12, *N,N'*-dimethyl-nylon-6,12 and copolymers with variable content of the latter were used. It has been shown that (i) hydrogen bonds are formed between the blend components; (ii) they dissociate on heating and restore on cooling and (iii) the introduction of a small amount of hydroxyl groups into PS improves compatibility of such incompatible polymers as

PS and polyamide. Hence, the copolymer considered can serve as a compatibiliser.

Compatibility of substituted phenol condensation resins with PMMA was studied²⁹ and it was shown that the formation of hydrogen bonds between the blend components plays an important role for the improvement of compatibility. Thermodynamic parameters (enthalpy and entropy) of hydrogen bond dissociation were determined. The strongest effect on the compatibility have such substituents as NO₂ and Cl. All blends of these phenol resins with PMMA had one glass transition temperature, which indicated that the components were compatible. Dependences of the glass transition temperature on composition of the blends considered corresponded to three different cases.

1. The glass transition temperatures of blends are higher than the averaged glass transition temperature.

2. The glass transition temperatures of blends are lower than the averaged glass transition temperature.

3. The dependence of the glass transition temperature on the composition is S-shaped.

It was suggested that the behaviour of the blend corresponding to the first and the second case be describes using the following relationship:²⁹

$$T_g = W_1 T_{g1} + W_2 T_{g2} + q W_1 W_2, \quad (24)$$

where T_{g1} and T_{g2} are the glass transition temperatures of the polymers 1 and 2, respectively; W_1 and W_2 are the weight fractions of the polymers 1 and 2, respectively; the parameter q characterises the strength of hydrogen bonding and can be interpreted as the contribution of hydrogen bonds, which can be considered as pseudocross-links.

It was found experimentally that the q values are negative and approximately equal in absolute values for NO₂ and Bu^t groups as substituents and positive for the Cl substituent. If F and Cl atoms are used as substituents, the q values are positive. (All the aforesaid is true in the case of *para*-substitution of the aromatic nucleus.) Hence, the dependences of the glass transition temperature on the composition of blends of phenol resins containing 4-*tert*-butyl or 4-nitro groups in the aromatic nucleus with PMMA correspond to the second case. For unsubstituted resins, these dependences correspond to the third case. Finally, for chlorine-substituted resins, the dependences correspond to the first case.

The S-like shape of the curve of the T_g dependence on the composition can be described by the following expression, which is more general than relationship (24)

$$T_g = \frac{W_1 T_{g1} + k W_2 T_{g2}}{W_1 + k W_2} + q W_1 W_2, \quad (25)$$

where k is a coefficient.

Relationship (25) was used to describe the dependence of the glass transition temperature on the concentration of components in blends of substituted phenol resins (see above) with poly(ethyl methacrylate) and PMMA (F and Bu^t were used as substituents in the resin) and in blends based on the unsubstituted phenol resin.³⁰ All three above-mentioned cases of changes in the glass transition temperature of the blends were established and all the parameters of Eqn (25) were found.

Hydrogen bonding of macromolecules in these polymer blends was studied by FT-IR spectroscopy,^{31,32} using the Patterson and Robard theory³³ and by construction of lower critical solution temperature (LCST) diagrams. Solubility and compatibility of poly(2-ethyl-2-oxazoline) was studied.

To assess the compatibility of poly(ethyloxazoline) with other polymers, two series of experiments were carried out. In the first series, films were studied based on blends of pairs of polymers, one of which was poly(ethyloxazoline), while in the second series the complexes were studied based on the same pairs of polymers. These complexes were prepared by mixing polymer solutions, separating the precipitate and drying it *in vacuo* to constant weight. It was established that the composition of the complex

differs from that of the initial blend, the former being determined by the ratio of polar groups responsible for the strong intermolecular interaction. The glass transition temperatures of blends of poly(ethyloxazoline) with polyacrylic acid are lower, whereas those of the complexes are higher than the additive values. The authors believe that this is due to the formation of a network of physical bonds in the complexes.

When studying the compatibility of PVME and styrene–methyl methacrylate copolymers, a critical composition of the copolymer was found³⁴ at which compatibility was observed. The PS content in such a copolymer must be ~ 60 mol. %. Phase diagrams were constructed on which the so-called ‘compatibility windows’ of these blends were determined.

In addition to the glass transition temperature, thermal stability of blends was also studied taking blends of poly(*p*-hydroxystyrene) with poly(vinylpyrrolidone) and poly(ethyloxazoline) as examples.³⁵ It was established that a small weight loss of poly(*p*-hydroxystyrene) (6%) on heating in the temperature interval 200–250 °C is due to the cross-linking reaction with the formation of ether bonds. It was mentioned that hydrogen bonds between the polymer chains affect the compatibility of the polymers.

Intermolecular complexes can be formed directly in the course of polymerisation.³⁶ For instance, they are formed upon photopolymerisation of acrylic acid in which PEO is dissolved. The glass transition temperatures of intermolecular complexes are higher not only than those of blends, but also than those of the initial components. These complexes are soluble in such solvents as dimethylformamide and dimethyl sulfoxide and swell to a certain degree in water and methanol; however, they do not swell in dioxane. A decrease in the number of groups capable of forming hydrogen bonds, *e.g.*, by copolymerising acrylic acid with methyl methacrylate, reduces the ability for complexation.

The stability to thermal oxidation also depends on the formation of hydrogen bonds between the polymer chains (*e.g.*, for blends of PVME with modified PS).³⁷ The modified PS was a copolymer of styrene and *p*-(hexafluoro-2-hydroxy-2-propyl)styrene (2.5 mol. %), *i.e.*, it contained functional groups prone to form hydrogen bonds. However, due to the presence of hydroxyl groups in the copolymer, the stability of the system to thermal oxidation was enhanced (*i.e.*, these groups ‘operated’ as antioxidants). This resulted in lengthening of the induction period of the thermal oxidation of PVME and in a decrease in the rate of the process.

The above-mentioned formation of intermolecular complexes was also observed for poly(*N,N'*-dimethylacrylamide) and a phenol–formaldehyde (PF) resin.³⁸ The complexes were precipitated from solutions in acetone, ethyl acetate and dioxane. As before, the compositions of the complexes corresponded to the molar ratios of the components. The glass transition temperatures of the complexes were higher than those of the initial components. Complexes of poly-*N,N'*-dimethylacrylamide with *p*-methoxyphenol–formaldehyde resin were also formed; their glass transition temperatures were much higher than that of each component.^{39,40}

Synthesis of interpenetrating polymer networks (IPN) based on compatible polymers, *viz.*, poly(1-hydroxy-2,6-methylphenylene) and PMMA, was reported.⁴¹ Hexamethylenetetramine and 1,3-dioxolane were used as the cross-linking agents at different temperatures. The strength of hydrogen bonding in blends and IPN was shown to be determined by the change in the cross-linking temperature and by the decrease in the concentration of the groups capable of forming hydrogen bonds. The concentrations of these groups were varied by using methyl methacrylate–styrene copolymers. It was shown by FT-IR spectroscopy that the compatibility in these blends is retained unless the intermolecular interaction due to hydrogen bonds is lower than a certain critical value.

Hydrogen bonding affects the phase behaviour of polymer blends.⁴² This study was performed with blends of poly(methyl

methacrylate-*co*-styrene) with a PF resin in which hydroxyl groups were partially methylated. Compatibility diagrams were constructed and the so-called ‘compatibility windows’ were found, *i.e.*, regions of the diagram corresponding to complete compatibility or to the microphase separation.

The compatibility of homopolymer–copolymer blends was studied.⁴³ The first pair was a blend of poly(4-hydroxystyrene) with poly(*n*-butyl acrylate-*co*-*tert*-butyl acrylate). These blends are compatible when the butyl methacrylate content in the copolymer is $\geq 64\%$. The second pair was poly(*tert*-butyl acrylate) and poly(styrene-*co*-4-hydroxystyrene). The ‘compatibility window’ for this pair was observed at a concentration of 4-hydroxystyrene in the copolymer between 28 mol. % and 66 mol. %. The glass transition temperatures of compatible blends of poly(*tert*-butyl acrylate) and poly(styrene-*co*-4-hydroxystyrene) are much lower than the additive values and, which is the most interesting, they depend only slightly on the blend composition and are approximately equal to the glass transition temperatures of the copolymers. This can be explained only by the formation of hydrogen bonds between the blend components, which was experimentally confirmed by IR spectroscopy.

The concepts of the effect of strong intermolecular interactions on the compatibility of polymers were developed by Kim, Kwei and Pearce⁴⁴ who studied hydrogen bonding in IPN prepared from a compatible polymer blend of poly(1-hydroxy-2,6-methylphenylene) and PMMA. To decrease the number of carbonyl groups, poly(methyl methacrylate-*co*-styrene) at different monomer ratios was also used. Different cross-linking agents, *e.g.*, hexamethylenetetramine and 1,3-dioxolane, were used to prepare IPN. The strength of hydrogen bonding in IPN was varied by varying the conditions of the cross-linking reaction (in particular, temperature). Hydrogen bonding in the compatible blend of two above-mentioned polymers demonstrated reversible temperature dependence. In the case of semi-IPN and IPN prepared at temperatures higher than the T_g of the blend, the number of hydrogen bonds after cooling to room temperature differed from that in the initial blend. If poly(PMMA-*co*-styrene) was used instead of PMMA (*i.e.*, the number of carbonyl groups was appreciably decreased), semi-IPN did not form a single phase. However, semi-IPN and IPN synthesised at relatively low temperatures (below T_g of the blend) were homogeneous and contained a larger number of hydrogen bonds as compared with semi-IPN and IPN synthesised at high temperatures.⁴⁵

Makhija *et al.*⁴⁶ studied poly[2,2'-(5,5'-bibenzimidazole)diyl-*m*-phenylene] (PBI). Its blends with poly(4-vinylpyridine) of various monomer ratios were characterised by one glass transition temperature, which indicated that the components were compatible, and the T_g values were higher than the additive values. As in the previous studies, the authors explained this fact by the formation of the N–H–N hydrogen bonds. This was confirmed experimentally by FT-IR spectroscopy.

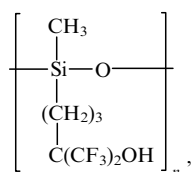
Based on the aforesaid, the following practically significant conclusion can be drawn, *viz.*, the compatibility of polymers in a blend can be improved by introducing a small number of functional groups (*e.g.*, hydroxyl groups) into one of the blend components; this will lead to the formation of hydrogen bonds between the blend components. In this case, domains of different size can be formed. To reduce the size of domains, it is sufficient to introduce a certain number of hydroxyl groups. For instance, compatibility of PS with poly(*n*-butyl acrylate) is achieved by introducing 4.4 mol. % of hydroxyl groups. Relaxation times and domain size were assessed by NMR spectroscopy.^{47–52}

Complexes based on poly(4-hydroxystyrene) and poly-*N,N'*-dimethylacrylamide were studied by ¹³C CPMAS NMR spectroscopy. The size of inhomogeneous domains determined by this method was ~ 2.5 nm.⁵¹ Analogous study of inhomogeneous domains in IPN has shown that the domain size in this case is smaller (~ 2.2 nm).⁵⁰

The effect of microtacticity of PMMA on its compatibility with poly(styrene-*co*-4-hydroxystyrene) was studied by NMR

spectroscopy.⁴⁸ It turned out that syndiotactic PMMA possesses better compatibility with the above copolymer and that the blend based on both methyl methacrylates is homogeneous over a wide range of compositions. The size of inhomogeneous domains for most blends established by NMR spectroscopy was ~ 2 nm. Analogous studies of poly[(4-vinylphenyl)dimethylsilanol] (PVPDMS) and its copolymers with styrene^{49,50} also showed a strong effect of hydrogen bonding between the phenol and phosphate groups, which was confirmed by IR and ^{13}C and ^{31}P NMR spectroscopy.⁵³

Blends were studied⁵⁴ of PEO and poly(butyl methacrylate) with modified poly(butyl methacrylate) that contained groups capable of forming hydrogen bonds.^{55–60} Introduction of 4-hydroxy-4,4-bis(trifluoromethyl)butyl group even in the siloxane polymer

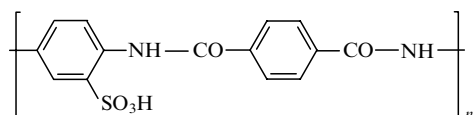


possessing low surface energy, makes it possible to prepare compatible blends with PEO and PBMA.

The parameter of the polymer–polymer interaction was assessed on the basis of studies of steam diffusion and solubility in blends.⁶¹ In all cases its value was negative and became more negative on introduction of hydroxyl groups into the polymer, thus indicating better compatibility. Correlations between the diffusion coefficient and the specific free volume of the polymer were found.

Functionalisation of polystyrene due to introduction of hydroxyfluoroalkyl (or hydroxyl) groups enhances its thermal stability, oxidation stability, retards combustion and improves compatibility with other polymers.⁶²

The compatibility of a number of polyamides in blends was studied.^{63–65} Huang *et al.*⁶⁴ studied the sulfonated poly(*p*-phenyleneterephthalamide)



Based on its blends with poly(vinylpyrrolidone), poly(4-vinylpyridine) and poly(vinyl alcohol) (PVA), the so-called molecular composites were prepared in which the rigid-chain sulfonated polyamide was used as reinforcing element. It was established that hydrogen bonding between the elements of the molecular composite has a strong effect on its properties. The glass transition temperatures of blends with poly(vinylpyridine) and PVA were lower than the additive values, which, according to the authors' opinion, indicates a small number of contacts between the macromolecules.

Modifications of nylon-6, *viz.*, its blends with small amount of PF resins, were studied.⁶⁵ The addition of 1.2% of PF resins results in an increase in the modulus of elasticity and in lowering of moisture absorption. In this case, spherulites of larger size are formed. Further increase in the content of PF resins in the blend does not improve its properties. It was thus concluded that the compatibility of nylon-6 with PF resins is limited (to 3% of PF resins).

The mechanism was studied⁶³ of polymer-analogous reactions of poly(trichlorobutadiene) (PTCB) with aliphatic amines, *viz.*, *tert*-butylamine, diethylamine and triethylamine, which simulate chemical processes occurring in individual fragments of polymer chains in the reaction of PTCB with branched poly(ethyleneimine).

Using FT-IR and electronic spectroscopy, it was shown that hydrogen-bonded ionic charge-transfer complexes are formed in the reaction of poly(1,1,2-trichlorobutadiene) with amines in

parallel to the substitution reactions of the chlorine atom of the allyl group by the amino group and dehydrogenation reactions. The contribution of each of these processes to the overall conversion of functional groups of the polymer depends on the nature of the amine (the degree of N-substitution) and on the type of the solvent. Primary and secondary amines are more prone to form stable hydrogen-bonded complexes with the polymer, whereas the tertiary amine causes mostly dehydrochlorination of the polymer and the formation of polyene fragments of various length. If dioxane is used as solvent, then dehydrochlorination predominates, whereas substitution and complexation predominate in chloroform.

A model in the framework of the Flory theory was developed⁶⁶ that makes it possible to describe self-association and inter-association of the molecules of the components in the case of hydrogen bonding between them. This model was experimentally tested in studies of poly(4-hydroxystyrene)–PMMA blends. These studies have been extended.⁶⁷ This model uses the equilibrium constants that are determined from the IR spectral data, so there is no need to use fitting parameters for the description of the phase properties.

In studies of compatibility of poly(vinylpyridine) and a polyethylene–PVA copolymer, this model was used to analyse the equilibrium association of hydroxyl groups present in the copolymer with the pyridine fragment.⁶⁸

Thus, to predict compatibility of polymers and to establish the reasons for the compatibility, one should pay attention not only to the properties of individual components, but also to the specific intermolecular interaction between them.

IV. The effect of hydrogen bonding and strong dipole–dipole interactions on the glass transition temperature of compatible polymer blends

If no specific intermolecular interaction occurs between cross-linked polymers, the glass transition temperature of a homogeneous blend of compatible polymers is calculated using Eqn (15) in which the glass transition temperatures of homopolymers based on the components 1 and 2 (T_{g1} and T_{g2} , respectively) appear. The T_g value of the blend can be assessed using either calculated or experimental values of T_{g1} and T_{g2} . Equation (15) can be written in another form

$$T_g^0 = \left[\alpha_1 \left(\sum_i \Delta V_i \right)_1 + \alpha_2 \left(\sum_i \Delta V_i \right)_2 \right] \times \left[\alpha_1 \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_1 + \alpha_2 \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_2 + 2\alpha_1\alpha_2 \times 0.03 \right]^{-1}, \quad (26)$$

where a_i and b_j are constants related to the energy of the weak dispersion forces and strong intermolecular interaction (dipole–dipole interaction, hydrogen bonding), respectively.

Let us assume that the addition of polymer 2 to polymer 1 gives rise to hydrogen bonding.

Then, the term $\left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_1$ should contain an addend (a constant) characterising the contribution of hydrogen bonds, *viz.*,

$$b_h = -140 \times 10^{-3} \text{ \AA}^3 \text{ K}^{-1},$$

since a portion of repeating units of the polymer 1 becomes bonded to the component 2 by hydrogen bonds. In this case we have

$$T_g = \left[\alpha_1 \left(\sum_i \Delta V_i \right)_1 + \alpha_2 \left(\sum_i \Delta V_i \right)_2 \right] \times \left[\alpha_1 \left(\sum_i a_i \Delta V_i + \sum_j b_j + 2\alpha_2 b_h \right)_1 + \alpha_2 \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_2 + 2\alpha_1 \alpha_2 \times 0.03 \right]^{-1} \quad (27)$$

This equation was derived assuming that two repeating units (one unit of the polymer 1 and one unit of the polymer 2) are bonded by hydrogen bonds. Taking into account Eqn (15) and the relationship $\alpha_1 = 1 - \alpha_2$, we obtain

$$T_g = \left[(1 - \alpha_2) \left(\sum_i \Delta V_i \right)_1 + \alpha_2 \left(\sum_i \Delta V_i \right)_2 \right] \times \left[(1 - \alpha_2) \frac{\left(\sum_i \Delta V_i \right)_1}{T_{g1}} + 2(1 - \alpha_2)\alpha_2 b_h + \alpha_2 \frac{\left(\sum_i \Delta V_i \right)_2}{T_{g2}} + 2(1 - \alpha_2)\alpha_2 \times 0.03 \right]^{-1} \quad (28)$$

Let us analyse the dependence of the glass transition temperature on the blend composition, which is described by Eqns (27) and (28). Let us consider three cases.

1. The van der Waals volumes of repeating units of the polymers 1 and 2 are approximately equal

$$\left(\sum_i \Delta V_i \right)_1 \approx \left(\sum_i \Delta V_i \right)_2 \quad (29)$$

2. The van der Waals volume of the repeating unit of polymer 1 is much smaller than that of the repeating unit of the polymer 2

$$\left(\sum_i \Delta V_i \right)_1 < \left(\sum_i \Delta V_i \right)_2 \quad (30)$$

3. The van der Waals volume of the repeating unit of the polymer 1 is much larger than that of the repeating unit of the polymer 2

$$\left(\sum_i \Delta V_i \right)_1 > \left(\sum_i \Delta V_i \right)_2 \quad (31)$$

The initial values of $\left(\sum_i \Delta V_i \right)_1$, $\left(\sum_i \Delta V_i \right)_2$, T_{g1} , T_{g2} , $\left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_1$ and $\left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_2$ for blends corresponding to all three cases are listed in Table 2.

Table 2. Initial parameters for calculation of the glass transition temperature of a compatible blend of two homopolymers ($T_{g1} = 376$ K, $T_{g2} = 426$ K).

Curve number	$\left(\sum_i \Delta V_i \right)_1 / \text{\AA}^3$	$\left(\sum_i \Delta V_i \right)_2 / \text{\AA}^3$	I	II
For dependences shown in Fig. 5a				
1	110	115	293	260
2	250	260	665	588
3	350	360	931	814
4	450	460	1197	1041
For dependences shown in Fig. 5b				
1	105	240	279	543
2	105	340	279	769
3	105	440	279	995
4	105	540	279	1222
For dependences shown in Fig. 5c				
1	225	115	598	260
2	340	115	904	260
3	440	115	1170	260
4	540	115	1436	260

Note. Here and in Table 3 the parameters $\left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_1 \times 10^3$ and $\left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_2 \times 10^3$ are denoted as I and II, respectively; both parameters have dimensions of $\text{\AA}^3 \text{ K}^{-1}$.

The dependences of the glass transition temperature of blends on the content of the component 2 shown in Fig. 5a correspond to the first case. The blends were chosen so that $T_{g1} \approx T_{g2}$, whereas the van der Waals volumes vary over a wide range. If the van der Waals volume of a repeating unit is small, the sum $\left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_2$ is also small. In this case the value of the b_h constant is rather large. From Eqns (27) and (28) it can be seen that the smaller the van der Waals volume, the higher the glass transition temperature of the blend and the larger the difference between T_g of the blend and that of a blend in which no additional specific interaction between components occurs [see Eqns (15) and (26), i.e., $T_g > T_{g1}^0$]. This affects the shape of the dependences of T_g on α_2 (see Fig. 5a). If the van der Waals volumes of repeating units of both components increase, the effect of additional interaction

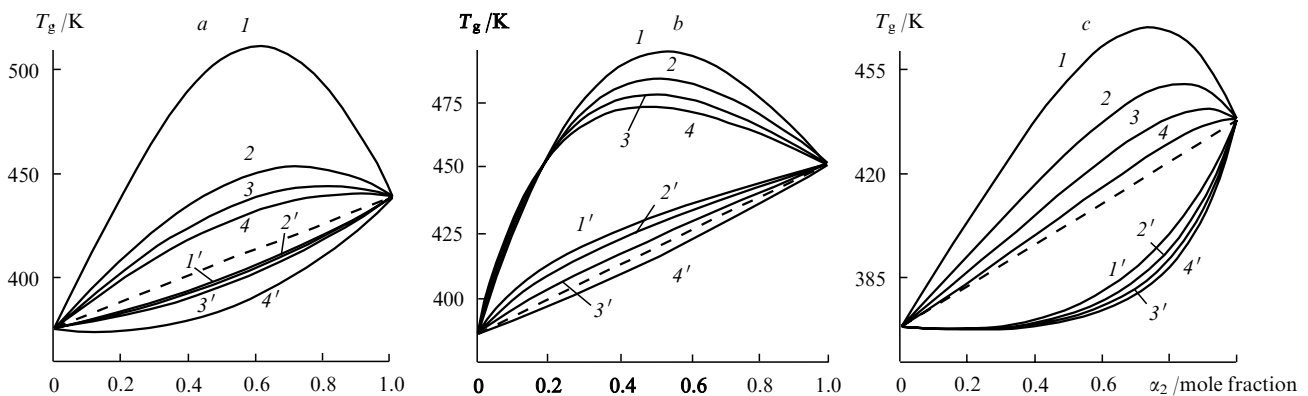


Figure 5. Dependences of the glass transition temperatures on the content of the second component for blends of compatible polymers in which the components are bonded by hydrogen bonds. Relationship (29) (a), (30) (b) and (31) (c) holds. The values of initial parameters for constructing curves (1–4) are listed in Table 2. Curves (1'–4') correspond to the case where no additional hydrogen bonding between the components occurs.

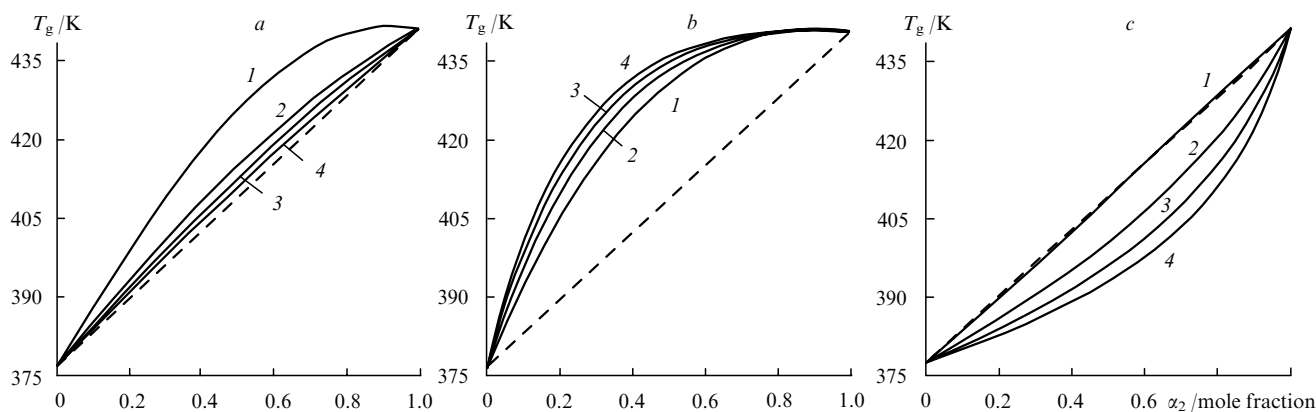


Figure 6. Dependences of the glass transition temperature on the content of the second component for blends of compatible polymers in which dipole–dipole interaction between the components occurs. Relationship (29) (a), (30) (b) and (31) (c) holds.

decreases and the glass transition temperatures of blends are only slightly higher than the T_g values calculated using Eqns (15) and (26).

The dependences shown in Fig. 5b illustrate the second case. Here $T_g > T_g^0$. Even if no additional hydrogen bonding occurs, the T_g values are higher than those of blends calculated on the basis of the mole fractions of the components.

In the third case [see relationship (31) and Fig. 5c], the effect of additional hydrogen bonding decreases, since the total energy of dispersion interaction is appreciably higher than that of the hydrogen bonding.

A similar situation is observed when mixing of blend components gives rise to additional dipole–dipole intermolecular interaction due to the presence of polar groups in repeating units. This interaction is characterised by the b_d constant. In this case, to calculate the T_g values of the blend, one should use the b_d constant instead of b_h in Eqns (27) and (28).

If relationship (29) is valid, the effect of additional intermolecular interaction on the dependence of T_g on composition is much weaker than in the case of hydrogen bonding between the components (Fig. 6a), since $b_d < b_h$.

If inequality (30) holds, the deviation of T_g of blends from the average values is positive (Fig. 6b); however, it is not as large as in the case of hydrogen bonding. If condition (31) is met, the effect of additional intermolecular interaction is not so strong (Fig. 6c) and the T_g of blends are rather close to T_g^0 .

The curves of dependences of the glass transition temperature on the blend composition may have maxima, minima and be S-shaped (Fig. 7). This is due to the fact that one of the blend components is a copolymer containing a limited number of polar groups capable of forming hydrogen bonds. Let us assume that the copolymer 2 whose formula is as follows

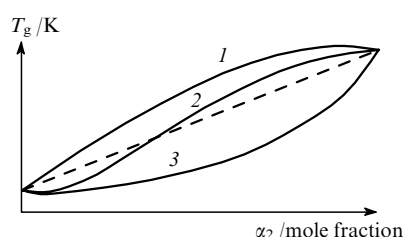
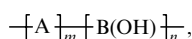


Figure 7. Dependences of the glass transition temperature on the composition of blends of compatible polymers: convex (1), S-shaped (2) and concave (3) curves.

contains a limited number of the $-[B(OH)]-$ repeating units capable of forming hydrogen bonds.

Let us denote the mole fraction of repeating units of the type $-[B(OH)]-$ by β . Let us assume that the second polymer (polymer 1) is capable of forming hydrogen bonds with the repeating units of the type $-[B(OH)]-$, contained in the copolymer 2. Taking into account the notation introduced, Eqns (27) and (28) can be written in the form

$$T_g = \left[(1 - \alpha_2) \left(\sum_i \Delta V_i \right)_1 + \alpha_2 \left(\sum_i \Delta V_i \right)_2 \right] \times \quad (32)$$

$$\times \left[(1 - \alpha_2) \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_1 + 2(1 - \alpha_2) \alpha_2 \beta b_h + \alpha_2 \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_2 + 2(1 - \alpha_2) \alpha_2 \times 0.03 \right]^{-1},$$

$$T_g = \left[(1 - \alpha_2) \left(\sum_i \Delta V_i \right)_1 + \alpha_2 \left(\sum_i \Delta V_i \right)_2 \right] \times \quad (33)$$

$$\times \left[(1 - \alpha_2) \frac{\left(\sum_i \Delta V_i \right)_1}{T_{g1}} + 4(1 - \alpha_2) \alpha_2 \beta b_h + \alpha_2 \frac{\left(\sum_i \Delta V_i \right)_2}{T_{g2}} + 2(1 - \alpha_2) \alpha_2 \times 0.03 \right]^{-1}.$$

Let us consider the cases where conditions (29)–(31) are met.

If the van der Waals volumes of repeating units are approximately equal, the initial parameters for calculating the glass transition temperature of the blend are $T_g = 376$ and 426 K,

$$\sum_i \Delta V_i = 110 \quad \text{and} \quad 115 \text{ \AA}^3, \quad \sum_i a_i \Delta V_i + \sum_j b_j = 293 \quad \text{and}$$

$260 \text{ \AA}^3 \times \text{K}^{-1}$ for the polymer 1 and the copolymer 2, respectively. The content of the $-[B(OH)]-$ component in the copolymer 2 was varied in calculations. The results of calculations are shown in Fig. 8a. The S-like shape of the dependences of the glass transition temperature of blends on composition is observed as β varies from 0.1 to 0.4.^{23, 26, 27, 38, 46, 54, 56}

If strong dipole–dipole interactions occur between the copolymer 2 and the polymer 1 [the condition (30) is met], the glass transition temperature is calculated using Eqns (32) and (33); however, the b_d constant is used in this case instead of b_h . The initial parameters required to calculate the dependence of T_g on the composition are the same as in the former case. The results of calculations are shown in Fig. 8b. It should be noted that the

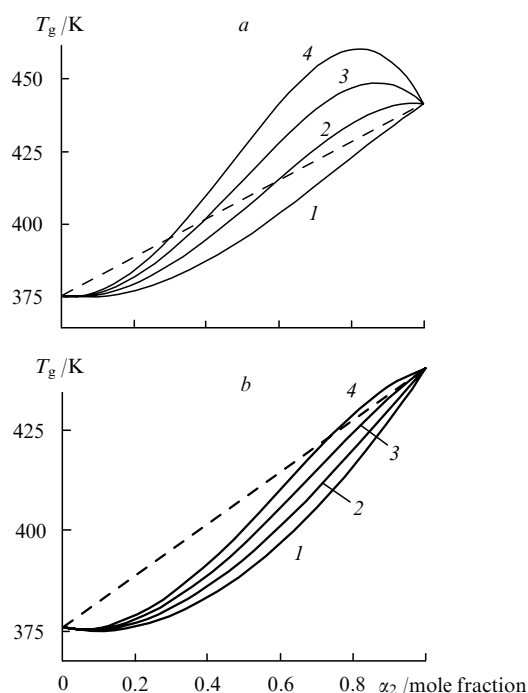


Figure 8. Dependence of the glass transition temperature on the content of the second component for a blend of compatible homopolymer and copolymer in the case of hydrogen bonding (*a*) and strong dipole–dipole interaction (*b*) between the blend components; β : (1) 0.1; (2) 0.2; (3) 0.3; and (4) 0.4.

S-like shape of the curves is observed only if the content of the $-\text{B}(\text{OH})-$ component in the copolymer 2 is high. In all cases, these dependences differ from those obtained without consideration of an additional dipole–dipole interaction between the blend components. Calculations of changes in glass transition temperatures due to the additional intermolecular interaction between the components show that these interactions play a significant role. The T_g values differ from the T_g^0 values. It should be emphasised that the equations used for analysing the dependences of the glass transition temperature on the blend composition contain no fitting parameter and all calculations are performed using only the data on the chemical structure of the blend components.

Let us consider particular blends of compatible polymers taking PBMA–poly(styrene-*co*-VPDMS) blends⁵⁶ as the first example.

It is required to calculate the glass transition temperature of poly(styrene–VPDMS) at different content of the second component. The results of calculations performed using Eqn (15) and experimental T_g values are listed in Table 3. To calculate the glass transition temperatures of blends of PBMA with this copolymer,

one should know the $\left(\sum_i a_i \Delta V_i + \sum_j b_j\right)_{\text{PBMA}}$ and $\left(\sum_i a_i \Delta V_i + \sum_j b_j\right)_{\text{styrene-VPDMS}}$ values, which can be determined using the following equation¹⁰

$$T_g = \frac{\sum_i \Delta V_i}{\left(\sum_i a_i \Delta V_i + \sum_j b_j\right)}, \quad (34)$$

where $\sum_i \Delta V_i$ is the van der Waals volume of the repeating unit.

These values for copolymers of different compositions are also listed in Table 3. They were used to calculate the glass transition temperatures of a number of PBMA–poly(styrene-*co*-VPDMS)

Table 3. Composition and characteristics of PS–PVPDMS copolymers.

Specimen ^a	[PVPDMS] (mol. %)	T_g /°C		$\sum_i \Delta V_i /$ $\text{\AA}^3$	I
		experiment	calculation		
PS	100	105	103	110	293
PBMA	100	29	14	148	516
PVPDMS-2	1.9	97	103	111	295
PVPDMS-4	4.1	98	103	113	301
PVPDMS-9	8.7	98	103	116	309
PVPDMS-11	11.4	99	103	117	311
PVPDMS-18	18.2	101	104	122	324
PVPDMS-34	33.9	115	109	133	348
PVPDMS-60	60	121	122	151	382
PVPDMS-100	100	—	153	178	418

^a Figures denote the content of silanol groups (%) in PVPDMS.

blends. The results of calculations for two blends are shown in Fig. 9 in the form of dependences of the glass transition temperature on the composition. These dependences for compatible blends containing poly(styrene-*co*-VPDMS-34) and poly(styrene-*co*-VPDMS-9) were obtained using Eqn (32). For each blend, the calculated values are in fairly good agreement with experimental data (see Figs 9*a,b*). In addition, let us analyse the dependence of T_g on the composition for the PBMA–poly(styrene-*co*-VPDMS-9) blend using Eqn (33) and experimental T_g values. As a result, good agreement is observed between the calculated and experimental data (Fig. 9*b*).

If the content of modified polystyrene [*i.e.*, poly(styrene-*co*-VPDMS)] in the blend is low, the glass transition temperatures of blends are lower than the additive values. As the content of this component in the blend increases, the glass transition temperatures appear to be higher than the average values. This is explained by the formation of a large number of hydrogen bonds between the components on their mixing.

Blends of PBI and poly(4-vinylpyridine) have been studied.⁴⁶ It was shown that hydrogen bonds are formed between the 4-vinylpyridine residues and the NH groups in PBI. Therefore homogeneous blends based on these polymers are formed. The dependences of experimental and calculated glass transition temperatures on blend compositions are shown in Fig. 10. Glass transition temperatures of the blends are higher than the T_g values of the initial components. The calculated curve fits well the experimental points if the mole fraction of PBI in the blends does not exceed 0.3. Deviation of the experimental points from the calculated curve at high PBI content is associated with the fact that destruction of poly(4-vinylpyridine) begins above 375 °C. It should be noted once again that calculations were carried out using the equations containing no fitting parameters.

Thus, the aforesaid makes it possible to draw the following conclusions. In the case of compatible blends of two homopolymers, the shape of the dependence of the glass transition temperature on the blend composition can be different. If the van der Waals volumes of repeating units of the homopolymers are approximately equal and no additional strong intermolecular interaction between the components occurs, the glass transition temperature is lower than the average values. If the van der Waals volume of the unit of a homopolymer 1 is substantially smaller than that of the unit of a homopolymer 2, the glass transition temperature is slightly higher than the average values (even in the absence of additional intermolecular interactions). If these interactions occur, the T_g value of the blend is always higher than the average values.

For blends of a homopolymer with a copolymer containing a limited number of polar groups that can participate in strong intermolecular interaction with the other component (dipole–dipole interaction, hydrogen bonding), the dependences of T_g on

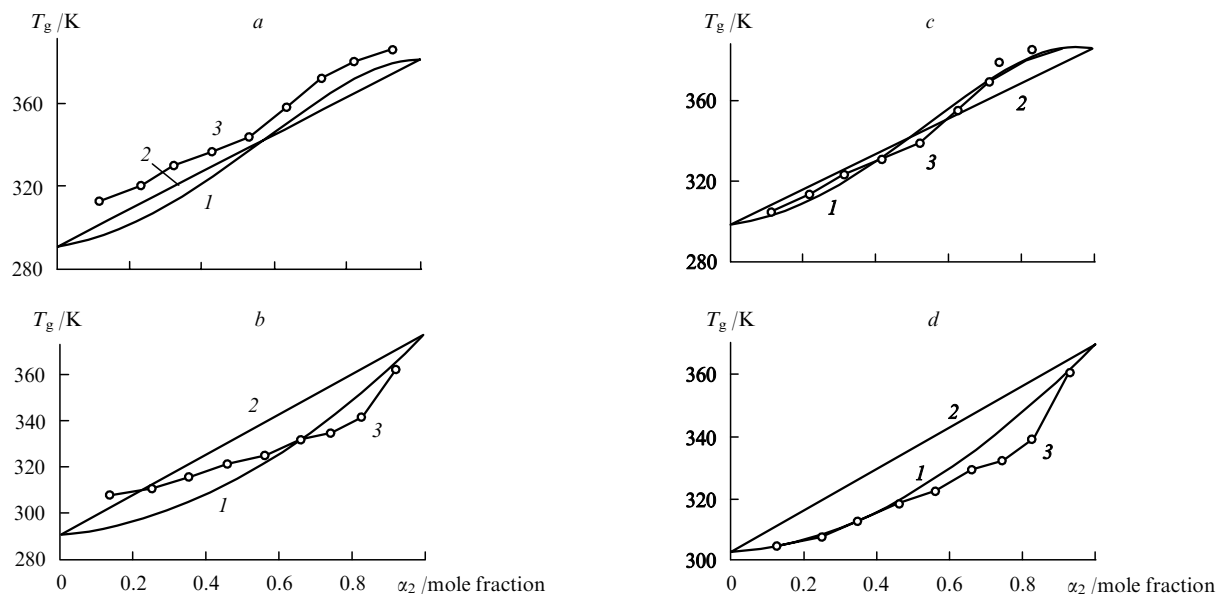


Figure 9. Dependences of the glass transition temperature on the content of the second component for compatible poly(styrene-co-VPDMS-34)–PBMA (*a, c*) and poly(styrene-co-VPDMS-9)–PBMA (*b, d*) blends; calculations using Eqns (32) (*a, b*) and (33) (*c, d*); (1) calculations; (2) average values; and (3) experiment.

composition are *S*-shaped. The above peculiarities of changes in the characteristics of compatible blends can be described by the equations given above which contain the parameters obtained using the data on the chemical structure of the components. It is needless to say that this approach is not versatile and further investigations are needed to understand how should, *e.g.*, the effects of various specific interactions and peculiarities of the structure of blend components on their thermomechanical behaviour be taken into account.

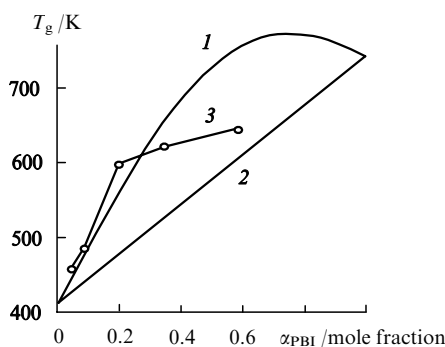


Figure 10. Dependence of the glass transition temperature for compatible polyvinylpyridine–polybenzimidazole blends; (1) calculations; (2) average values; and (3) experiment.

V. Formation of chemical bonds between components of polymer blends

Processing of polymers often results in the formation of chemical bonds between the components, which improves their compatibility.⁶⁹ Let us consider a case of the so-called ‘forced mixing’ of two incompatible polymers by synthesising interpolymers.[†] The reaction is conducted in solution and repeating units of the polymers contain functional groups capable of chemical reaction

with one another. Such an approach makes it possible to prepare macromolecules composed of finished polymers whose repeating units cannot be united in the course of synthesis.

In Fig. 11, the structures of various polymers are represented schematically. The difference between interpolymers and random copolymers is obvious and needs no special explanation. The difference between interpolymers and block copolymers lies in the fact that the chemical reaction between two unlike macromolecules (blocks), resulting in the addition of one block to another one, involves functional groups within the repeating units of macromolecular chains rather than the end functional groups.

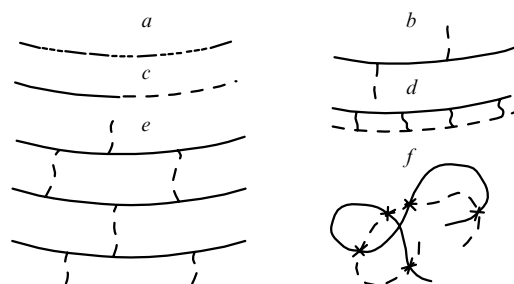


Figure 11. Different types of structures of polymers and copolymers: (a) random copolymer; (b) graft copolymer; (c) block copolymer; (d) a fragment of interpolymer; (e) a polymer network; and (f) a macromolecular interpolymer coil.

Graft copolymers and interpolymers differ not only in the structure, but also in the procedure for preparation. Grafting of chains in solution is due to the interactions of the end functional groups in repeating units of the polymers. Grafting from the gas phase on the surface of a polymeric product is carried out by polymerisation of a monomer on this surface and the product obtained has nothing to do with an interpolymer.

Additional explanation is required as to cross-linking reactions, even in the case where one polymer is cross-linked by the other polymer (*e.g.*, curing of epoxide resin with polyanhydride belongs to this type of reaction). In this case, branched products are formed in the first stage of curing due to the interaction of one

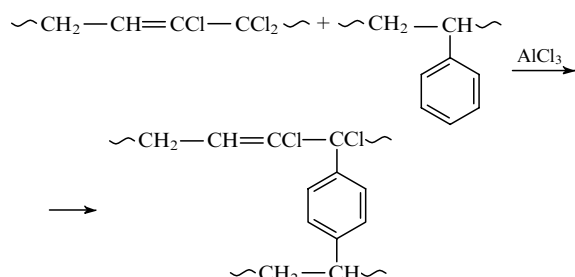
[†] Interpolymers are polymacromolecular compounds formed in a chemical reaction occurring in a solution of two polymers.^{70–78}

or several polymer (or oligomer) macromolecules with those of the curing agent, whereas in the second stage the reaction proceeds in such a way that an increase in the degree of conversion leads to an increase in the degree of cross-linking up to complete insolubility of the product.

In the synthesis of interpolymers, chemical reactions between functional groups in repeating units of unlike macromolecules occur in a different manner. The conditions of reaction in solution are chosen so that the increase in the degree of conversion is due to consumption of functional groups in the chemically bonded macromolecules rather than to the formation of cross-links. In this case, conversion of functional groups is not accompanied by an increase in the molecular weight of the system and the reaction occurs in the region of mutual penetration of unlike coils (see Fig. 11d). Such a reaction results in the formation of soluble products, *viz.*, interpolymers. It should be noted that the degree of conversion of functional groups does not exceed 10%.

Without dwelling on peculiarities of chemical reactions between two unlike polymers in dilute solutions, we should note that the degree of conversion of the same functional groups in the case of two polymers is always much lower than in the case of one polymer and a low-molecular weight substance. Chemical reaction between polymers can occur only in the region of their mutual penetration and the role of excluded volume is of particular importance in those cases where functional groups are arranged in the repeating units along the chain.

Preparation of interpolymers can be exemplified taking the reaction of PTCB with PS. It should be noted that if AlCl_3 is used as catalyst, PTCB readily reacts with the aromatic nuclei of low-molecular weight compounds, *e.g.*, with benzene and its derivatives, and the degree of conversion can be very high. In the reaction of PTCB with PS using the same catalyst, interaction with the aromatic nucleus of PS also occurs



The reaction between PTCB and PS is carried out in nitrobenzene at a low blend concentration (from 0.5 to 5 g dl^{-1}). Fractionation of the interpolymer obtained gives several fractions (A–D) that can be isolated and characterised. Fractions A and B are soluble in the same solvents as the initial polymers; however, unlike fraction A, fraction B is insoluble in carbon tetrachloride. Fraction C is soluble only in tetrachloroethane and nitrobenzene on heating. Finally, fraction D is insoluble.

It should be noted that the increase in the degree of conversion is virtually not accompanied by the increase in the molecular weight of the product, which indicates that the chemical process occurs in the region of mutual penetration of two bonded macromolecules formed in the first reaction stage. In other words, interpolymers are the products of reactions between two or several unlike macromolecules; the molecular weight of the interpolymer is approximately equal to the sum of those of the macromolecules that had reacted.

The aforesaid can be contrasted with the following. First, the molecular weight mentioned above is the apparent molecular weight rather than the true molecular weight, since the experiments have been carried out in one solvent.^{73, 74} However, the true molecular weight can only be lower than the apparent molecular weight; therefore, one cannot say that the process occurs as conventional chaotic branching resulting in a considerable increase in the molecular weight.

Second, it can be assumed that in the case of polydisperse specimens, substantial enlargement of individual macromolecules can be accompanied by a slight increase in the weight-average molecular weight. This issue requires a special consideration. Let us perform such an analysis in the general form.

The weight-average molecular weight is determined from the relationship

$$M_w^0 = \left(\sum_i n_i M_i^2 \right) \left(\sum_i n_i M_i \right)^{-1}, \quad (35)$$

where n_i is the number of macromolecules with the molecular weight M_i .

Let us assume that both reacting polymers have equal molecular weights, which can be calculated using formula (35), and the same molecular weight distributions (MWD). Different variants of chemical reactions can be considered. Let small macromolecules of different types react respectively in pairs with one another and let the same be true for medium-size and large macromolecules. Then the formula for calculating the M_w of the reaction product will have the form

$$M_w = \left[\sum_i n_i (2M_i)^2 \right] \left[\sum_i n_i (2M_i) \right]^{-1} = 2M_w^0, \quad (36)$$

i.e., the M_w value becomes doubled as compared to the initial M_w^0 value. If n macromolecules of each type react in the same way, then

$$M_w = \left[\sum_i \frac{2n_i}{n} (n_i M_i)^2 \right] \left[\sum_i \frac{2n_i}{n} (n_i M_i) \right]^{-1} = n_i M_w^0, \quad (37)$$

i.e., the weight-average molecular weight of the reaction product is equal to the number of macromolecules that had reacted multiplied by the initial molecular weight. In other words, in this case the weight-average molecular weight of the reaction product is equal to the sum of those of the initial macromolecules.

If the smallest and the largest macromolecules react in pairs (cross reaction), the formula for calculating the M_w of the product has the form

$$M_w = \frac{n_1(M_1 + M_x)^2 + n_2(M_2 + M_{x-1})^2 + \dots}{n_1(M_1 + M_x) + n_2(M_2 + M_{x-1}) + \dots}, \quad (38)$$

where M_x is the molecular weight of the final fraction x .

The dependence of the molecular weight of a fraction on its number can be linear: $M_i = M_1 i$, where M_1 is the molecular weight of the first fraction and i is the fraction number. In this case, from Eqn (38) it follows that

$$M_w = M_1 + M_x,$$

i.e., a monodisperse specimen is obtained.

Thus, in all cases considered above, the weight-average molecular weight of the reaction product is equal to the sum of the molecular weights of the macromolecules that had reacted. Clearly, if initial specimens and reaction products are monodisperse, the M_w of the reaction product will be equal to nM_w^0 , where n is the number of the macromolecules that had reacted.

Experiments shows that the reaction product has a very broad MWD.^{73, 74}

Let us consider a case of exaggeratedly broad MWD where all fractions are present in equal proportions, *i.e.*, each fraction also contains an equal number of macromolecules ($n_1 = n_2 = \dots = n_x = n$). In this case, the weight-average molecular weight M_w^0 of the initial products is

$$M_w^0 = \left(\sum_i^x n M_i^2 \right) \left(\sum_i^x n M_i \right)^{-1} = \left(\sum_i^x M_i^2 \right) \left(\sum_i^x M_i \right)^{-1}, \quad (39)$$

where x is the number of fractions.

The number-average molecular weight M_n^0 of the initial product is

$$M_n^0 = \left(\sum_1^x n M_i \right) (nx)^{-1} = \left(\sum_1^x M_i \right) x^{-1}. \quad (40)$$

The polydispersity index of such a system is

$$\frac{M_w^0}{M_n^0} = x \left(\sum_1^x M_i^2 \right) \left(\sum_1^x M_i \right)^{-2}. \quad (41)$$

Let us assess the polydispersity of the initial system, which is characterised by a linear dependence of the molecular weight of a fraction on the fraction number, $M_i = M_1 i$. The formulae for calculating the M_w^0 and M_n^0 values will take the form

$$M_w^0 = \sum_1^x (i M_1)^2 \left(\sum_1^x i M_1 \right)^{-1} = \quad (42)$$

$$= M_1 \sum_1^x i^2 \left(\sum_1^x i \right)^{-1} = M_1 \frac{2x+3}{3},$$

$$M_n^0 = M_1 \sum_1^x \frac{i}{x} = M_1 \frac{x+1}{2}. \quad (43)$$

The polydispersity index is

$$\frac{M_w^0}{M_n^0} = \frac{x \sum_1^x i^2}{\left(\sum_1^x i \right)^2} = \frac{x \times x(x+1)(2x+1)4}{6(1+x)^2 x^2} = 1.33 \quad (x \rightarrow \infty). \quad (44)$$

Therefore, if the condition $M_i = M_1 i$ is met, the polydispersity index cannot be high and for $x \rightarrow \infty$ its value approaches 1.33. This also holds for the reaction products. The polydispersity index can be high (as is observed in the experiment) if the dependence of the molecular weights fractions on their numbers is nonlinear.

Let us consider the modes of reactions between unlike polymers to form highly polydisperse specimens, assuming that the initial specimens are monodisperse.

If the products of reaction between such polymers also are monodisperse, their weight-average molecular weights will be equal to the sum of the molecular weights of the chains that had reacted with one another. This statement requires no special proofs.

To prepare specimens with high polydispersity index, it is necessary that the molecular weights of the final fractions be markedly different. Let us consider the exaggeratedly broad MWD once again. Let us assume that the number of chemically bonded macromolecules in each fraction is $n_1 \times 10^i$, where n_1 is a constant for each fraction and i is the fraction number. Then the molecular weight of the macromolecules in the first fraction will be $M_1 n_1 \times 10$, that of the macromolecules in the second fraction will be $M_1 n_1 \times 10^2$, etc., where M_1 is the weight-average molecular weight of the initial monodisperse specimens. Then the weight-average molecular weight of specimens obtained will be

$$M_w = \left[\sum_1^x (M_1 n_1 \times 10^i)^2 \right] \left(\sum_1^x M_1 n_1 \times 10^i \right)^{-1} = \quad (45)$$

$$= \left(M_1 n_1 \sum_1^x 10^{2i} \right) \left(\sum_1^x 10^i \right)^{-1}.$$

After simplification of this formula we get (to some approximation) $M_w \approx M_1 n_1 \times 10^x$.

If $M_w^0 = M_1$, then $M_w/M_w^0 \approx n_1 \times 10^x$, i.e., this ratio is equal to the number of chemically bonded macromolecules in each fraction. Therefore, the weight-average molecular weight of the reaction products must be equal to the sum of the molecular weights of the macromolecules constituting the interpolymer.

Let the dependence of the molecular weight of a fraction on its number be of power type, which means that the number of bonded

macromolecules in each fraction is n_1^i . Then, the molecular weight of a fraction is

$$M_i = M_1 n_1^i,$$

and the weight-average molecular weight is

$$M_w = \left[\sum_1^x (n_1^i M_1)^2 \right] \left(\sum_1^x n_1^i M_1 \right)^{-1} = \left(M_1 \sum_1^x n_1^{2i} \right) \left(\sum_1^x n_1^i \right)^{-1}. \quad (46)$$

After simplification of this equation we get (to a certain approximation)

$$M_w = M_1 n^x,$$

i.e., in this case the weight-average molecular weight of the reaction product is also equal to that of the initial specimen M_1 multiplied by the number of macromolecules in each fraction.

Let us assume now that the initial specimens of two polymers are polydisperse. The weight-average molecular weight of a blend of such macromolecules is calculated using relationship (35). A polydisperse reaction product can be prepared using different procedures. One of them was considered above, viz., small macromolecules should react in pairs with one another and large macromolecules should react in pairs with large macromolecules. In this case the weight-average molecular weight of the reaction products formed is higher than that of the initial specimens. The ratio of these weights is equal to the number of macromolecules which react with one another and bind to form the interpolymer.

Let us consider an exaggerated case where all large macromolecules in the fraction x , as well as all other macromolecules in other fractions, react with one another. As a result, only two giant macromolecules are formed. Analogous situation is also observed upon completion of the network formation. The weight-average molecular weight of such a reaction product will be

$$M_w = \left[\left(\sum_1^{x-1} n_i M_i \right)^2 + (n_x M_x)^2 \right] \left(\sum_1^{x-1} n_i M_i + n_x M_x \right)^{-1}. \quad (47)$$

The ratio of this weight to that of the initial specimens, M_w^0 , is

$$\frac{M_w}{M_w^0} = \left[\left(\sum_1^{x-1} n_i M_i \right)^2 + (n_x M_x)^2 \right] \left(\sum_1^x n_i M_i^2 \right)^{-1}. \quad (48)$$

For an exaggeratedly broad MWD, $n_1 = n_2 = \dots = n_x = n$. After several transformations, we get

$$\frac{M_w}{M_w^0} = n \left[\left(\sum_1^{x-1} M_i \right)^2 + M_x^2 \right] \left(\sum_1^x M_i^2 \right)^{-1}. \quad (49)$$

Let us assume that $M_i = M_1 \times 10^i$, where i is the fraction number. Then

$$\frac{M_w}{M_w^0} = n \left[\left(\sum_1^{x-1} 10^i \right)^2 + 10^{2x} \right] \left(\sum_1^x 10^{2i} \right)^{-1} \approx n, \quad (50)$$

i.e., in this case the ratio of the weight-average molecular weight to that of the initial specimens is also equal to the number of macromolecules that are chemically bound to one another.

Thus, in both cases of (i) initially monodisperse and exaggeratedly polydisperse specimens and (ii) monodisperse and exaggeratedly polydisperse reaction products, the ratio of the weight-average molecular weights of the reaction products to those of the initial specimens is equal to the number of macromolecules in the interpolymer.

In studies of fractions A and B of interpolymers by dynamic mechanical analysis⁷⁵ it was shown that the formation of chemical bonds between the macromolecules decreases the mobility of each macromolecule. In the plot of temperature dependence of the loss factor $\tan \delta$ the peaks or their 'shoulders', characteristic of PTCB and PS, are shifted toward higher temperatures as compared to those of the mechanical mixture. The interpolymer is characterised by a large storage modulus E' and a higher glass transition

temperature as compared to that of each of the polymers and of their mechanical mixture.

Studies of thermomechanical properties of interpolymers⁷⁶ have shown that their glass transition temperatures increase from 58 to 100 °C as the polymer blend is converted into the polymer A and then into the polymer B. This effect is analogous to that observed at the formation of a ladder polymer the glass transition temperature of which is higher than that of the strands that form the ladder. The T_g value decreases to 30 °C in the later reaction stages, *i.e.*, as the polymer B is converted into the polymer C and then into the polymer D. In the case of formation of conventional polymer networks, the T_g value monotonically increases as the number of cross-links increases.

Blends of PTCB with PS form transparent solutions up to a concentration of 10%; however, in studies of these blends by electron microscopy it was found⁷⁵ that phase separation of blend components occurs even in dilute solution. The interpolymer solution is also transparent; however, unlike the polymer blend, no indications of phase separation are observed in this case. Uniformly distributed large spherical particles are clearly seen when analysing the interpolymer using electron microscopy.

Interpolymer films are transparent and display no indications of phase separation, whereas films of PTCB–PS blends are turbid, with distinct phase separation. However, indications of microphase separation were found in the studies of interpolymer films by physical methods.⁷⁵ Two separated peaks characteristic of PTCB and PS and shifted toward higher temperatures are observed in the plot of the temperature dependence of the loss factor $\tan \delta$ of the interpolymer. Two maxima characteristic of PS are also seen in the X-ray diffraction patterns of interpolymers isolated in the initial reaction stages; however, their intensities decrease as the extent of reaction increases. In the latest stage (polymer D), the maximum completely disappears.⁷⁶ Most likely, microaggregation of PS and PTCB fragments occurs on solution casting; however, the size of domains built of unlike fragments is small and therefore the films retain transparency.

It was also shown⁷⁹ that poly(vinyl chloride) (PVC) also can enter into the Friedel–Crafts reaction with PS; however, it is less reactive than PTCB. From the data in Tables 4 and 5 it can be seen that the mechanical properties of films and moulded blocks of interpolymers based on PVC (and PTCB) with PS depend largely on their composition. The characteristics of mechanical properties of interpolymers are intermediate between those of the initial polymers and in some instances even surpass them. Particularly large is the increase in the impact strength of PVC–PS interpolymers in the range of compositions close to the equimolar composition. The strength of interpolymers is much higher than that of mechanical mixtures of the initial polymers of the same composition (Table 6).

Table 4. Tensile strength (σ_t) and percentage elongation at rupture (ε) of films of interpolymers based on PTCB and PS.

Parameter	PTCB:PS (mol. %)					
	100:0	75:25	50:50	34:66	10:90	0:100
σ_t /MPa	2.6	11.0	32.0	29.0	36.0	32.0
ε (%)	1190	8	4	4	5	5

Table 5. Specific impact strength (γ) and bending strength (σ_b) of moulded monolithic specimens of interpolymers based on PVC and PS.

Parameter	PVC:PS (mol. %)						
	100:0	78:22	54:46	30:70	15:85	10:90	0:100
γ /kJ m ⁻²	2.1	1.7	3.0	4.0	2.2	1.1	1.3–2.1
σ_b /MPa	—	—	30.0	36.0	25.2	29.0	—

Table 6. Mechanical properties of interpolymers of equimolar composition.

Initial polymers	Characteristic	Polymer blend	Interpolymer
PTCB + PS	σ_t /MPa	10.8	32.0
PVC + PS	γ /kJ m ⁻²	1.2	3.0
	σ_b /MPa	6.7	30

Chemical reaction between two unlike macromolecules in solution was theoretically analysed using the Monte Carlo dynamic simulation.⁷⁴ The major conclusion drawn on the basis of results of the computer experiment is that the reaction between unlike macromolecules occurs by a mechanism of disordered formation of chemical bonds between the macromolecules of the ‘coil-in-coil’ type. The reacting macromolecules are ‘drawn into’ each other (the distance between their centres of gravity is shortened), and the reaction proceeds inside the region of interpenetration.

In actual experiments, changes in the number of chemical bonds between macromolecules were monitored using a specially developed precise refractometric method.⁸⁰ In the first stage, a very small number of chemical bonds between the macromolecules is formed; however, most of the macromolecules become bonded in pairs. In the second stage, the reaction proceeds in the macromolecular coils formed in the first stage and consists in an increase in the number of chemical bonds between macromolecules already bonded, *i.e.*, it is an intramolecular reaction of the first kind. Acceleration of this reaction compared to the interchain reaction is due to the appreciably lower activation energy, which is equal to 96.6 and 37.4 kJ mol⁻¹ in the first and in the second stage, respectively.

Thus, preparation of interpolymers is an efficient method for the preparation of compatible polymers from initially incompatible ones. Such a compatibility can be called ‘forced compatibility’. Interpolymers should be considered as individual class of polymers which possess the same and even improved properties compared with those of the initial polymers.

VI. Conclusion

The results of numerous studies show that there are several methods for the improvement of compatibility of polymers.

First, it is selection of polymer pairs or modification of polymers. These are performed to give rise to strong intermolecular interaction (*e.g.*, hydrogen bonding) between unlike polymer chains. This issue was analysed in detail above.

Second, it is conducting of chemical reactions between blend components that result in the formation of interpolymers.

Third, it is introduction of compatibilisers into the system. Compatibilisers are low-molecular weight and high-molecular weight compounds whose molecules contain functional groups capable of strengthening specific intermolecular interactions between the chains. Copolymers can be used as compatibilisers.

Analysis of compatibility of polymers showed that the dependences of the glass transition temperature of blends on the composition vary in shape and can be described by relationships that require no fitting parameters; only the chemical structure of the components needs to be known to perform such an analysis. It is needless to say that this approach does not cover all possible cases of compatibility of polymers. Further investigations, including those in the framework of the approach considered, are required in order to take into account all peculiarities of the chemical structure of polymers that strongly affect their compatibility and properties.

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Chemical approaches to the study of supramolecular biological structures with chromatin as an example

D G Knorre, N D Kobets

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Abstract. Chemical approaches to the study of the chromatin structure and certain aspects of its functioning are reviewed. The main attention is given primarily to those based on the method of 'zero-length cross-linking' aimed at the investigation of the structure of histone complexes within nucleosomes and of the interactions of histones and other proteins with chromosomal DNA. The changes in the nucleosome structure during chromatin transcription are discussed. Recent data on the chemical modification of DNA and several chromatin proteins with reactive oligonucleotide derivatives are considered and analysed. The bibliography includes 89 references.

I. Introduction

Chromatin is one of the most complex supramolecular structures of eukaryotic cells which is responsible for the storage, multiplication, repair and expression of genetic information.¹ Chromatin comprises a great number of constituents and its structure manifests high dynamism associated with dramatic changes both during the cell cycle and as cell responses to incoming (mitogenic, *etc.*) signals. The eukaryotic nucleus is made up of several molecules of double-stranded DNA distributed between individual chromosomes. The human haploid genome consists of 3×10^9 base pairs (b.p.). Assuming that this DNA exists entirely in the *B* form where one loop (10 b.p.) has the length of 3.4 nm, the total length of DNA is ~ 1 m, *i.e.*, the whole set of 23 chromosome pairs measures ~ 2 m in length. This DNA is packed into a nucleus with a diameter ~ 20 μ m. Thus, the degree of compactisation must be of about five orders. In the course of its functioning (replication, transcription, repair, recombination and formation of mitotic chromosomes), DNA is subject to substantial topological rearrangements, so that the array of proteins interacting with it changes drastically.

At the molecular level, the structure and function of chromatin cannot be adequately investigated by physical methods alone. Not only the whole chromatin, even its domains are too large to allow their crystallisation for X-ray analysis, NMR studies or

calculation of the DNA structure by the molecular dynamics method. Therefore, chemical methods appear to be highly suitable for the study of chromatin structure. Affinity modification of chromatin seems to hold especially great promise in gaining information about the structural rearrangements occurring in the nucleus during its functioning. In the first place, this refers to photomodification, which allows specific modifications of definite sites of chromatin over a very short time. The latter circumstance opens up new possibilities for the investigation of events that take place during the functioning of chromatin components.

Chromatin represents a nucleoprotein complex of DNA with nuclear proteins, *viz.*, with basic proteins (histones) and nonhistone proteins including the most well-studied HMG proteins which are considered in this review. It should be noted that during its functioning the nucleoprotein complex interacts with a large set of proteins involved in matrix synthesis, with nuclear matrix proteins (the structure of the nucleus which remains intact after its dissociation from the central nucleoprotein), *etc.* These compounds may be regarded as chromatin-associated proteins.¹

The first level of chromatin organisation is the nucleosomal fibril with a diameter of ~ 10 nm. It represents a DNA chain wound with definite periodicity around a complex made up of four histone pairs (an octamer) designated as H2A, H2B, H3 and H4. These discrete repeat units are obtained by mild treatment of nuclei or isolated chromatin with micrococcal nuclease. A complete nucleosome contains DNA of up to 200 b.p. in length. The core particle contains DNA of 145–146 b.p. in length, which forms 1.75 turns of the left superhelix around the histone octamer. The rest of the nucleosome is regarded as a linker. The structure of the core nucleosome has been solved by X-ray analysis with a 7 Å resolution.² The linker region of DNA of a variable length is complexed with histone H1. This histone seems to play an important role in the formation of the next level of the structural organisation of chromatin, *viz.*, the packing of the nucleosomal chain into a solenoid (a fibril which contains six nucleosomes per turn and has a diameter of 30 nm). In addition to histone H1, chromatin of avian, reptilian, amphibian and fish erythrocytes also contains linker histone H5. After removal of all nuclear histones with a concentrated sodium chloride solution containing detergents, DNA remains bound with the nuclear matrix and forms supercoiled loops.³ It was concluded from these data that DNA is attached to the protein backbone of the nucleus (the nuclear matrix) at definite sites. Electron microscopic studies revealed that after treatment of metaphase chromosomes with 2 M NaCl or an ionic detergent DNA forms loop-shaped domains fixed on the proteins of the chromosome backbone ('scaffold').⁴

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Thus, a fibril with a diameter of 30 nm forms domains appearing as 18 radial loops (each of them has an average length of 60 000 b.p.) that are fixed on the nuclear matrix. These densely stacked rosettes form the next organisational level, *viz.*, the chromatid (Fig. 1).⁵

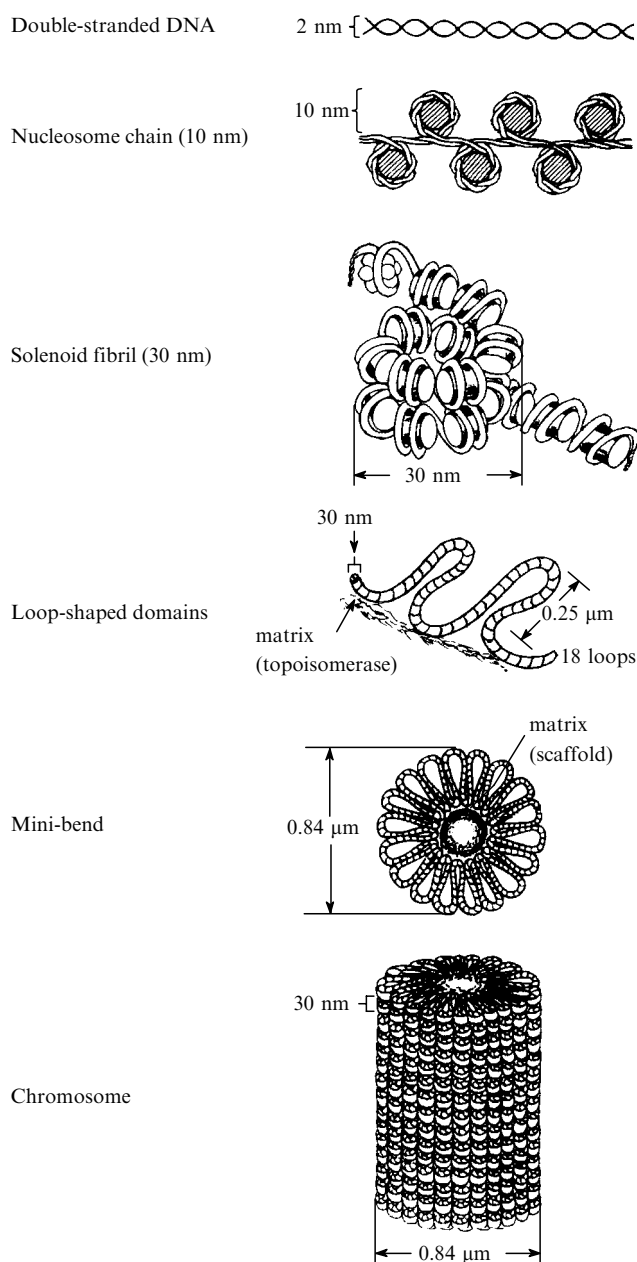


Figure 1. Various levels of chromatin organisation.⁵

The chemical approaches to the study of nucleosome structure were used to solve three main problems, *viz.*, to establish the structure of histone complexes, to identify the sites of DNA interaction with histones and to study the rearrangements in chromatin resulting from the transition of genes into an active or inactive state.

II. Study of interhistone interactions in chromatin

The relative arrangement of histones in the octamer was studied using cross-linking with bifunctional reagents. Such bifunctional reagent as dimethyl suberimidate, which has a large 'radius of action' (10–20 Å), cross-links practically all histone pairs within

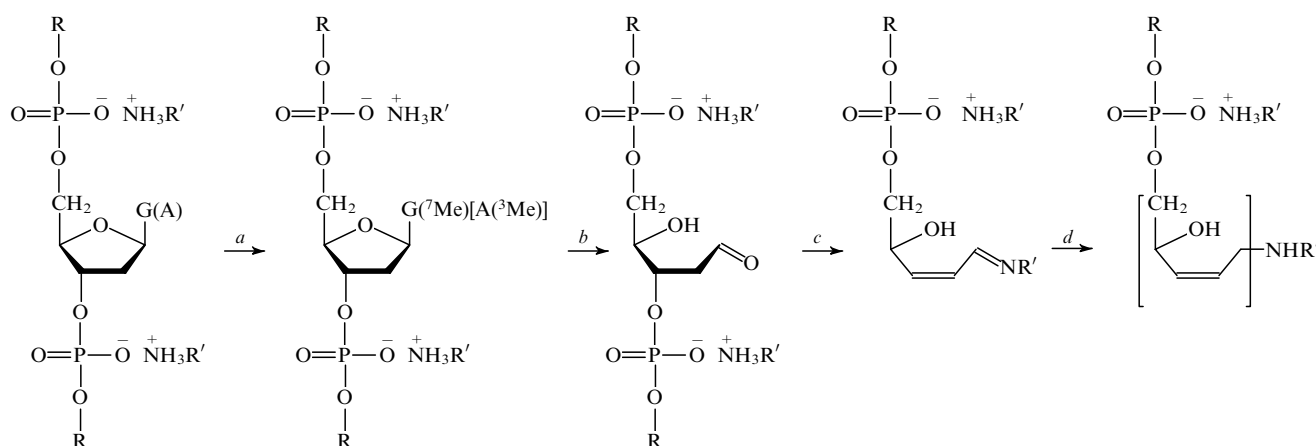
the nucleosome. This finding corroborates the theory according to which the histone octamer is the basic structural element of the nucleosome.^{6–8} The use of dimethyl suberimidate has made it possible to establish the following interactions: Lys74(H2A)–Lys24 and Lys27(H2B), Lys85(H2B)–Lys115(H3) and Lys77(H4), Lys85(H2B)–Lys91(H4).^{9–11} However, the radius of action of this lysine-specific reagent was too large to allow one to obtain information about the relative arrangement of histones in the core. Experiments with chemical (tetranitromethane and formaldehyde) and UV-induced cross-linking of nucleosomes gave more extensive information.^{9,12–14} The strongest contacts were established between histone pairs H2A–H2B, H2B–H4 and H3–H3. UV irradiation of nucleosomes has made it possible to detect the interaction of histone H2A (Pro26) with histone H2B (Tyr37, Tyr40, Tyr42).¹⁵ Histones H4 and H2B are cross-linked with tetranitromethane and formaldehyde as well as upon UV irradiation. The strongest contacts are localised in the C-terminal fragment of histone H2B and the N-terminal fragment of histone H4. It was thus concluded that histone H2B has two domains which interact with other histones. One of these domains localised in the C-terminal fragment interacts with histone H4, while the other one localised in the central domain interacts with histone H2A.⁹ Analysis of a large body of experimental evidence on cross-linking of histones with bifunctional reagents of various lengths did not reveal a single case of histones H4–H4 interaction even where 'lengthy' cross-linking reagents were used. This prompts a conclusion that a crucial role in the formation of the (H3–H4)₂ tetramer is played by H3–H3 contacts. The use of carbodiimides as the cross-linking reagents has made it possible to establish the presence of H1–H2A contacts.^{16–18} Cross-linking of nucleosomal chain histones with carbodiimide has shown that the 74–106 segment of histone H1 interacted with the 58–129 segment of histone H2A. Moreover, cross-links of histone H1 to all core histones, especially to histone H3, could be obtained through the use of bifunctional reagents.^{19–22} It may thus be concluded that histones H3 and H2A are localised in the sites where DNA enters and leaves the nucleosomal core, which is consistent with the model of a nucleosome proposed by Mirzabekov *et al.*²³

III. Study of DNA interactions with histones. 'Zero-length cross-linking'

The works by Mirzabekov *et al.*^{23–31} have made a weighty contribution to the study of the fine organisation of nucleosomes by chemical methods. The approach suggested is based on methylation of DNA resulting in 7-methylguanine and 3-methyladenine derivatives. Comparison of kinetics of formation of 7-methylguanine and 3-methyladenine derivatives upon methylation of free DNA and DNA within chromatin revealed that histones have no effect on the alkylation of adenine residues from the side of the minor groove. However, the rate of methylation of guanine residues from the side of the major groove of chromatin DNA is by 15% lower in comparison with that of free DNA.^{27–29} Determination of the length of DNA fragments in chromatin obtained by cleavage of the modified molecule at the sites of methylation revealed that histones do not protect from methylation rather extended regions of DNA in the nucleosomal chains. It was therefore concluded that histones shield the major groove of chromatin DNA uniformly, over its whole length by 15% but do not shield the minor groove. Similar results were obtained in experiments with the binding of antibiotics distamycin A and netropsin with the minor groove of DNA.³¹

The method used to determine DNA–protein interactions in chromatin is based on chemical cross-linking of definite monomeric units in the DNA molecule with amino acid residues of histones that directly interact with them. Such cross-linking (Scheme 1) involves: (a) labilisation of glycosidic bonds of deoxyribose residues with purine bases resulting from methylation of the latter at position 7 of guanine or at position 3 of adenine; (b)

Scheme 1



R is the fragment of DNA; R' is the fragment of a protein molecule; (a) Me_2SO_4 ; (b) pH 6.8, 45 °C; (c) formation of the Schiff base; (d) NaBH_4 or NaBH_3CN .

cleavage of the glycosidic bond at the modified residues to yield deoxyribose fragments carrying the aldehyde groups; (c) formation of covalent linkages of partially depurinated DNA with the protein (in particular, the Schiff bases with the ϵ -amino groups of lysine provided these are nearby) followed by cleavage of the polynucleotide chain at the site of formation of these derivatives through the reaction of β -elimination and (d) reduction of the histone–DNA covalent bond that formed. As the covalent bond is formed directly between the deoxyribose residue of the nucleotide and the amino acid residue of the histone without any spacer, this method was named 'zero-length cross-linking'.^{25, 30}

Methylation [step (a)] is carried out with dimethyl sulfate. Generation of a positive charge in the 7-methylguanine or 3-methyladenine fragment makes possible hydrolysis of the glycosidic bonds of DNA at the sites of modification by gentle heating at neutral pH. The deoxyribose residue that formed exists in an equilibrium between the open aldehyde and cyclic hemiacetal forms. The reaction of the aldehyde group with the neighbouring amines results in covalent addition of the DNA fragment to the histone to yield the Schiff base. The length of the cross-linked fragment is equal to the distance from its 5'-end to the cross-linking site. At low degree of DNA modification, when DNA is mostly cross-linked at only one site, the length of the cross-linked fragment indicates the position of the contact site relative to the end of nucleosomal DNA. Since the Schiff bases are rather labile, they should be stabilised by reduction with sodium borohydride or sodium cyanoborohydride to the corresponding alkylamines for further manipulations. If the reduction of the primary cross-links is carried out with NaBH_4 , the number of cross-links formed will be close to the number of histidine residues in the protein molecule interacting with DNA. Thus, this approach is sometimes referred to as histidine cross-linking. If reduction is performed with NaBH_3CN simultaneously with cross-linking, this favours the cross-linking of DNA *via* lysines. This procedure has been termed the 'lysine' protocol.³²

The next step is sizing of the DNA fragments that formed and identification of the nature of the histones cross-linked to each of these fragments. This was carried out by two-dimensional diagonal electrophoresis, which is the second principal element of the approach proposed by Mirzabekov *et al.*^{23–31} Polyacrylamide gel electrophoresis of the whole cross-linked material in the first direction was carried out under denaturing conditions in the presence of urea and sodium dodecyl sulfate (SDS). The DNA fragments cross-linked to histones are separated according to the sizes of both the DNA fragment and the protein cross-linked to them. In other words, nucleoproteins containing polynucleotide

fragments of identical lengths migrate at different rates, this being the slower the larger is the size of the cross-linked histone. After treatment of the gel with pronase, which hydrolyses completely the proteins, the DNA fragments are fractionated according to their lengths in the second (perpendicular) direction. This procedure allows one to determine the lengths of these fragments using the corresponding markers. Identical fragments that had been attached to different histones appear to be displaced relative one another depending on the retardation upon separation in the first direction. On the other hand, each set of DNA fragments of different lengths which corresponds to cross-linking with the same protein is partitioned into diagonal stripes. Such DNA fragments contain no protein and can be regarded as 'protein images'. The position of the diagonal points to the relatedness of each DNA fragment of particular size to a definite histone. In most experiments, an isotope label has been introduced into the 5'-end of DNA by a conventional procedure. It consists in enzymic phosphorylation of DNA with polynucleotide kinase, which transfers [^{32}P]phosphate from [γ - ^{32}P]ATP. The separated fragments are identified by autoradiography (for detailed description, see Ref. 33). It was found that the sites of DNA contacts with histones on each DNA strand are separated by a distance multiple of 10 nucleotides, which corresponds to the size of one turn of the double helix. This means that the histone octamer with the DNA wound around it interacts with one side of the double helix. Then, the opposite site is exposed to the action of DNase I.

The arrangement of histones on both strands of the nucleosomal core DNA established by the above-described method is shown in Fig. 2.³⁴ Each histone forms several contacts with DNA;

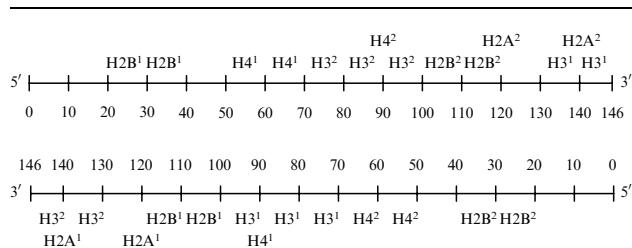


Figure 2. A symmetrical model of arrangement of histones on both strands of DNA within the core nucleosome particle. The numbers from 0 to 146 designate the distance (the number of nucleotide residues) from the 5'-end of DNA. Each of the two histone copies in a core particle is marked with a superscript 1 or 2. The histones are arranged along one strand of DNA in the following order: $\text{H2B}_{25,35} - \text{H4}_{55,65} - \text{H3}_{75,85} / \text{H4}_{88} - \text{H2B}_{105,115} - \text{H2A}_{118} - \text{H3}_{135,145} / \text{H2A}_{145}$.^{23, 26}

histones H3 and H4 are associated with the centre of the core particle, while histones H2A and H2B are shifted to the periphery of the nucleosomal core. The contacts between the 3'-terminal fragment of the core DNA and histones H3 have also been established. The positions of the histone dimers H2A–H2B and the histone octamer (H3–H4)₂ on the double-helical molecule of the core DNA are rather autonomous (Fig. 2). This is consistent with the leading role of such specific complexes in the nucleosome assembly.³⁵ [Presumably, nucleosomes are assembled during chromatin replication by cross-linking of the (H3–H4)₂ octamer to DNA to form a primary unstable nucleoprotein particle, to which the H2A–H2B dimer is then attached to stabilise the nucleosome].

Thus, the full pattern of interactions of each of the four histones with the DNA molecule within the nucleosomal core emerges. The main structural nucleosome components revealed by this approach are largely identical both in the isolated nucleosomes and within intact chromatin. The similarity of the primary organisation of nucleosomes isolated from different sources provides support for their conservative structure.^{24, 25, 36}

The crucial role of histone H1 in chromatin condensation and maintenance of the 30 nm fibril, which is the next hierarchic level of chromatin organisation, was demonstrated in early studies of Georgiev *et al.*³⁷ The zero-length cross-linking method allowed one to establish that DNA of chromatin from *Drosophila* embryos is bound simultaneously with histone H1 and core histones.^{38, 39} It is known that the linker histone H1/H5 has three structurally and functionally different domains, *viz.*, a central globular domain which is evolutionarily the most conservative, a relatively short N-terminal domain and a highly basic lengthy C-terminal domain (terminal domains are the most variable parts of the histone).^{40, 41} Cross-linking revealed that histone H1 interacts with the termini of the core DNA. It was found that the conservative, globular part of the H1 molecule interacts with the termini of the nucleosomal DNA and the nonstructured N- and C-terminal fragments of histone H1 interact with the external regions of the nucleosomal DNA. It was supposed that the H1 molecule serves as a bridge which binds together two neighbouring nucleosomes by folding the nucleosomal chain into a 30-nm fibril.²⁶

Many polycyclic molecules having a rigid planar structure are able to intercalate, *i.e.*, to be incorporated between two adjacent, stacked base pairs in the double helix of DNA. Intercalators, such as acridine, are bound predominantly to the linker site of DNA.⁴² A photoaffinity reagent based on acridine, *viz.*, AcrNH(CH₂)₃N(COC₆H₄N₃-p)-(CH₂)₃NHAc, where Acr is the acridine residue, was proposed for elucidation of the contacts of the linker DNA.⁴³ Irradiation of a complex of this reagent with a complete nucleosome results in photoaffinity modification, predominantly of proteins H1, H2A and H3. These data are in agreement with the results of binding of histone H1 with the linker DNA and corroborate the position of the other two histones on the periphery of the nucleosomal core DNA (see Fig. 2).

In its original version, the zero-length cross-linking method provided information only about the nature of the nucleotide residue involved in the interaction with one or another histone. However, a methodology of identification of amino acid residues involved in the cross-linking has been exemplified with the interaction of chromosomal DNA with histones H5⁴⁴ and H4.^{45, 46} To this end, the cross-linked product was treated with nucleases or with 66% HCOOH/2% diphenylamine, after which the short oligo- or di-nucleotide fragment which remained bound to the protein was labelled with ³²P using polynucleotide kinase. Identification of labelled fragments was carried out by traditional methods of peptide chemistry. It was shown that modifications in histone H5 predominantly affected the histidine residues (His25 and His62) in the globular fragment of the histone molecule and the N-terminal amino group of the threonine residue (Thr1). In histone H4, the cross-linking occurred predominantly at the His18 residue localised in the central globular domain.⁴⁶

IV. Study of functionally active chromatin

Elucidation of the mechanism of rearrangements of chromatin, which take place during its passage into a functionally active state, primarily as a result of its involvement in transcription, is of considerable importance. Identification of nucleosomes associated with regulatory and transcribed sites is carried out by the method of diagonal electrophoresis with nonlabelled DNA. Then the 'protein images' formed are hybridised with the corresponding ³²P-labelled probes. Heat shock genes of *Drosophila* cultured cells the heating of which to 37 °C triggers transcription of heat shock proteins (*hsp*), are studied in most details. This approach allows one to conduct parallel experiments with transcriptionally active and transcriptionally silent chromatin.^{32, 47–49}

The first investigations of this kind were carried out using zero-length cross-linking approach and employed both the 'histidine' cross-linking method and the 'lysine' protocol. The results of these studies were not identical, though. In the 'histidine' method, where cross-linking of DNA to histones mostly occurs in the promoter, structural and 3'-flanking sites of heat shock activated *Drosophila* genes with the central globular protein domain, transcription evokes initial reduction of the number of core histones followed by complete removal of the linker histone H1 and, ultimately, of all histones.⁴⁷ In the case of the 'lysine' protocol, cross-linking of histones affects their terminal domains, there was no significant difference in cross-linking of active and silent chromatin. It was concluded from these data that activation of transcription did not result in complete removal of histones from the transcriptionally active site of chromatin with the exception of the promoter site where histone–DNA interactions are practically absent (at least the sites in the promoter region with the length of up to 200 b.p. are free from histones). With further progress of transcription, the interactions of central globular domains of histones with DNA are weakened but the contacts of histone N- and C-terminal fragments with DNA are preserved.³² Thus, the passage from transcriptionally silent to transcriptionally active chromatin is accompanied by loosening or unfolding of the nucleosome structure, *i.e.*, significant structural rearrangements take place.

More recent studies made use of UV irradiation of whole cells for cross-linking of DNA to proteins. Hybridisation with 'protein images' was carried out with DNA probes which represent a promoter fragment of *hsp70* gene DNA, a fragment with the length of 900 b.p. within the transcribed subunit of the *hsp70* gene and a nontranscribed fragment of ribosomal DNA. It was found that interactions of histone H1 with DNA occur even under conditions of active transcription. The exception is the promoter region where DNA–histone H1 contacts are absent. At the same time, in the case of active chromatin the promoter site interacted with two additional proteins with molecular weights of 50 and 100 kDa. Probably, these proteins are the factors responsible for the regulation of transcription. The 100 kDa protein binds predominantly to the encoding strand, whereas the 50 kDa protein binds to the complementary noncoding strand.⁴⁹ It should be noted that cross-linking of the promoter to these two proteins takes place only upon activation of the heat shock gene and is absent in the inactive gene. It was shown⁵⁰ that the set of histones modified with azidoarylhisacridinylspermidine and cross-linkable to the active fraction of chromatin which is preferentially split with nucleases is different from that of the total preparation of chromatin. In the active fraction of chromatin, only histone H1 is subject to photoactive labelling, whereas histones H2A and H3 are not. This finding seems to corroborate the conclusion that DNA in the active fraction of chromatin is less tightly bound to the histone core and the active chromatin has a more loose structure.

Among nonhistone proteins of chromatin, HMG proteins with high electrophoretic mobility are studied in most details. HMG14 and HMG17 (10 000 and 9247 kDa, respectively) have been defined as proteins of transcriptionally active chromatin.⁵¹

These proteins are known to bind to nucleosomes, this binding being especially tight in the case of active chromatin. Core nucleosomes and nucleosomes containing histone H1 were isolated from chicken erythrocyte chromatin, reconstituted with HMG14/17 proteins and then the proteins were cross-linked to DNA.⁵² Analysis of the cross-linked material by two-dimensional gel electrophoresis revealed that cross-linking of HMG14/17 to nucleosomes does not influence the distribution of histones along the DNA strand either in the core particle or in the complete nucleosome. The main contact sites of these proteins with DNA are at a distance of 25 and 115 nucleotides from the 5'-end of the core particle. The contacts of the core histones H2A, H2B and H3 are grouped in the same terminal fragment of core DNA (see Fig. 2). These data are consistent with the results of cross-linking of proteins HMG14/17 and core histones to the lysine-specific bifunctional reagent, 2-iminothiolane.⁵³ The photoactivated reagent, *N*-hydroxysuccinimide 3-[(4-azidophenyl)dithio]propionate (SADP), cross-linked HMG proteins to the central fragment of histone H3.⁵⁴ The proteins isolated from cell suspensions of chicken blood were used.⁵⁴ The radioactive label was introduced into the proteins by reductive alkylation with [¹⁴C]H₂CO after which the proteins were derivatised with SADP. Acylation at lysine residues converted the individual proteins HMG14 and HMG17 into their photoactive analogues carrying the N₃C₆H₄SS(CH₂)₂C(O) fragment at amino groups of several lysine residues. UV irradiation of a complex with nucleosomes generated nitrene from the azide residue, which was cross-linked to one of the neighbouring proteins. After separation of the cross-linked proteins, the disulfide bridge can be cleaved by disulfide exchange with mercaptoethanol, which facilitates identification of histones cross-linked to HMG proteins. A more lengthy reagent, *viz.*, *N*-hydroxysuccinimide 3-[(1-(2-nitro-4-azidophenyl)-2-aminoethyl)-dithio]propionate (SNAP), preferentially cross-links HMG14/17 to histone H2A.⁵⁵ Probably, owing to differences in the geometry and size of SNAP and SADP molecules, they interact through their hydrophobic and photoreactive termini with different groups on the histone core surface where histones H2A and H3 are in close proximity to each other. These results suggest that the HMG fragment cross-linked to histone H3 is close to the Cys110 residue of histone H3 localised on the nucleosome surface. The Cys110 residue is in the open state; its conformation is characteristic of transcriptionally active chromatin.⁵⁶ This finding prompts a conclusion that cross-linking of HMG14/17 proteins to the nucleosome may strengthen this conformation.

Experiments with Ehrlich ascites cell nuclei fixed with formaldehyde and subjected to DNA–protein cross-linking were undertaken to study the distribution of histones in the *de novo* synthesised DNA strand. The latter was synthesised in the presence of 5-bromodeoxyuridine 5'-triphosphate. Thus, it contained 5-bromodeoxyuridine residues and could therefore be identified and investigated using polyclonal antibodies against 5-bromodeoxyuridine. It was shown that histones of *de novo* synthesised chromatin had the same stoichiometry as the original one. Histone H1 binds to the daughter DNA strand simultaneously with, or immediately after, the cross-linking of core histones, although the cross-linking to the *de novo* synthesised DNA is weaker in comparison with the original chromatin.⁵⁷

An important role in the cross-linking of transcription factors to nucleosomes is played by specific proteins, *viz.*, nucleoplasmin, or its yeast analogue, NAP-1 (nucleosome assembly protein). These proteins induce the formation of a ternary complex of the transcription factor (nucleoplasmin or NAP-1). The use of a chemical approach based on cross-linking of histone octamer proteins with dimethyl suberimidate confirmed the fact that the mechanism of action of these proteins consists in elimination of the H2A–H2B dimer followed by elimination of the remaining histone tetramer (H3–H4)₂. This study made use of the yeast activating factor GAL4-AH, which binds to a definite DNA sequence preceding the lacZ gene. This factor was investigated with the help of a specially designed system which included a DNA

fragment (153 b.p.) and a binding site for GAL4 separated by a distance of 35 b.p. from one of the ends of the nucleosomal core. It was found that the stimulating effect of nucleoplasmin or NAP-1 (which under normal conditions stimulate the binding of GAL4-AH to native nucleosomes) was not manifested when nucleosomes with histone octamers cross-linked with dimethylsuberimidate were used. However, after reconstitution of nucleosomes from the cross-linked H2A–H2B complex with subsequent introduction of all the other core histones, the functions of nucleoplasmin and NAP-1 were not disturbed. Thus, separate removal of the first pair of histones H2A–H2B from the remaining part is problematic.⁵⁸ According to previous reports, such removal may not be complete but rather result from significant bond loosening.

Mapping of DNA–protein contacts along definite sequences of DNA was carried out using a model of ribosomal genes. This model is very convenient for establishing the relationship between the regulation of gene activity and structural rearrangements in chromatin.^{59,60} Ribosomal RNA genes are present in *Drosophila* cells as 250 copies where they are grouped into tandem repeats in which transcription elements are separated by spacers containing repeating sequences (239 b.p.) flanked by recognition sites for AluI restrictase. Restriction enzymes (restrictases) catalyse the cleavage of DNA at tetra- or hexa-nucleotide sequences which are strictly specific for each restrictase. These repeating sequences are homologous to the promoter sites of ribosomal genes and play a prominent role in their transcription. UV-induced cross-linking and hybridisation with 'protein images' allowed one to identify two proteins (mol. masses 50 and 70 kDa) associated with the Alu-repeat.

V. Study of chromatin using reactive oligonucleotide derivatives

Studies of affinity modification of chromatin with various oligonucleotide derivatives are of interest as an approach to the investigation of the structure of this most important type of DNA–protein complexes as well as due to the necessity of elaboration of methods for targeted attack on definite genes and mRNA with complementary oligonucleotides aimed at modulating their expression and induction of directed mutagenesis. This approach was first proposed by Grineva *et al.*⁶¹ and exemplified with reactive oligonucleotide derivatives in order to direct (address) a bound reactive group to a definite site in the target nucleic acid with the help of a complementary oligonucleotide. Hence, the original name of this method is 'complementarily addressed modification'. At present, the methods based on the reactions of definite sense sites of a target nucleic acid with specific oligonucleotides, their derivatives or analogues are referred to as the antisense approach. This approach is gaining popularity as a helpful tool in molecular-biological studies and the reagents are considered as potential therapeutically valuable compounds, in the first place, antiviral and antitumour preparations which interact with genetic structures.^{62,63}

In the majority of cases, antisense oligonucleotides are used for cross-linking to single-stranded (matrix or viral) RNA. The possibility to act upon DNA by suppressing the effects of oncogens or integrated viral genomes would significantly extend the range of their therapeutic applications. Therefore, DNA presents an attractive object for application of such oligonucleotide derivatives.

In this connection, a great deal of effort is given to the design of oligonucleotides able to suppress the DNA function due to the formation of ternary complexes.⁶³ However, an alternative approach consisting in the treatment of unwound regions of DNA that exist in chromatin with oligonucleotide derivatives is also possible.

Chromatin DNA of eukaryotic cells is not a strictly double-helical structure over its whole length. In the course of cell functioning (*e.g.*, during replication or transcription), definite

sites of DNA can be temporarily unwound. The DNA of complex nuclear structures may contain single-stranded regions which can interact with oligonucleotide derivatives. Such single-stranded sites of the DNA molecule can be formed as a result of DNA interaction with specific proteins able to unwind the double helix or due to the presence of superhelical domains in DNA. The possibility of specific chemical modification of DNA within chromatin and in the intact nuclei with complementarily addressed reagents was experimentally studied at the Novosibirsk Institute of Bioorganic Chemistry of the Siberian Branch of the Russian Academy of Sciences (see below).^{64–68}

Repeating sequences, which are abundant in the eukaryote genome and represent a fundamental distinction of the genome organisation in higher eukaryotes, were selected as targets to study the interaction of oligonucleotides with chromatin DNA.⁶⁹ The human genome contains short (about 300 b.p.) repeats which alternate with unique sites and contain a site recognisable by restrictase AluI.⁷⁰ These repeats are referred to as Alu-repeats and constitute about 3% of the human genome (3×10^5 copies per genome). The left and the right halves of the Alu-repeat are characterised by a high degree of homology and are flanked with oligoadenylic regions (up to 20 b.p. in length). The dinucleotide repeat (dG-dT)_n with its complementary oligonucleotide p(dA-dC)₆ comprises about 0.5% of the eukaryotic genome. The occurrence of relatively short (up to 50 b.p.) sites of this repeat occur in the eukaryotic genome in 1 per 30 000–100 000 base pairs, on the average.^{71,72} According to numerous reports, the (dG-dT)_n repeat was detected in the sites of transition of DNA from the B- to the Z-conformation.^{73–75} Such a transition may provoke local unwinding of DNA in these sites of chromatin and thus make them accessible to complementary interaction with the corresponding oligonucleotide derivatives, *e.g.*, p(dT)₁₆, p(dA)₁₆, p(dA-dC)₆ and pd(TTCTCCTGCCTCAGCCTCTT) (which is complementary to the most conservative site of the Alu-repeat family).

In the first series of these investigations, oligonucleotide derivatives, *e.g.*, p(dT)₁₆, were used containing a reactive alkylating group, *viz.*, 4-[(N-2-chloroethyl-N-methyl)amino]benzylamine attached through a phosphamide bond to the 5'-terminal phosphate group. The experiments were carried out on chromatin isolated from rodent and human cells as well as on metaphase chromosomes and intact nuclei.

The study of a possibility of specific cross-linking of an oligothymidylate derivative, complementary to the polyA-repeats of DNA widely distributed in the eukaryotic genome, to DNA from the soluble fraction of human placenta chromatin demonstrated that the alkylating derivative modifies chromatin at room temperature.⁶⁴ Nonmodified p(dT)₁₆ strongly inhibits the modification. At the same time, the oligonucleotides which are not complementary to the polyA-repeats do not influence the modification, which points to the specificity of interaction. Preliminary treatment of chromatin with RNase A under conditions ensuring hydrolysis of polyriboadenylate sequences present in the majority of chromatin matrix RNAs does not virtually exert any influence on the degree of modification with the same reagent. Hence, it is DNA that is subjected to modification.

It was shown that reactive oligonucleotide derivatives can specifically modify DNA both within chromatin and in the most densely packaged deoxyribonucleoproteins, *viz.*, metaphase chromosomes. However, nuclear DNA was not subjected to modification under identical conditions.^{65,76}

In the case of modification of the Alu-repeat, the specificity of modification was additionally confirmed by data from restriction analysis. An oligonucleotide selected for modification was complementary to one of the most conservative sites of the Alu-repeat localised inside the 170 b.p. fragment cut out with Sau3A restrictase. After modification of human HeLa cell chromatin, DNA was isolated and cleaved with restrictase Sau3A. The resulting fragments were separated by electrophoresis in polyacrylamide

gel. Autoradiography of the gel revealed that the radioactivity imparted by the covalently attached oligonucleotide derivative was detected in the 170-b.p. fragment, whereas in control experiments where the oligonucleotide derivative had a different sequence, the radioactivity was not found.⁷⁷

It was shown that preliminary treatment of chromatin preparations with S1-nuclease, which cleaves under mild conditions single-stranded regions of DNA with preservation of the general morphology of these specimens, results in practically complete inhibition of chromatin modification with oligonucleotide derivatives.^{76,77} This indicates that the interaction of oligonucleotide derivatives with DNA occurs *via* the formation of their complementary complexes with unwound regions of chromatin DNA.

A study of the interaction of the alkylating oligothymidylate derivative with chromatin isolated from various types of cells (*e.g.*, replicating cells of regenerating rat liver and chicken erythrocyte cells in which chromatin was completely repressed both in transcription and replication) made it possible to gain insight into the nature of structural peculiarities of DNA in chromatin that are responsible for the formation of local unwound regions allowing for specific interaction with oligonucleotide derivatives.^{67,68}

Regenerating rat liver is a classical object for investigation of various processes occurring in the cell during intensive replication. The maximum replication in liver cells is observed 22–24 hours after partial hepatectomy. The nuclei isolated from intact and regenerating rat liver cells were treated with the p(dT)₁₆ alkylating derivative. The relative degrees of modification of DNA appeared to be identical in both cases. This suggests that the formation of replication forks does not cause any significant increase in the number of polydeoxyadenylate sites accessible to the complementarily addressed reagent. Similar results were obtained in the studies designed to compare the degree of modification of DNA at polydeoxyadenylate sequences in the nuclei of both non-synchronised cells and cells synchronised in the S-phase of the cell cycle where DNA synthesis occurs with the greatest intensity.

Differentiation of erythroblasts into erythrocytes is accompanied by inhibition of replication and transcription. Fully repressed (both in transcription and replication) chicken erythrocyte chromatin is modified at poly(dA) sequences with the same efficiency as does chromatin isolated from regenerating rat liver. This suggests that activation of replication and transcription does not increase the accessibility of poly(dA) sites of DNA to complementarily addressed modification.⁶⁸

It has been shown that the presence of a nuclear membrane is not an obstacle to the penetration of the oligonucleotide inside the cell. The degree of modification of DNA in both intact nuclei and the 'suspension' chromatin obtained by mechanical disintegration of the nuclear membrane are nearly identical. Therefore, it would be logical to suppose that the existence of unwound sites of DNA containing the targets is most likely determined by the level of superhelicalisation of DNA and the structural and functional characteristics of chromatin.

It is known that in contrast with suspension chromatin and intact nuclei, the soluble fraction of chromatin in a buffer containing no bivalent metal ions is largely represented by unwound nucleosome strands. The degree of modification of DNA of the 'soluble' fraction was one order of magnitude lower than that of the 'suspension' chromatin and intact nuclei.⁷⁶ This result may be due to the presence in the latter of loop-shaped structures formed by DNA fibrils fixed on the nuclear matrix (which enhances superhelicalisation of DNA) and nonhistone proteins.

Evidence for the role of superhelicalisation of DNA in addressed alkylation of chromatin can be also derived from the dependence of the relative degree of DNA modification in intact nuclei on ionic strength. An increase in NaCl concentration up to 0.15–0.2 M is accompanied by a decrease in the degree of modification of DNA.⁶⁷ In this concentration range, the activity

of endogenous topoisomerase I, which favours relaxation of the superhelical conformation of DNA, is at maximum.

The effect of changes in chromatin structure caused by removal of definite protein groups on the degree of accessibility of DNA for affinity modification was studied in experiments with deoxyribonucleoproteins DNP-0.35, DNP-0.6 and DNP-2.0 obtained from chromatin by treatment with 0.35, 0.6 and 2.0 M NaCl, respectively.

It is known that treatment of chromatin with 0.35 M NaCl yields a fraction of nonhistone proteins containing HMG-proteins. Removal of these proteins from HeLa cell chromatin decreases the relative degree of modification of poly(dA) and (dG-dT)_n sites of DNA by addressed reagents.

Treatment of chromatin with 0.6 M NaCl results in the removal of histone H1 and some nonhistone proteins. The degree of modification may increase under these conditions because the removal of histone H1, which binds to the linker sites of chromatin DNA, results in their liberation. It is these sites that are potentially more accessible to complementarily addressed modification with the chloroalkyl derivative. Treatment of chromatin with 2 M NaCl results in the removal of the majority of nonhistone proteins and of all histones. The relative degree of modification of poly(dA) and (dG-dT)_n sites of DNA decreases, but still markedly exceeds that of isolated DNA. Electron microscopy of DNP-2.0 obtained by such treatment revealed DNA fibrils as loops fixed on the nuclear matrix. Our experimental results may testify to the contribution of specific chromatin proteins preserved in the structure of chromatin after its treatment with 0.6 M NaCl but completely removed by treatment with 2 M NaCl to the appearance of sites in DNA that are accessible for modification and enriched with poly(dA)- and (dG-dT)_n-repeats.

Among alkylating oligonucleotide derivatives, that with a cholesterol residue at its 3'-end manifested the greatest efficiency for modification of DNA from intact nuclei which exceeded that of the oligonucleotide derivative devoid of cholesterol residue by an order of magnitude.⁷⁸

Later it was shown that the alkylating oligonucleotide derivatives modify not only DNA when they form specific complexes with chromatin DNA, but also definite proteins, presumably localised at the site of their interaction with the DNA 'target'.^{76, 77, 79}

Despite intensive investigations into the structure of metaphase chromosomes and interphase chromatin, the topography of chromosomal proteins is still poorly examined. Most often, specific binding of proteins to definite sequences of DNA is carried out by gel filtration or affinity chromatography on columns with immobilised DNA. However, the conditions for complex formation provided by these methods do not strictly simulate the conditions inside the cell. Moreover, they do not reflect the dependence on the DNA conformation stabilised by superhelicalisation or DNA-protein interactions. Therefore, the use of these methods for the study of dynamic changes in the protein environment of DNA sequences in chromatin and regulatory processes is limited. In this context, addressed modification may become promising in the study of protein environment of DNA sequences in the unwound regions of chromatin.

The chromatin proteins subjected to specific modification with oligonucleotide derivatives that are complementary to poly(dA)-, (dG-dT)_n- and Alu-repeats were analysed by gradient SDS electrophoresis. Protein specimens were treated with micrococcal nuclease to destroy the oligonucleotide fragment covalently attached to the protein. This fragment might change the mobility of the modified protein in electrophoresis.

It has been shown that modification with the p(dT)₁₆ alkylating derivative affects at least two major proteins in intact rat liver nuclei with average molecular weights of 19–20 and 27–28 kDa.⁷⁹ Addition of a 10-fold excess (with respect to the reagent) of nonlabelled p(dT)₁₆ results in inhibition of alkylation of these proteins. However, an excess of the oligonucleotide pd(CATGCAAACCTTCCC) having the same length but a

random nucleotide sequence does not interfere with the protein alkylation, which points to the specificity of the interaction of the reagent with the proteins. Such interaction may occur in both the complementary complexes of the oligonucleotide with the target DNA and with proteins showing affinity for oligothymidylate. Analysis of the chromatin protein components alkylated with p(dA)₁₆ and p(dT)₁₆ derivatives revealed them to be the same in both cases. These data suggest that this reaction occurs through the formation of a complementary complex between the oligonucleotide address of the reagent and the corresponding sites of the unwound chromatin DNA.

Interestingly, the protein with the molecular weight of 19–20 kDa is modified with the reagent within both intact chromatin and the DNP complex prepared by treatment of chromatin with 2 M NaCl (DNP-2.0). Hence, this protein can be related to the group of nuclear matrix proteins.⁷⁹

Alkylation of nuclei with the (dA-dC)₆ derivative yields a radically different set of modified proteins. Six proteins (or groups of proteins) are specifically modified with the p(dA-dC)₆ derivative. An oligonucleotide having the same length but a different sequence has no effect on their modification.

Treatment of HeLa cell nuclei with the p(dA-dC)₆ derivative gave a more complex set of modified proteins.⁷⁶ In addition to proteins presumably analogous to modified proteins from rat liver (19.5, 21, 25.5, 31, 33 and > 66 kDa), modification affects a number of other proteins the alkylation of which is not inhibited by an excess of the oligonucleotide. Since inhibition of modification with an excess of the oligonucleotide of the same sequence does not rule out the possibility of alkylation of proteins that are not associated with local unwinding sites but show affinity for the address oligonucleotide, cell nuclei were treated with S1-nuclease (under conditions of cleavage of single-stranded regions of chromatin DNA) to demonstrate the specificity of modification of the proteins in the complementary complex. This study showed that seven proteins presumably localised in local unwinding sites were subjected to specific modification.⁷⁶

Several researchers have demonstrated^{80–83} that natural polyamines (spermine and spermidine) induce the transition of DNA from the *B*- to the *Z*-conformation and stabilise the left-helical *Z*-conformation under physiological ionic conditions. The affinity modification of chromatin and intact eukaryotic (human and rat liver) cell nuclei with the p(dA-dC)₆ alkylating derivative at the (dG-dT)_n-repeats of DNA has been studied under physiological conditions and at high concentrations of spermine and spermidine.⁸⁴ Analysis of chromatin proteins subjected to specific modification with this oligonucleotide derivative revealed that the efficiency of modification of both DNA and the proteins increases in the presence of high concentrations of spermine and spermidine and sharply decreases after preliminary treatment of chromatin with S1-nuclease under conditions of mild hydrolysis of single-stranded regions of DNA. These data testify to the fact that the *B* → *Z* transition is a reason for the presence of unwound sites accessible for the interaction with a complementary oligonucleotide in the DNA containing the (dG-dT)_n repeating units.

Modification of HeLa cell nuclei with the p(dT)₁₆ derivative affects four proteins (19, 47, 61 and > 66 kDa). Their modification is inhibited by an excess of the nonmodified oligonucleotide and by preliminary treatment with S1-nuclease.

Treatment of cell nuclei with the alkylating derivative of pd(TTCTCCTGCCTCAGCCTCTT), which is complementary to the most conservative site of the Alu-repeat, allowed one to identify a number of proteins that are modified apparently during the formation of a complementary complex between the oligonucleotide address and the unwound regions of chromatin DNA. Data from modification with an excess of the free oligonucleotide and its inhibition upon prior treatment with S1-nuclease testify to specific modification of proteins or groups of proteins with molecular weights of 18, 22, 26, 28, 43, 68 and 93 kDa and of two proteins with molecular weights > 94 kDa.

The transition of chromatin from the interphase state to metaphase chromosomes is accompanied by significant structural rearrangements resulting in structures with the maximum level of DNA compactisation. The use of reactive oligonucleotide derivatives for modification of interphase nuclei and metaphase chromosomes clearly demonstrates that the sets of specifically modified proteins for these two chromatin states differ essentially. Thus, the 28 kDa protein is not subjected to modification within chromosomes, while proteins with molecular weights of 27, 31 and 40 kDa, which are not modified within the interphase nuclei, do undergo modification.

Comparison of the sets of the alkylated proteins isolated from the nuclei of intact and regenerating rat liver cells has demonstrated the presence in the latter of two additional modified proteins with molecular weights of 22–23 and 29–30 kDa along with 19–20 and 28–29 kDa proteins.⁷⁹

The differences in the sets of modified proteins can be explained either by changes in their accessibility for alkylation due to the structural rearrangements resulting from activation of chromatin during replication or by changes in the protein environment in the poly(dA) sites of DNA.

In order to make sure that the given set of proteins is not directly related to the chemical nature of the reagents used for their modification, analogous experiments were carried out with p(dT)₁₆ derivatives. In this study, photoactivated fragments carrying an azido group, instead of the alkylating group, *viz.*, XC(O)NH(CH₂)₂NH, where X = 2-NO₂-5-N₃C₆H₃, 4-N₃C₆H₄ and 4-N₃C₆F₄, have been attached to the 5'-ends. The set of modified proteins was practically identical in both cases. The degree of DNA modification with photoactivated reagents was lower, whereas the degree of protein modification was much higher than with the alkylating reagent. In all cases studied, the modification was specific, *viz.*, oligothymidylate, which contained no reactive group, strongly inhibited this process.⁸⁵

Recently it has been established that reagents with a *p*-azidoaniline residue as a photoreactive group stand out among other commonly used photoactivated reagents in terms of specificity. Such reagents have practically no effect on the nucleotide components.⁸⁶ Therefore, the spectrum of proteins modified by the oligothymidylate derivatives carrying a photoreactive arylazido group, 2-NO₂-5-N₃C₆H₃C(O)NH(CH₂)₂NH(pdT)₁₆ (**1**) and 4-N₃C₆H₄NH(CH₂)₄NH(pdT)₁₆ (**2**), have been compared.⁸⁷ Photomodification of intact nuclei isolated from HeLa cells has shown that the degree of modification with the reagent carrying a *p*-azidoaniline residue (**2**) is much higher, while the set of modified proteins is practically identical.

In the same study,⁸⁷ the authors compared the sets of proteins photomodified with reagent **1** within the nuclei isolated from HeLa cells and synchronised at the G₁/S interface and in the S-phase. In this case, the spectra of modified proteins were different, *viz.*, the 160 kDa protein was present only in the nuclei isolated from cells synchronised at the G₁/S interface. This result points to the possibility of usage of photoreactive oligonucleotide derivatives for the analysis of changes in the protein environment in regions containing unwound DNA sequences and for the study of their accessibility in different stages of the cell cycle.

A p(dT)₁₆ derivative which contains simultaneously an alkylating group (CIX) at the 5'-end and a biotin residue (Bio) at the 3'-end of the oligonucleotide [CIX-p(dT)₁₆-Bio] has been synthesised in order to visualise the sites of cross-linking of oligodeoxyribosylthymidylate to chromatin.⁸⁸ Biotin manifests extremely high affinity for streptavidin and its conjugates. It was demonstrated that the introduction of the biotin residue into the 3'-end of the alkylating derivative of the oligonucleotide does not influence its reactivity. The efficiency of DNA modification with both CIX-p(dT)₁₆ and CIX-p(dT)₁₆-Bio is nearly identical. This fact was used to visualise the modification sites by luminescence microscopy. The study was carried out on HeLa cells and on cells of hybrid clones containing human and Chinese hamster chromo-

somes.⁸⁹ Modified cells were treated with the streptavidin–fluorescein isothiocyanate conjugate.

The specific luminescence of nuclei after treatment of hybrid cells was of two types. The luminescence was the most intense in the nucleoli. However, in some cells point luminescence was observed in the sites that are not directly linked with the nucleoli but are discretely distributed over the nucleus volume. This suggests that the regions of active transcription of chromatin (nucleoli) are subjected to the most intense modification, whereas the densely packaged DNA of heterochromatin is inaccessible.

Modification of HeLa cell chromatin has demonstrated that in these cells the common signal elicited by the nucleus is much higher in comparison with hybrid human–hamster cells, apparently as a result of intensive proliferation of HeLa cells. In addition, the genome of a hybrid cell is partly inactivated. Apart from nucleolar and point signals, HeLa cell nuclei display a third type of specific luminescence, namely the luminescence of the near-membrane region of the nucleus where polyA sites are especially abundant.

We have developed⁸⁹ a procedure for visualisation of modification sites in chromatin which is based on *in situ* hybridisation but differs essentially from it. In the case of standard technologies, the preparations used for hybridisation are first fixed to preserve the morphology, after which DNA is denatured for further hybridisation with the probe. This method involves specific modification of a target sequence of DNA within the native chromatin or intact nuclei, which affects only those sequences of DNA that are localised in the sites of its local unwinding.

VI. Conclusion

In-depth studies of chromatin by chemical methods based on molecular resolution and registration of the dynamic events are still in the initial stage. However, one can see from the above data that chemical approaches make it possible to establish the fine structure of nucleoprotein complexes within chromatin, to identify even the interacting amino acid residues in the case of protein–protein contacts and the interacting amino acid and nucleotide residues in the nucleoproteins. A methodology has been developed for establishing these contacts for one of the most essential functional processes, *viz.*, the transition of chromatin into a transcriptionally active state. There is no doubt that these approaches will gradually progress to hold a central position in the study of other vital processes, such as replication, repair and recombination.

Another important feature of chemical methods is the possibility to detect new components of nucleoprotein complexes as can be evidenced from the discovery of two novel proteins interacting with the promoter sites of the hsp gene. At present, separation of hundreds of proteins by two-dimensional electrophoresis does not present any problem. However, establishing of physical and functional contacts between individual proteins and between proteins and nucleic acids (especially those localised directly in the intact nucleus) is a task which can be successfully solved through the use of chemical approaches.

Finally, the changes in the spectrum of protein contacts observed during activation of transcription in chromatin and interactions of oligonucleotides with proteins in different phases of the cell cycle provide evidence that chemical approaches offer new possibilities for recording the changes that take place during transitions from one state of chromatin to another.

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To the 275th anniversary of the Russian Academy of Sciences

The Russian Academy of Sciences was founded as an ‘assembly of educated people’ by a decree of Peter the Great dated January 28, 1724. The three main goals clearly defined in the decree were (1) production of the scientific knowledge itself, (2) training of scientists and (3) education of young people in the fundamentals of sciences.

It is remarkable that none of these goals has lost its urgency nowadays and the modern Charter of the RAS could easily begin with the decree of Peter the Great. Moreover, Peter the Great thought the activity of the Academy of Sciences in the education sphere to be one of the most important. That is why in 1726, a secular University (a higher-education establishment), later called Academic, which was the first in Russia, was founded by the Academy. Unfortunately, it stopped existing in 1766, despite the efforts of M V Lomonosov, who was the vice-chancellor of the University from 1758 to 1765. Thus, the efforts undertaken now for integration of the fundamental science and higher education are directed to the realisation of the idea put forward by the founder of the Academy of Sciences, of course, in the present-day conditions.

The beginning of the establishment of the chemical science in Russia is associated with the name of M V Lomonosov. Chemical laboratories with analytical, technological and pharmaceutical profiles had also existed in Russia before Lomonosov, but he created the first research chemical laboratory. And what is more, his laboratory had been the prototype of the research institutes of the Academy, which appeared later. This laboratory existed till 1793 in its original form. Then hard times began, when academicians in chemistry had to carry out their research work either in their home laboratories or in the chemists’ shops or higher-education establishments. It was not until the beginning of the XIX century that a room in the main building of the Academy on the Neva quay was allocated for a chemical laboratory. K S Kirchhoff, G I Gess and Yu F Fritzsche carried out their experiments there. After a conflagration in 1859, a new laboratory was built by the initiative of Yu F Fritzsche and N N Zinin in the Eighth Line of the Vasil’evskii island; this building still exists. A M Butlerov, N N Beketov, F F Beilstein, P I Walden, N S Kurnakov and V N Ipatieff also worked in this well-known laboratory.

An Academy printing office and type-foundry were founded during the Peter the Second’s reign. The Academy started spreading its scientific production in publications. In the course of time, the Russian Academy of Sciences started publishing periodicals and monographic editions in various fields of science.

In the early stages, virtually no reviews were published in scientific journals because there was no need for them. However, the increase in the amount of scientific information and the appearance of new fields of science, mostly in border areas, caused the necessity of summarising and analysis of the scientific information.

In 1932, the ‘Uspekhi Khimii’ journal was founded by a decree of the USSR People’s Commissariat on Education in order to ‘publish the major reviews in theoretical and experimental chemistry and chemical technology, which are of high generalising and summarising importance and are the result of creative and critical

thought uniting the latest scientific achievements into a harmonious single whole.’

The early stage of activity of the ‘Uspekhi Khimii’ journal is associated with the names of its founders — N P Gorbunov, A N Bakh, A M Berkengeim, B M Berkengeim, S I Vol’fkovich, N D Zelinsky, N S Kurnakov and A N Frumkin.[†]

The main aim of the journal in those years was to acquaint people with the achievements of the fundamental chemical science and the practical use of them in the national economy. ‘Uspekhi Khimii’ efficiently responded to the needs of the chemical industry in the solution of fuel and energy problems, development of the effective chemical and technological processes, chemisation of agriculture and forestry and development of the mineral-stock base. In particular, an article by A E Fersman entitled ‘New problems in the investigation of mineral raw materials’ was published in the first issue of the journal.

In the initial stage, ‘Uspekhi Khimii’ paid considerable attention to the reviewing of monographs and information material. Reports on scientific sessions and general meetings in the USSR Academy of Sciences, on international conferences and congresses and Mendeleev Congresses on General and Applied Chemistry were published.

From the methodological point of view, the most significant achievement of ‘Uspekhi Khimii’ in its starting period was elaboration of an independent and consistent strategy of reporting on the present-day chemical achievements. This strategy, in particular, was to orient the journal towards the quantitative aspects of various fields of chemistry and elucidation of the physical processes underlying chemical transformations.

Yet another important feature of ‘Uspekhi Khimii’ was the fact that since its foundation, the journal has published not only reviews in chemistry but also those in related branches of science. Papers on X-ray diffraction analysis (W Bragg), Raman spectroscopy (L I Mandel’shtam and G S Landsberg), geochemistry (A P Vinogradov), internal rotation in molecules and rotational isomerism (M V Vol’kenshtein) and the problems of chemical topology (V Prelog) were published in the journal in different years. Being aware of the fact that the progress of chemical science is largely determined by the advances in modern theoretical and experimental physics, the journal published in these years many purely physical reviews of Russian and foreign researchers such as P Debye, E V Shpolsky, F Joliot-Curie, I Joliot-Curie, O Hahn, N Bohr, E Rutherford, E Schrödinger and others. The development of quantum mechanics in these years served as a powerful stimulus for the progress in the classical fields of physical chemistry and for the creation of a new one referred to as chemical physics.

The pre-war decades have been marked by great achievements in the development of chemical physics. The journal showed a great efficiency at publishing the fundamental works on this

[†] A comprehensive analysis of the activity of the ‘Uspekhi Khimii’ journal from 1932 to 1982 can be found in the paper by V A Nikanorov published in issue 11, 1982.

subject, which were performed not only in Russia but also abroad. N N Semenov, D A Frank-Kamenetsky, S Hinshelwood and V N Kondratiev were among its authors.

For a long period, along with the reviews specially written for it, the journal also published translations of articles from foreign review journals. Later, this was no longer necessary and the journal became written mainly by Russian scientists, although some outstanding works of foreign authors still appeared.

The scope of publications in 'Uspekhi Khimii' at that period was extremely broad. It included organic chemistry (the reviews by N Ya Dem'yanov and M Tiffeneau on the molecular rearrangements of cyclic hydrocarbon systems discovered by them), coordination chemistry (works by I I Chernyaev and A A Grinberg), the chemistry of organometallic compounds (A N Nesmeyanov and K A Kocheshkov), geochemistry (A P Vinogradov), and the polymer chemistry (H Staudinger and W Carothers).

It is typical that in different years, the journal has published reviews by almost all the winners of the Nobel Prize in chemistry.

The 1930s were characterised by intense development of the chemistry of natural compounds. Suffice it to say that during fifteen pre-war years, about ten Nobel Prizes were awarded in this field. The majority of the laureates appeared in the pages of 'Uspekhi Khimii' with their reviews: A Windaus (sterols), P Karrer (carotenoids and flavins, vitamins A and B₂), R Kuhn (carotenoids and vitamins of group B), A Butenandt (hormones) L Ružička (polymethylenes and higher terpenoids), and H Wieland (cholic acids and oxidative dehydrogenation in the series of natural products).

During the post-war years, the journal published reviews by R Robinson (study of plant anthocyanines), R B Woodward (vitamin B₁₂ and the development of the chemistry of natural substances), A Todd (nucleotides and coenzymes), D Crowfoot-Hodgkin (X-ray diffraction analysis of protein crystals) and I N Nazarov (the chemistry of vinylethynylcarbinols).

In the pre-war and post-war years, the journal published a series of important reviews by N D Zelinsky, A A Balandin, B A Kazansky, N I Kobozev and A V Frost devoted to various aspects of catalysis and catalytic transformations.

During the war and the first post-war years, the size of scientific publications in 'Uspekhi Khimii' diminished but the information and bibliographic material was exceptionally diversified.

In the 1950s and the 1960s, vigorous development of chemical science and industry started. The size of the journal in that period increased and the activity of the Editorial Board, which directed the journal to new lines of research in chemistry and promising related branches of science, was enhanced.

One new branch of science was the chemistry of organoelement compounds. Beginning with the paper by A N Nesmeyanov entitled 'The organoelement compounds and the Periodic system,' which appeared just after the war, the journal has regularly published reviews on various aspects of the chemistry of organoelement compounds.

The chemistry of polymers was yet another priority of the journal in the 1960s; various aspects of this branch of chemistry have been considered in reviews by V A Kargin, V V Korshak and other scientists.

The 1960s were marked by one more event important for the journal. Since 1960, it started to be translated into English under the title 'Russian Chemical Reviews'; this significantly broadened the area in which the journal was distributed and gave the possibility for the foreign readers to get acquainted more extensively with the achievements of Russian scientists.

When observing the present-day period of activity of 'Uspekhi Khimii,' it is necessary to mention the truly avalanche-like growth of the size of primary information accompanied by an increase in its difficulty and weight. In this connection, review journals become even more important. In addition, a modern review

journal is not only to inform the reader on the new scientific achievements but also to orient him correctly and neatly.

An important quality characteristic of review scientific literature is the so-called 'data compression index,' which is the ratio of the size of primary information to the size of the review. As early as 1936, this coefficient for the 'Uspekhi Khimii' journal was equal to 20 and by 1976, it reached 50, which is considered by specialists to be the optimum value. On further increase in this index, the information may become distorted.

Yet another quantitative parameter for estimating the quality and topicality of scientific publications is the 'citation index'. It is not by chance that the highest citation index among all the chemical periodicals belongs to 'Chemical Reviews'. Regarding this index, the 'Uspekhi Khimii' journal occupies a honourable place among other journals with similar subject matter all over the world and has the highest citation index among all the chemical periodicals in Russia.

The citation index sharply increased after the English version of the journal started being published by the Russian Academy of Sciences together with the Royal Chemical Society of the UK in 1993. The English version of the journal is an exact translation of the Russian one and appears almost simultaneously with it.

The whole size of the journal is approximately 1200 pages per year, which makes up 12 issues. Each issue contains 4 to 6 reviews. From 1996 the reviewing of the papers has become stricter (two Russian referees and one British referee), which contributes to the quality of publications.

Since 1997, in addition to the hard copy of the journal, an electronic version has also been produced. Annual archive CD-ROM's are also produced. Undoubtedly, all this is favourable for the popularity and availability of the journal.

At present, the journal publishes reviews on the following fields of chemistry: molecular structure and quantum chemistry, chemistry of coordination compounds, analytical chemistry, chemical physics, physical chemistry (including catalysis), organic and organometallic chemistry, chemistry of macromolecules, biochemistry and bioorganic chemistry and materials science.

The majority of papers published in the last years have been submitted by scientists working in the RAS or in the Academies of Sciences of the CIS countries. The geographic area in which the authors of the journal work is quite large. Moscow together with some nearby scientific centres (Chernogolovka, Pushchino) comes first in the number of articles published, St. Petersburg occupies the second place.

The 'Uspekhi Khimii' journal makes a significant contribution to the development of the chemical science in Russia and to popularisation of the achievements of the Russian science abroad. It properly represents the Russian Academy of Sciences, which celebrates its 275th anniversary.

Molecular ferromagnets

V I Ovcharenko, R Z Sagdeev

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Abstract. The state-of-the-art, achievements, problems and prospects of an actively developing area of supramolecular chemistry, viz., the design of molecular ferromagnets, are considered. The bibliography includes 343 references.

I. Introduction

This review deals with a rapidly developing area of modern chemistry, viz., the design of molecular ferromagnets. Like any other area of natural sciences which is still in its infancy, it is not yet liable to generalisations, as many works are pioneering. Various approaches are used to solve the diverse problems arising in these studies, which require a high level of integration of the efforts of specialists in different fields of knowledge. Nevertheless, certain approaches to the design of molecular ferromagnets have now taken shape.^{1–18}

It is obviously impossible for a single review to consider every aspect of the design of molecular ferromagnets in detail. Therefore, in this paper we dwell on the basic classes of the chemical compounds which are characterised by established synthetic strategies and the principal ways for the construction of highly dimensional multispin systems.

When the development of methods for the synthesis of highly dimensional systems is concerned, one has, to some extent, to part with the classical chemical thinking, which generally deals with the design, modification or transformation of an individual molecule. No doubt, a molecule taken as a subunit is also important. However, the arrangement of the molecules is no less important in the design of molecular ferromagnets. Even more important is their selective arrangement in a highly dimensional assembly. Arrangement of individual molecules in a highly effective assembly bound by exchange interactions is a key problem in the design of molecular ferromagnets. Before we start a detailed discussion of this problem it is necessary to define the notion of a 'molecular ferromagnet'.

The term 'molecular ferromagnet' may seem to a certain degree paradoxical. The classical ferromagnet is a macroobject, for example, a piece of iron, nickel, or cobalt or an alloy of these metals, but in no way a separate molecule. By its very nature, a magnetic phase transition into the ferromagnetic state is a cooperative phenomenon inherent in a macroobject as a phase. Nevertheless, in recent years the term 'molecular ferromagnet' has been widely used in scientific publications dealing with the design of multispin systems.[†] Let us define the essence of this term more precisely.

The studies in the field of molecular ferromagnets deal with the synthesis of organic, organometallic and, currently, mostly coordination compounds the solid phases of which are formed from separate molecules or ions that existed initially in a solution and contained paramagnetic centres. In these solid phases, as in classical ferro- and ferrimagnets or weak ferromagnets, magnetic phase transition into the ferro-, ferrimagnetic or weak ferromagnetic state is detected below a critical temperature.

These days, researchers can plan beforehand, with a certain degree of success, the synthesis of compounds with a desired solid state structure that will be formed from molecular precursors in solution. These molecules should form layered or framework polymers when crystallised from solution. As a matter of fact, this field of studies which implies the design of highly dimensional structures is the subject of supramolecular chemistry.

The formation of layered or framework structures in the solid phase of molecular ferromagnets is a prerequisite for the magnetic phase transition into the ferromagnetic state. This condition is necessary but insufficient in the chemical design of molecular ferromagnets. For this transition to occur, the paramagnetic centres in polymers should be linked with such an atomic chain serving as an exchange channel¹³ that the polymer has the ability to undergo magnetisation in a magnetic field. The following consideration is important in this case: the higher the efficiency of the exchange channels in exchange interactions between the unpaired electrons of the paramagnetic centres the higher critical temperature (T_c) that can be achieved. It is within the limits set by these requirements that regular studies of the effect of conditions of directed chemical synthesis on the magnetic parameters (the

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[†] Reviews and monographs on 'molecular ferromagnets' have been published, the titles of which, like the present paper, sometimes contain this word combination (or the equivalent expressions: 'molecular magnetics', 'molecular magnets', 'molecule-based ferromagnets') as the key words.^{1–14}

Curie temperature or the Neel temperature, spontaneous magnetisation, *etc.*) of the final magnetically active product are being performed, *i.e.*, the effects of the composition, structure of the starting molecules, conditions of the synthesis and crystallisation on the magnetic properties of the resulting solid phases are being studied. Magnetic-structural relationships understood as relationships between the observed magnetic properties of a compound and its chemical and structural characteristics are used in the search for subjects with the required properties. These relationships are either calculated or determined experimentally.

Thus, the word 'ferromagnet' in the term 'molecular ferromagnet' is used in the ordinary sense, while the definition 'molecular' reflects the methodology of the approach: the starting individual molecules and/or molecular ions should have a structure which would enable them to form a spatial structure favourable for a magnetic phase transition during formation of a solid phase. The problem can be solved by various chemical methods combined by the term 'chemical design of molecular ferromagnets'.

The development of principles for the synthesis of molecular ferromagnets and the determination of their inherent magnetic-structural relationships are fundamental problems. There are few natural magnetic materials. Most of them are transition metals and their oxides; the number of magnetic materials was mainly increased by virtue of metal alloys and binary oxides. However, studies on the design of molecular ferromagnets make it possible to expand considerably the range of magnetically active compounds and magnetic materials. In addition, the design of molecular magnets and conventional, mild synthetic approaches provide a possibility to create new magnetic materials using technologies alternative to the traditional power-consuming metallurgical technologies for the production of magnetically active oxides materials.

The number of studies in the field of the design of molecular ferromagnets increases rapidly. Owing to the aforementioned high integration requirements concerned with the problem, experts in the field of inorganic, organometallic or organic chemistry and in materials science, chemical physics and physics of magnetism are involved in collaboration. The results of these studies are extremely 'scattered' in scientific publications; therefore, biennial international conferences on molecule-based magnets play an important uniting role (see, *e.g.*, Refs 15 and 16). The proceedings of these conferences are published in the journal *Molecular Crystals and Liquid Crystals* (see, *e.g.*, Refs 17 and 18). However, these are far from being the only international conferences with scientific sections devoted to molecular ferromagnets (see, *e.g.*, Refs 19 and 20).

In this review, we made an attempt at the generalisation and systematisation of the main approaches and strategies existing at present in the field of the synthesis of molecular ferromagnets. As a rule, the design of particular compounds triggers an entire complex of studies dealing with the analysis of structure, magnetic-structural relationships and mechanisms of exchange interactions between the unpaired electrons in paramagnetic centres. In all of the molecular ferromagnets discussed in the present review the structure of a molecule or a bridging ligand involves at least one carbon atom. The presence of one carbon atom, or better several carbon atoms, reflects the common desire of the researchers to use as soon as possible all the potential of synthetic organic chemistry in the given area.

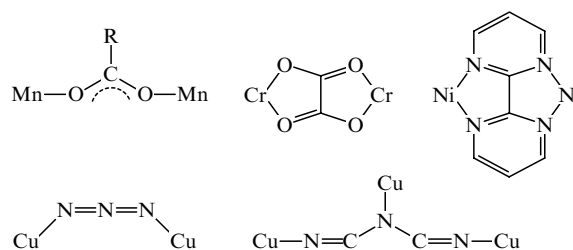
Here we do not consider the classical magnetically active systems in which the metal atoms in the solid phase are separated by the individual oxygen, carbon, sulfur, halogen or boron atoms.

II. Systematisation principles

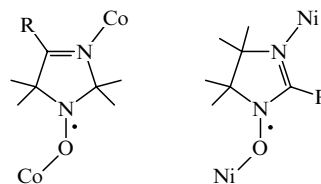
For a systematic generalisation of chemical compounds involved in the design of molecular ferromagnets, we offer a specific

'language'. It is therefore reasonable to discuss the principles underlying its construction. In this work we speak of metal-containing molecular ferromagnets as being two or three-dimensional systems (as regards their structures);[‡] hence the common features of all of the systems under consideration are the presence of a paramagnetic metal ion in a compound and the presence of a bridging group of atoms linking the metal ions to form a layer or a framework. Therefore, the description of a particular system can be given by the key formula M_nM' , where M and M' are paramagnetic metal ions (the same, different or existing in different oxidation states) and n is the smallest number of atoms in a bridging unit connecting the M and M' ions.

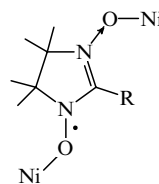
Thus, we shall refer cyanide complexes of metals containing, *e.g.*, such fragments as $V^{3+} - C \equiv N - V^{3+}$, $Cr^{3+} - C \equiv N - Ni^{2+}$ and $Fe^{2+} - C \equiv N - Fe^{3+}$ to the $M2M'$ class, since the bridging cyanide is a diatomic unit. Carboxylate, oxalate, bipyrimidine, azide or dicyanamide polynuclear complexes containing triatomic bridges as the shortest ones belong to the $M3M'$ class.



According to the above approach, the complexes with 3- and 2-imidazoline derivatives are regarded as $M4M'$ systems.

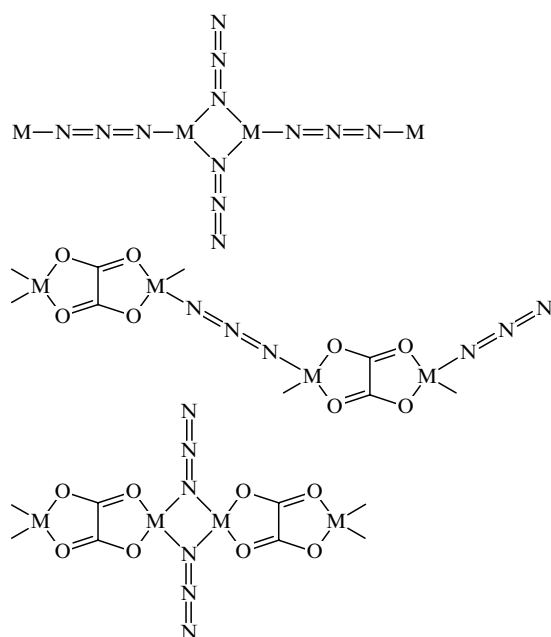


Heterospin polynuclear metal complexes with nitronyl nitroxyl radicals or 2-imidazoline 3-oxide paramagnetic derivatives, which play the bridging role, belong to the $M5M'$ systems.



More complicated situations are also possible where one bridging ligand can form exchange channels with different numbers of atoms between the metal ions or the bridging function is played by several ligands creating the exchange channels with different numbers of bridging atoms. We designate such systems as $MnnM'$, if the ligands are the same, and $Mn(n')M'$ if the ligands are different. Fragments of an $M31M'$ system with one ligand and $M3(3)M'$ and $M3(1)M'$ systems with different bridging ligands are shown below as examples.

[‡] It should be noted that structural dimensionality, *i.e.*, molecular (zero-dimensional), chain (one-dimensional), layered (two-dimensional) and framework (three-dimensional) compounds, should not be confused with magnetic dimensionality, *i.e.*, isolated exchange clusters (zero-dimensional), exchange chains (one-dimensional), *etc.*; in many cases, the structural and magnetic dimensionalities do not correlate.

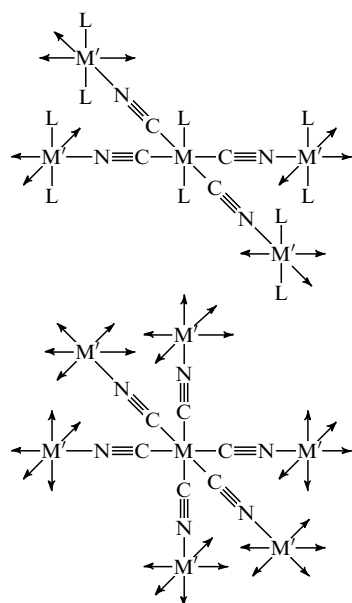


The systematisation suggested here is general and is not limited to specific metal ions or bridging ligands.

III. M2M' systems

The molecular ferromagnets of the M2M' class primarily include coordination compounds with the bridging cyanide ligands. The ability of homo- and heterometallic hexacyanides to undergo ferro- and ferrimagnetic ordering at low temperatures has been known for a long time (see, *e.g.*, Refs 21 and 22). However, the problem was recently considered in a different way^{23–31} and an essentially new contribution to the design of high-temperature molecular ferromagnets of the M2M' type based on metal cyanide complexes was made.

The first synthetic coordination compound, *viz.*, Prussian blue, whose framework structure was established by Buser *et al.*,³² may be considered as an ancestor of this group of molecular ferromagnets. The highly symmetrical octahedral coordination anion $[\text{M}(\text{CN})_6]^{n-}$ serves as a starting block for the construction of two- and three-dimensional structures.³³ If an additional M' ion is introduced, the system can undergo polymerisation along two or three mutually perpendicular directions.



Prussian blue itself, $\text{Fe}_4^{\text{III}}[\text{Fe}^{\text{II}}(\text{CN})_6]_3 \cdot x\text{H}_2\text{O}$ ($x = 14–16$), has a framework structure (cubic face-centred structure) and undergoes a magnetic phase transition at 5.6 K.³⁴ The low temperature of the magnetic ordering is due to the fact that the Fe^{II} ion is in the low-spin d^6 state. As a result, the exchange interactions between the paramagnetic centres (the Fe^{III} ions) located in the $\text{Fe}^{\text{III}}-\text{N}\equiv\text{C}-\text{Fe}^{\text{II}}-\text{C}\equiv\text{N}-\text{Fe}^{\text{III}}$ fragments at a distance of 10.6 Å from each other are rather weak.²⁶ Thus, it seemed reasonable to assume that the magnetic ordering temperature will be higher if all of the metal ions are paramagnetic. Verdaguer *et al.*,^{23–31} were the first to perform a directed synthesis of Prussian blue analogues in which the iron ions were replaced by other metal ions in variable ratios. Table 1 presents some data for hexacyanometallates of the general formula $\text{M}_3[\text{M}'(\text{CN})_6]_2$ from which it is possible to follow the regularities of changes in the magnetic ordering temperature (we do not specify its type, *i.e.*, ferromagnetic, ferrimagnetic or antiferromagnetic).

Table 1. Magnetic ordering temperatures for hexacyanometallates $\text{M}_3[\text{M}'(\text{CN})_6]_2$.

M	T_c /K	M	T_c /K
$\text{M}_3[\text{Cr}(\text{CN})_6]_2$		$\text{M}_3[\text{Mn}(\text{CN})_6]_2$	
V^{II}	315	Mn^{II}	37
Cr^{II}	240	Ni^{II}	37
Cu^{II}	66		
Mn^{II}	60	$\text{M}_3[\text{Fe}(\text{CN})_6]_2$	
Ni^{II}	53	Cu^{II}	20
Co^{II}	23	Mn^{II}	9
Fe^{II}	16	Ni^{II}	23
		Co^{II}	15

In a series of complexes containing the $[\text{Cr}(\text{CN})_6]^{3-}$ anions, the values of T_c are always higher than those for the analogues with the $[\text{Mn}(\text{CN})_6]^{3-}$ or $[\text{Fe}(\text{CN})_6]^{3-}$ anions; the highest T_c values are observed for $\text{V}_3[\text{Cr}(\text{CN})_6]_2$ and $\text{Cr}_3[\text{Cr}(\text{CN})_6]_2$. The latter is commonly depicted as $\text{Cr}_5(\text{CN})_{12}$. Thus, there is an obvious trend of the increase in the critical temperature if the compounds involve V^{II} , Cr^{II} and Cr^{III} containing a significant number of unpaired electrons in the t_{2g} orbitals. Hexacyanometallates $(\text{Et}_4\text{N})_{0.5}\text{Mn}_{1.25}[\text{V}(\text{CN})_5](\text{H}_2\text{O})_2$ ($T_c = 230$ K), $\text{Cs}_2\text{Mn}[\text{V}(\text{CN})_6]$ ($T_c = 125$ K),³⁰ $\text{Cs}_{0.75}[\text{Cr}_{2.125}(\text{CN})_6]$ ($T_c = 190$ K)²⁵ characterised by high T_c also contain the V^{II} or Cr^{II} ions, which is not quite convenient from the practical viewpoint as they are unstable in this oxidation state under ordinary conditions. Nevertheless, the compound $\text{V}_{0.42}^{\text{II}}\text{V}_{0.58}^{\text{III}}[\text{Cr}^{\text{III}}(\text{CN})_6]_{0.86} \cdot 2.8\text{H}_2\text{O}$ with $T_c = 315$ K obtained in an inert atmosphere (it is sensitive to the atmospheric oxygen) retains its magnetic properties for several weeks when dispersed in kerosene or mixed with a glue.²⁷ Based on this compound, a thermomagnetic switch and a device for the absorption of solar energy were designed and these were shown to function properly.^{24, 35}

The character of exchange interactions in the $\text{M}-\text{N}\equiv\text{C}-\text{M}'$ clusters can be predicted with high reliability under the assumption that these interactions between the unpaired electrons on the e_g orbitals of one metal and the unpaired electrons on the t_{2g} orbitals, orthogonal to the former, of another metal should be ferromagnetic, while the interactions between the unpaired electrons on the t_{2g} orbitals of both metals should be antiferromagnetic.^{23–25, 36, 37} By calculating the number of possible channels of exchange interaction according to the ferromagnetic (F) and antiferromagnetic (AF) mechanisms, it is possible to predict the character of ordering in the solid phase of a specific hexacyanometallate. Below the critical temperature, ferromagnetic ordering

of the spins of the paramagnetic centres predominates if $F > AF$, and antiferromagnetic ordering predominates if $AF > F$.

According to this scheme, in all of the hexacyanometallates with $T_c > 100$ K discussed above, where the $t_{2g}-t_{2g}$ interactions predominate and the exchange interactions between the paramagnetic centres of the neighbouring metal ions are antiferromagnetic, the magnetic moments of the sublattices of one metal ion are partially compensated by the magnetic moments of the sublattices of the other metal ion below the critical temperature. In systems of the type $Ni_3[Cr(CN)_6]_2$ and $Cu_3[Cr(CN)_6]_2$, the unpaired electrons lie on orbitals of different symmetries (e_g and t_{2g}), and the exchange interactions between the paramagnetic centres in these systems are ferromagnetic, which is favourable for the synthesis of compounds with high spontaneous magnetisation.²³

The results obtained²³⁻³¹ stimulated the study^{38,39} of a series of solids $(Ni_xMn_{1-x})_{1.5}[Cr^{III}(CN)_6] \cdot 8H_2O$. The solids with this composition were obtained in two ways:

(1) by mechanically mixing pure $Ni_{1.5}[Cr(CN)_6] \cdot 8H_2O$ and $Mn_{1.5}[Cr(CN)_6] \cdot 7.5H_2O$; in the former, the unpaired electrons of the neighbouring paramagnetic centres (Ni^{II} , Cr^{III}) are coupled by ferromagnetic exchange interactions [the exchange interaction integral (J) is positive]; in the latter, the spins of the neighbouring centres (Mn^{II} , Cr^{III}) mostly interact antiferromagnetically ($J < 0$);

(2) by mixing at the molecular level, *i.e.*, in the synthesis of $(Ni_xMn_{1-x})_{1.5}[Cr^{III}(CN)_6] \cdot 8H_2O$; the value of x was set by the initial ratio of the reagents $NiCl_2$, $MnCl_2$ and $K_3Cr(CN)_6$.

As expected, the characteristics of the mixture obtained by the former method are additive values proportional to the fractions x and $1-x$ of the mixed compounds; for example, the magnetisation of the mechanical mixture grows linearly as x increases from 0 to 1. The variation of the characteristics of the phase obtained by the latter method (magnetisation, the Weiss temperature, coercive field) with x is essentially different due to the competition between the ferro- ($J > 0$) and antiferromagnetic ($J < 0$) interactions. As a result, *e.g.*, the spontaneous saturation magnetisation (J_s) quickly decreases from $4.38 \mu_B$ to almost zero when x increases from 0 to 0.43; when x increases from 0.43 to 1, J_s quickly increases from ~ 0 to $5.57 \mu_B$ according to the equation

$$J_s = 2\mu_B \left[\frac{3}{2} + \frac{3[x - 2.5(1-x)]}{2} \right].$$

The coercive field is a maximum (680 G) at $x \simeq 0.43$ where the parallel spins of Cr^{III} and Ni^{II} are almost completely compensated by the antiparallel spins of Mn^{II} . For this reason, the experimental temperature dependences of magnetisation for the $(Ni_{0.38}Mn_{0.62})_{1.5}[Cr^{III}(CN)_6] \cdot 8H_2O$ phase coincided with the theoretical Neel curves: when measurements were carried out in an external field of 1000 G (stronger than the coercive field), the $J_s(T)$ dependences contained two maxima, while in an external field of 10 G (weaker than the coercive field) one maximum was observed and the curve intersected the abscissa axis (*i.e.* the magnetisation sign changed) at ~ 40 K. (It should be noted that at $x = 0$ or 1, the magnetisation of the specimens below the critical temperature increased monotonically as the temperature was decreased; these measurements were carried out in a field of 1000 G.) As a result, the magnetisation of a specimen at temperatures below 40 K was positive in an external magnetic field of $H > H_c$ and negative in a field of $H < H_c$.

Thus, it was shown^{38,39} that by varying the composition of a compound by chemical methods, it was possible to obtain phases in which the direction of the magnetic poles of the species was changed under the effect of an external magnetic field.

The critical temperatures of Prussian blue analogues capable of magnetic ordering can also be changed by electrochemical⁴⁰ or optical stimulation.⁴¹ In the latter case, consecutive irradiation of, *e.g.*, $K_{0.2}Co_{1.4}[Fe(CN)_6] \cdot 6.9H_2O$ with red ($\lambda = 660$ nm) and blue ($\lambda = 450$ nm) light at a sufficiently low temperature (5 K) made it possible to increase and then to decrease the magnetisation of the

specimen; this is of undoubted interest for those engaged in the development of magnetic-optical memory blocks. Pioneer studies^{40,41} showed that the targeted selection of photosensitive hexacyanometallates can be carried out by molecular design. Japanese researchers implemented light-controlled inversion of magnetic poles on specimens of the mixed ferri-ferromagnet $(Fe_{0.4}Mn_{0.6})_{1.5}[Cr(CN)_6] \cdot 7.5H_2O$ ⁴² and developed a technology for growing thin coloured magnetic films of $(Fe_xCr_{1-x})_{1.5}[Cr^{III}(CN)_6] \cdot zH_2O$ on electrode surfaces.⁴³

A principle for the synthesis of hexacyanometallates with high critical temperatures was suggested.^{25,30} It was found in studies of specific hexacyanometallate series that the synthesis of molecular ferromagnets (structural analogues of Prussian blue) should be based on ions of the first transition period metals (V^{II} , V^{III} , Cr^{II}), despite their small stability under ordinary conditions. Comparison of the magnetic properties of $Cs_2Mn^{II}[V^{II}(CN)_6]$ (see Ref. 30) with those of $CsMn^{III}[Cr^{III}(CN)_6] \cdot H_2O$ (see Refs 44 and 45) and $Mn^{II}[Mn^{IV}(CN)_6] \cdot xH_2O$, which are isostructural to the former, is indicative in this respect (see also Table 1).⁴⁶ All the three compounds contain Mn^{II} ions in the high-spin d^5 configuration in a weak ligand field (N_6 -octahedral coordination environment) and metal ions in the d^3 configuration (V^{II} , Cr^{III} and Mn^{IV}) located in a strong ligand field (C_6 -octahedral coordination environment).

The basic difference between the compounds of this period is that the energy of the t_{2g} orbitals for d^3 ions decreases with an increase in the element atomic number, *i.e.*, on going from V^{II} to Cr^{III} and then to Mn^{IV} . For example, the magnetic ordering temperatures of 125, 89.8 and 48.7 K for $Cs_2Mn^{II}[V^{II}(CN)_6]$, $CsMn^{III}[Cr^{III}(CN)_6] \cdot H_2O$ and $Mn^{II}[Mn^{IV}(CN)_6] \cdot 1.14H_2O$, respectively, show that the introduction of a d^3 transition metal ion with higher energies of the t_{2g} orbitals results in compounds with higher temperatures of the magnetic phase transition into the ferromagnetic state. In other words, the more effective the dative bonding of the bridging cyanide ligands due to bonding of their π^* orbitals the higher the energy of interaction between the spins of the neighbouring paramagnetic centres. In addition, the increase in the energy of exchange interaction between the unpaired electrons of the neighbouring paramagnetic centres is known to correlate with the increase in the magnetic ordering temperature.⁴⁷

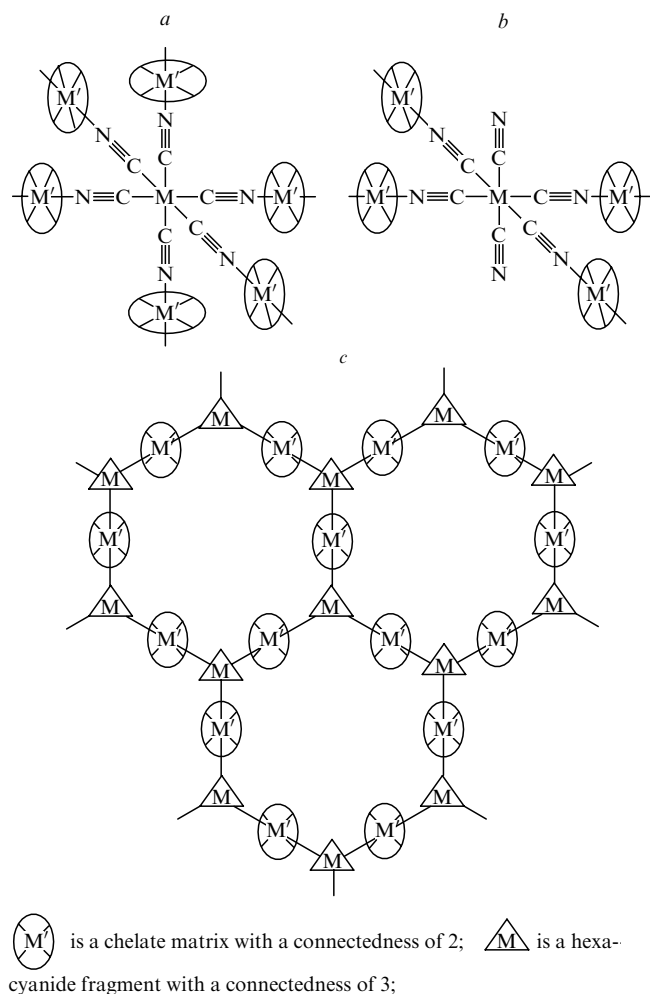
Unfortunately, it has to be noted that the technique for the synthesis of hexacyanometallates as single crystals of high quality, which is important for a detailed study of magnetic-structural relationships, has not been developed yet. As a rule, conclusions on the structure of compounds are based only on the analysis of powder diffractograms. In addition, all Prussian blue analogues with a cubic symmetry of the crystal structure do not manifest magnetic anisotropy.⁴⁸ These facts stimulated the synthesis of other cyanide complexes. Of the studies in this field, it is necessary to note the synthesis of the first paramagnetic tetrahedral cyanometallate $[Ph_3P=N=PPh_3]_2[Mn^{II}(CN)_4]$ the structure of which has been established completely.⁴⁹ Based on this compound, $Mn^{II}[Mn^{II}(CN)_4]$ having a interpenetrating diamond-like structure was obtained.⁵⁰ By itself, $Mn^{II}[Mn^{II}(CN)_4]$ is ordered antiferromagnetically, but the authors have a good reason to believe that representatives of the future family $M'[Mn^{II}(CN)_4]$ ($M' \neq Mn^{II}$), unlike $Mn^{II}[Mn^{II}(CN)_4]$, should have uncompensated spins and should behave as ferrimagnets below T_c . Single crystals of $Mn_2(H_2O)_5[Mo(CN)_7] \cdot 4H_2O$ (α -phase) and $Mn_2(H_2O)_5[Mo(CN)_7] \cdot 4.75H_2O$ (β -phase) were obtained by slow mutual diffusion of deoxygenated solutions of $K_4[Mo^{III}(CN)_7] \cdot 2H_2O$ and $Mn(NO_3)_2 \cdot 6H_2O$ in a nitrogen atmosphere.⁴⁸ Both phases are monoclinic and have the same temperature of magnetic phase transition into the ferromagnetic state (51 K). The phases are unstable in air, but in special experiments it was possible to detect strong magnetic anisotropy on single crystals of the α -phase.

Thus, the transition from Prussian blue analogues with cubic structure to less symmetrical compounds has expanded the range of magnetically active polymeric cyanometallates with strong

anisotropy of magnetic properties. Compounds of this type are still rather rare, but their number increases gradually. A two-dimensional heptacyanomolybdate-based polymer, *viz.*, $\text{KMn}_{1.5}(\text{H}_2\text{O})_3[\text{Mo}(\text{CN})_7] \cdot 3\text{H}_2\text{O}$ grown as single crystals,⁵¹ and octacyanometallates $[\text{M}(\text{CN})_8]^{3,4-}$, where $\text{M} = \text{Nb}^{\text{IV}}, \text{Mo}^{\text{V}}$ or W^{V} , were reported at the Sixth Conference on molecular ferromagnets. The latter also undergo magnetic phase transition at rather high temperatures, *viz.*, at ~ 40 K for $\text{Cu}_3[\text{W}(\text{CN})_8]_2 \cdot 3.4\text{H}_2\text{O}$ and at ~ 50 K for $\text{Ni}_3[\text{W}(\text{CN})_8]_2 \cdot n\text{H}_2\text{O}$.⁵²

A problem in the design of molecular ferromagnets based on cyanometallates is that the cyano group, which is a bridging ligand, cannot be functionalised. As a matter of fact, this limits the possibilities of synthetic organic chemistry in the design of molecular magnets to the variation of the metal ions. The situation can be improved if some of the metal ions have previously been 'dressed in a coordination coat' in such a way as to reserve coordination sites for the approach of bridging cyanide groups. Certainly, the number of bonds between such metal ions and the bridging cyanide ligands is decreased, but the coordination environment acquires the possibility to affect the electronic structure of M' and the steric structure (and hence the magnetic characteristics) of the compound as a whole. Scheme 1 shows the simplest versions of the formation of three- or two-dimensional polymeric structures with M and M' ions alternating along different directions, *viz.*, the framework motif (*a*),⁵³ the square (*b*)^{54, 55} and the honeycomb (*c*) lattices.⁵⁶

Scheme 1



In fact, the situation can turn out to be much more complex. In a hybrid version of the design of molecular ferromagnets based on a hexacyanometallate of one metal and a chelate of another,^{54, 57, 58} the reaction of $\text{K}_3[\text{Fe}(\text{CN})_6]$ with *trans*- $[\text{NiCl}_2(\text{en})_2]$ (where en is ethylenediamine) gave the complex

$[\text{Ni}(\text{en})_2]_3[\text{Fe}(\text{CN})_6]_2 \cdot 2\text{H}_2\text{O}$, whose structure was characterised. It was found that in the solid phase, only three of the six cyanide ligands in the $\text{Fe}(\text{CN})_6$ fragments participate in the formation of the bridging bonds with the Ni^{II} ions of the $\text{Ni}(\text{en})_2$ fragments; 2/3 of the $\text{Ni}(\text{en})_2\text{N}_2$ fragments contain a *cis*-coordinated Ni^{II} ion, while 1/3 contain a *trans*-coordinated Ni^{II} ion. As a result, in a crystal polymeric bands are extended along one of the crystallographic axes, while polymeric layers are formed along the other two directions. The interaction between the unpaired electrons in the $\text{Ni}^{\text{II}} - \text{N} \equiv \text{C} - \text{Fe}^{\text{III}}$ fragments, as in the usual hexacyanoferrate $\text{Ni}_3[\text{Fe}(\text{CN})_6]_2$ (see Table 1), is of ferromagnetic character, and at temperatures below 18.6 K the complex $[\text{Ni}(\text{en})_2]_3[\text{Fe}(\text{CN})_6]_2 \cdot 2\text{H}_2\text{O}$ undergoes a magnetic phase transition into the ferromagnetic state.

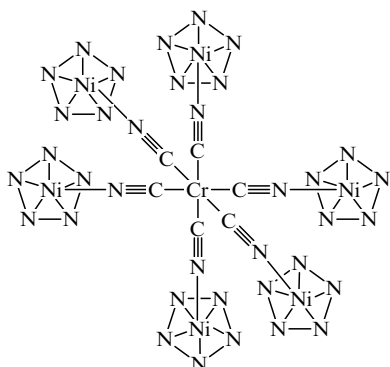
To date, a rather wide range of molecular ferromagnets of this group with various organic ligands have been studied. These include $\text{PPh}_4[\text{Ni}(\text{pn})_2][\text{M}(\text{CN})_6] \cdot \text{H}_2\text{O}$, $[\text{Ni}(\text{pn})_2]_2[\text{Fe}(\text{CN})_6]\text{X}$ and $[\text{Ni}(1,1\text{-dmen})_2]_2[\text{Fe}(\text{CN})_6]\text{X}$, where $\text{M} = \text{Fe}, \text{Cr}$ and Co , pn is 1,2-diaminopropane,⁵⁹ 1,1-dmen is 1,1-dimethylethylenediamine and $\text{X} = \text{ClO}_4^-, \text{BF}_4^-, \text{PF}_6^-, \text{CF}_3\text{SO}_3^-, \text{BzO}^-, \text{I}^-, \text{N}_3^-, \text{NCS}^-, \text{NO}_3^-$ (see Ref. 60) and $[\text{Ni}(\text{tren})]_3[\text{Fe}(\text{CN})_6]_2 \cdot 6\text{H}_2\text{O}$, where tren is the tetradentate tris(2-aminoethyl)amine.⁶¹ Using a classical macrocyclic ligand, 1,4,8,11-tetraazacyclotetradecane (cyclam), the following compounds: $[\text{Ni}(\text{cyclam})]_3[\text{Cr}(\text{CN})_6]_2 \cdot 5\text{H}_2\text{O}$,⁵⁶ $[\text{Ni}(\text{cyclam})]_3[\text{Fe}(\text{CN})_6]_2 \cdot 6\text{H}_2\text{O}$ and $[\text{Fe}(\text{cyclam})][\text{Fe}(\text{CN})_6]_2 \cdot 6\text{H}_2\text{O}$, which are polymeric in the solid phase, have been synthesised and studied.⁶² The efficiency of complexes of trivalent manganese with various polydentate Schiff's bases in the formation of heterometallic complexes with hexacyanometallates $[\text{Mn}(\text{CN})_6]^{3-}$ and $[\text{Fe}(\text{CN})_6]^{3-}$ has been shown.^{63–67} The critical temperatures range from 2 to 16.2 K for the group of compounds studied.

The $[\text{Ni}(\text{bpm})_2]_3[\text{Fe}(\text{CN})_6]_2 \cdot 7\text{H}_2\text{O}$ complex, where bpm is bis(1-pyrazolyl)methane, with a rather high critical temperature has been synthesised and studied.⁶⁸ The solid phase of this compound is formed from pentanuclear heterometallic complexes $[\text{Ni}(\text{bpm})_2]_3[\text{Fe}(\text{CN})_6]_2$ linked into a diamond-like lattice by a system of hydrogen bonds involving molecules of crystallisation water. Although water molecules are generally poor conductors of exchange interactions,^{69–72} high T_c (23 K) has been found for the $[\text{Ni}(\text{bpm})_2]_3[\text{Fe}(\text{CN})_6]_2 \cdot 7\text{H}_2\text{O}$ phase. Dehydration of the compound results in the destruction of the structure and, as a consequence, in the loss of the magnetic ability. This situation is rather typical, *i.e.*, the destruction of a system of hydrogen bonds forming a two- or three-dimensional structure of a compound results in the loss of the ability to undergo magnetic phase transition into the ferro- or ferrimagnetic state.^{73, 74} However, it should not be considered that disintegration of a highly dimensional structure into separate polynuclear exchange clusters always results in zero-dimensional magnetic systems.

In recent years, studies in a specific area of the design of molecular ferromagnets, namely, large exchange clusters, is being developed intensely.^{14, 75–78} Compounds of this type are nanoscale polynuclear molecular particles with a high degree of aggregation, such as $\text{Mn}_{12}\text{O}_{12}(\text{CH}_3\text{COO})_{16}(\text{H}_2\text{O})_4 \cdot 2\text{HOAc}$, $\text{Co}_8\text{O}_4(\text{PhCOO})_{12}(\text{DMF})_4$, $\text{NBu}_4[\text{Mn}_8\text{O}_6\text{Cl}_6 \cdot (\text{PhCOO})_7(\text{H}_2\text{O})_2]$ and $\text{Fe}_{11}\text{O}_6(\text{OH})_6(\text{PhCOO})_{15}$. Large polynuclear complexes arouse interest from the biochemical viewpoint as models of active polynuclear centres in enzymes.⁷⁹ On the other hand, despite the molecular nature of these compounds, the same effects as for the classical bulk magnets, including the original hysteresis loops that appear due to tunnelling effects between multiple spin conditions of different multiplicities, have been observed for them. One can find more details on the magnetic properties of these systems elsewhere, *e.g.*, in Refs 80–88. Almost all of them contain polynuclear complexes with carboxylate, oxo and/or hydroxo bridging ligands.

A new possibility in the design of heterometallic polynuclear molecular complexes with the use of hexacyanometallates discussed above was shown.^{24, 89} The reaction of $\text{K}_3[\text{Cr}(\text{CN})_6]$ with

$[\text{NiL}(\text{H}_2\text{O})](\text{ClO}_4)_2$, where L is tetraethylenepentamine, which blocks five coordination sites in the coordination sphere of Ni^{II} , resulted in $\{\text{Cr}[(\text{CN})\text{NiL}]_6\}(\text{ClO}_4)_9$; its solid phase is formed by heptanuclear molecular exchange clusters $\text{Cr}^{\text{III}}\text{Ni}_6^{\text{II}}$ with ferromagnetic exchange interactions between the Cr^{III} and Ni^{II} ions.



One cannot rule out that new dendritic molecular magnets will be obtained from polynuclear compounds of this type.^{90, 91}

The examples presented above show that the systematic development of methods for the synthesis of polymeric cyanide complexes with paramagnetic metal ions has made it possible to overcome, to a considerable degree, the above-mentioned 'drawbacks' inherent in the nature of Prussian blue analogues and, in addition, to contribute significantly to the supramolecular chemistry of metal cyanide complexes.^{33, 92–100}

IV. $\text{M}_3\text{M}'$ systems

1. Oxalates

The oxalate complexes of metals constitute the most representative group of molecular ferromagnets of the $\text{M}_3\text{M}'$ class.^{101–127} Okawa *et al.*^{101–103} were the first to pay special attention to polymeric heterometallic oxalates. They chose these compounds taking into account the available data on polynuclear complexes with ferromagnetic exchange interactions between the unpaired electrons of the paramagnetic centres located on orbitals of different symmetries.^{37, 104–108} It was thus desirable to obtain two- or three-dimensional heterospin structures 'pierced' by ferromagnetic pair exchange interactions (Fig. 1). It is absolutely unnecessary for a magnetic phase transition that all intra- and intermolecular exchange interactions be exclusively ferromagnetic; however, it should be noted that if only ferromagnetic exchange channels are present in the structure of a compound, higher values of magnetisation can be reached than in the case of

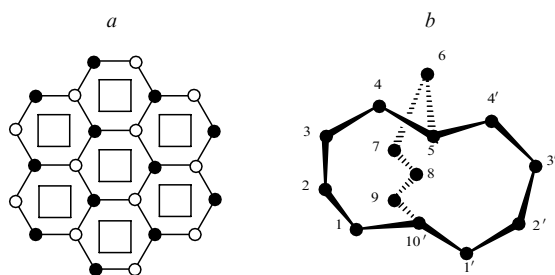


Figure 1. Scheme of the formation of a layered structure (a) and a fragment of framework structure with identical chiral centres (b); (a) 'honeycomb' motif; the light and dark circles indicate the alternating chiral (Λ and Δ) fragments of $\text{M}(\text{ox})_3$ (ox is oxalate); the squares indicate the cavities that can be occupied by spacers (lacking counterions or solvent molecules);¹⁰² (b) 'fused decagons' motif.^{111, 117}

Table 2. Critical temperatures for oxalate complexes.

Compound	T_c / K	Structure dimensionality	Ref.
$\text{NBu}_4[\text{Mn}^{\text{II}}\text{Cr}^{\text{III}}(\text{ox})_3]$	6	2D	102, 109
$\text{NPr}_4[\text{Mn}^{\text{II}}\text{Cr}^{\text{III}}(\text{ox})_3]$	6	2D	114
$\text{PPh}_4[\text{Mn}^{\text{II}}\text{Cr}^{\text{III}}(\text{ox})_3]$	6	2D	112
$\text{NBu}_4[\text{Cu}^{\text{II}}\text{Cr}^{\text{III}}(\text{ox})_3]$	7	2D	101
$\text{NBu}_4[\text{Co}^{\text{II}}\text{Cr}^{\text{III}}(\text{ox})_3]$	10	2D	102
$\text{NBu}_4[\text{Fe}^{\text{II}}\text{Cr}^{\text{III}}(\text{ox})_3]$	12	2D	102
$\text{NBu}_4[\text{Ni}^{\text{II}}\text{Cr}^{\text{III}}(\text{ox})_3]$	14	2D	102
$\text{NBu}_4[\text{Cr}^{\text{II}}\text{Cr}^{\text{III}}(\text{ox})_3]$	—	2D	116
$\text{PPh}_4[\text{Cr}^{\text{II}}\text{Cr}^{\text{III}}(\text{ox})_3]$	—	2D	116
$\text{NBu}_4[\text{Ni}^{\text{II}}\text{Fe}^{\text{III}}(\text{ox})_3]$	28	2D	115
$\text{NBu}_4[\text{Fe}^{\text{II}}\text{Fe}^{\text{III}}(\text{ox})_3]$	43	2D	115
$\text{NBu}_4[\text{Mn}^{\text{II}}\text{Fe}^{\text{III}}(\text{ox})_3]$	49	2D	123
$\text{N}(\text{C}_5\text{H}_{11})_4[\text{Mn}^{\text{II}}\text{Fe}^{\text{III}}(\text{ox})_3]$	27	2D	126
$[\text{Co}^{\text{III}}(\text{bipy})_3][\text{Co}^{\text{II}}\text{Co}^{\text{II}}(\text{ox})_3]\text{ClO}_4$	8	3D	122
$[\text{Fe}^{\text{II}}(\text{bipy})_3][\text{Co}^{\text{II}}\text{Co}^{\text{II}}(\text{ox})_3]$	6	3D	122
$[\text{Ni}^{\text{II}}(\text{bipy})_3][\text{Co}^{\text{II}}\text{Co}^{\text{II}}(\text{ox})_3]$	—	3D	122
$[\text{Fe}^{\text{II}}(\text{bipy})_3][\text{Fe}^{\text{II}}\text{Fe}^{\text{II}}(\text{ox})_3]$	—	3D	111
$[\text{Cr}^{\text{III}}(\text{bipy})_3][\text{Na}^{\text{I}}\text{Cr}^{\text{III}}(\text{ox})_3]\text{ClO}_4$	—	3D	120
$[\text{Cr}^{\text{III}}(\text{bipy})_3][\text{Mn}^{\text{II}}\text{Mn}^{\text{II}}(\text{ox})_3]\text{ClO}_4$	—	3D	120
$[\text{Cr}^{\text{III}}(\text{bipy})_3][\text{Mn}^{\text{II}}\text{Mn}^{\text{II}}(\text{ox})_3]\text{BF}_4$	—	3D	120
$[\text{Co}^{\text{III}}(\text{bipy})_3][\text{Na}^{\text{I}}\text{Cr}^{\text{III}}(\text{ox})_3]\text{PF}_6$	—	3D	120
$[\text{Ni}^{\text{II}}(\text{phen})_3][\text{Na}^{\text{I}}\text{Co}^{\text{III}}(\text{dto})_3] \cdot \text{C}_3\text{H}_6\text{O}$	—	3D	120
$[\text{Ni}^{\text{II}}(\text{bipy})_3][\text{Mn}^{\text{II}}\text{Mn}^{\text{II}}(\text{ox})_3]$	—	3D	118
$[\text{Fe}^{\text{II}}(\text{bipy})_3][\text{Na}^{\text{I}}\text{Fe}^{\text{III}}(\text{ox})_3]$	—	3D	118
$[\text{Fe}^{\text{II}}(\text{bipy})_3][\text{Li}^{\text{I}}\text{Cr}^{\text{III}}(\text{ox})_3]$	—	3D	118
$[\text{Fe}^{\text{II}}(\text{bipy})_3][\text{Li}^{\text{I}}\text{Fe}^{\text{III}}(\text{ox})_3]$	< 3.5	3D	118
$\text{NBu}_4[\text{Fe}^{\text{II}}\text{Ru}^{\text{III}}(\text{ox})_3]$	13	2D	127

Note. The following abbreviations are used: bipy is bipyridyl, phen is phenanthroline, and dto is dithiooxalate.

antiferromagnetic interactions between unpaired electrons. The directed design of heterospin systems has made it possible to obtain^{101–103} solid of $\text{NBu}_4[\text{M}(\text{ox})_3]$ ($\text{M} = \text{Cu}^{\text{II}}, \text{Mn}^{\text{II}}, \text{Fe}^{\text{II}}, \text{Co}^{\text{II}}, \text{Ni}^{\text{II}}$) with magnetic ordering at 6–14 K (Table 2).

A three-dimensional framework structure was originally postulated for $\text{NBu}_4[\text{M}(\text{ox})_3]$, although it was shown later^{109–113} that these solids have layered honeycomb structures. One has to note the studies of $\text{NBu}_4[\text{Mn}(\text{ox})_3]$ single crystal,^{109, 110} where strong anisotropy of the magnetic properties has been revealed. If measurements were made along the crystallographic axis c , which is perpendicular to the polymeric layers and coincides with the direction of the magnetic moments of Mn^{II} and Cr^{III} , the dependence of magnetisation on the magnetic field strength $M(H)$ was saturated in fields of ~ 0.05 T. If the external magnetic field was oriented perpendicularly, *i.e.*, inside the nets of the polymeric layers, the $M(H)$ curve was far from saturation in the field of 10^4 G = 1 T. Later, a study of magnetic-structural relationships for $\text{NPr}_4[\text{Mn}^{\text{II}}\text{Cr}^{\text{III}}(\text{ox})_3]$ and $\text{NBu}_4[\text{Mn}^{\text{II}}\text{Fe}^{\text{III}}(\text{ox})_3]$ single crystals and a study of the magnetic structure in a neutron diffraction experiment with $[\text{P}(\text{C}_6\text{D}_5)_4][\text{Mn}^{\text{II}}\text{Cr}^{\text{III}}(\text{ox})_3]$ ¹¹⁴ powder confirmed that the magnetic properties of this type of subjects have strong anisotropy.

From the conceptual viewpoint, a series of studies^{111, 117, 118} into the role of templates promoting the formation of either two-dimensional layered polymeric structures with a honeycomb motif (see Fig. 1 a) or three-dimensional frameworks with a motif of fused decagons (see Fig. 1 b) is important. The following principles for the construction of two- and three-dimensional polymeric oxalate structures were revealed: assembling a structure from various alternating distorted octahedral chiral (Λ and Δ) $\text{M}(\text{ox})_3$

fragments results in polymeric layers with metal ions arranged in one plane, whereas assembling a polymeric structure from the same fragments of the same chirality gives a polymeric framework structure. As a whole, the two-dimensional honeycomb structure is achiral, and the distance between the layers is determined by the size of the cations located in the space between the layers. The three-dimensional structure formed from fused decagons is always chiral.

It was found that the $[XR_4]^+$ cations, where $X = N$ or P and $R = Ph, Pr, Bu$ or C_5H_{11} , favour the separation of two-dimensional honeycomb-like layered structures containing $[M^{II}M^{III}(ox)_3]_n^{n-}$, where $M^{II} = V, Cr, Mn, Fe, Co, Ni, Cu, Zn$; $M^{III} = V, Cr, Fe$, into the solid phase, while tris-chelated metals cations, e.g., $[M(bipy)_3]^{2+/3+}$ (*bipy* is bipyridyl), cause the cross-linking of the polymeric anionic oxalate framework of $[M^{II}_2(ox)_3]_n^{2n-}$, $[M^I M^{III}(ox)_3]_n^{2n-}$ or $[M^{II}M^{III}(ox)_3]_n^{n-}$ into a three-dimensional framework of decagons.^{117, 120} Another motif found in the solid phase of lanthanide-containing oxalates $[Ln^{III}-Cr^{III}(ox)_3] \cdot nH_2O$ is composed of polymeric chains the shape of which resembles 'rope ladders'.¹¹⁹ It was also found that framework structures similar to oxalates can also be obtained with the use of dithiooxalates (dto, see Table 2) as the bridging ligands.¹²⁰

The progress of studies into the design of layered and framework molecular ferromagnets based on oxalate complexes has also stimulated interest in these compounds as a new type of microporous materials suitable for the separation of racemic mixtures and for directed asymmetric synthesis, as well as for catalysis. It has been shown for the layered polymeric microporous compound $Na_2(NMe_3Ph)_3[Cr(ox)_3]_2Cl \cdot 5H_2O$ that partial removal of the template from the compound by cation exchange at room temperature and even its complete removal by thermal treatment of the specimen accompanied by removal of water of crystallisation did not result in the loss of crystallinity.¹²¹ This behaviour is similar to that of zeolite materials, therefore the phases under consideration can actually prove to be efficient for the separation of chiral subjects.

Compounds with high negative magnetisation of approximately the same magnitude as that of solid solutions of classical ferrosilicates and the cyanide phases $(Ni_x^{II}Mn_{1-x}^{II})_{1.5} \cdot [Cr^{III}(CN)_6] \cdot 8H_2O$ discussed above, were described in Refs 124 and 125. The authors studied the specially selected series of layered polymeric oxalate complexes $A^I[M^{II}Fe^{III}(ox)_3]$, where $A^I = NPr_4^+, NBu_4^+, N(n-C_5H_{11})_4, PBu_4^+, PPh_4, NBu_3^+(C_6H_5CH_2), Ph_3PNPPh_3, AsPh_4$; $M^{II} = Mn, Fe$, in which the interlayer distance can be adjusted by varying the cation A^I . Compounds with $M^{II} = Fe$ behave as ferrimagnets with the ordering temperature of 33–48 K. For five of these compounds, transition from positive to negative magnetisation has been recorded at ~ 30 K in weak magnetic fields (~ 100 G). Such transitions are most characteristic of compounds with the highest critical temperatures. Moreover, characteristic changes were found in the series $N(n-C_nH_{2n+1})_4[Fe^{II}Fe^{III}(ox)_3]$, where $n = 3-5$. It was established that T_c increases with the interlayer distance; at low temperatures, magnetisation changes from positive for $n = 3$ to negative for $n = 4$ and 5.¹²⁵

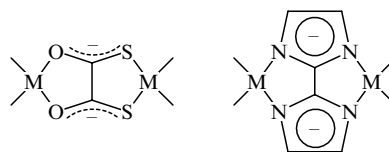
Single crystals of the layered polymeric heterometallic oxalate $N(n-C_5H_{11})_4[Mn^{II}Fe^{III}(ox)_3]$ could be grown and the anisotropy of its magnetic properties was studied.^{109, 110, 114, 125} Studies into the anisotropy of the magnetic properties of single-crystal molecular ferromagnets are still rather rare, therefore they always arouse vivid interest. It was found¹²⁶ that $N(n-C_5H_{11})_4 \cdot [Mn^{II}-Fe^{III}(ox)_3]$ with $T_c = 27$ K, as $NBu_4[MnCr(ox)_3]$ discussed above, has strong magnetisation anisotropy. The uncompensated magnetic moment directed perpendicularly to the plane of the polymeric layers (*i.e.*, in the same direction as in $NBu_4[MnCr(ox)_3]$) is rather small, *viz.*, $8.78 \times 10^{-5} \mu_B$ per magnetically active atom, which can be explained by the small angle of rotation of the

magnetic sublattices ($\sim 0.001^\circ$) and the small difference between the *g*-factors of the d^5 metal ions.¹²⁶

Table 2 lists the characteristics of a large group of polymeric metal oxalates, which allows some generalisations to be made. However, the overall picture for the understanding of the magnetic properties of compounds belonging to this class is still far from completion.^{127, 128} Nevertheless, methods for directed synthesis of layered polymeric or framework polymeric metal oxalates have been developed to date, and it has become clear what the resulting chirality of the subjects would be and what spatial structure they would have. In addition, it is possible to adjust the distances between the layers in a series of layered compounds by varying the size of the cation A^I located in the interlayer space.^{74, 121}

Experiments show that the highest magnetic ordering temperatures ($\sim 40-50$ K) are reached if a compound contains a combination of metal ions having high spins (high-spin Mn^{II} , Fe^{II} , Fe^{III}), in accordance with the correlation $T_c \propto JS_1S_2$ (where S_1 and S_2 are the spins of the first and second paramagnetic centres, respectively). When metal ions are combined, it is possible to predict the temperature range in which the critical temperature of the expected compound will fall. Thus, the introduction of diamagnetic ions (for example, lithium or sodium ions) in polymeric oxalate systems leads to an increase in the distances between the paramagnetic centres, a reduction of the energy of exchange interaction between them and, hence, a sharp decrease in the critical temperature. On the other hand, the fact that the critical temperatures of the known framework oxalates (3D structures) are much lower than those of layered polymeric compounds (2D structures) requires a quantum-chemical explanation. The role of relativistic effects is not quite clear; the necessity of taking them into account in the description of the magnetic properties of heterometallic polymeric oxalates containing paramagnetic 4*d*- or 5*d*-metal ions was pointed out in Ref. 127. Such properties appear due to a significant spin-orbital interaction in these elements.

It may seem that the design of oxalate systems is limited only to the replacement of metal ions and template cations. This is hardly true. Certainly, oxalate polymers are the basic systems for the synthesis of the M3M' class ferromagnets. On the other hand, current studies encourage a wider use of various diamagnetic and paramagnetic ligands which are structural analogues of the oxalate anion and hence favour the development of the synthesis of new molecular magnets. For example, the aforementioned dithiooxalate,^{120, 129, 130} imidazoles,¹³¹ imidazoleacetate¹³² and biimidazole¹³³ may be regarded as such ligands.



In addition, investigations into the design of polynuclear mixed-ligand compounds, in which not all but only one or two ligands are oxalates,^{134, 135} are certainly of interest. For example, the structure of complexes $M_2^{II}(dpm)(ox)_2 \cdot xH_2O$, where $M = Mn, Cu$; $x = 6, 5$, respectively, and *dpm* is bipyrimidine (Fig. 2),^{135, 136} is topologically identical with the honeycomb structure of layered polymeric oxalates (see Fig. 1*a*). The way of self-organisation of three-dimensional frameworks upon formation of mixed-ligand complexes with an oxalate anion and bipyridyl has been studied.¹³⁷ Thus, addressing mixed-ligand complexes is also promising in the design of new molecular ferromagnets.

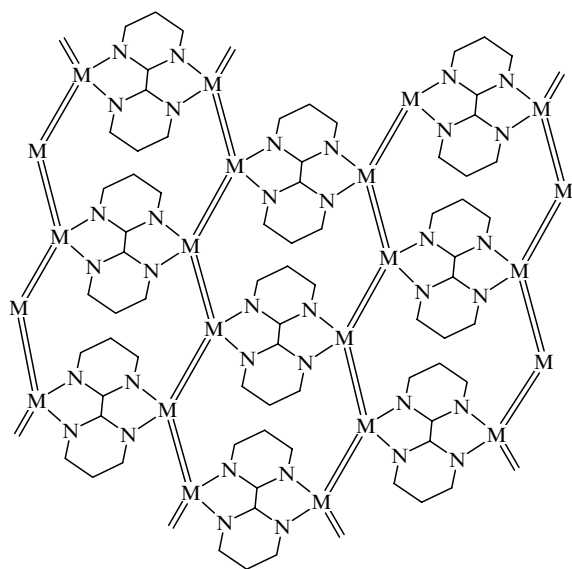


Figure 2. Scheme of a layered polymeric structure ('honeycomb' motif) of $M_2^{\text{II}}(\text{dpm})(\text{ox})_2 \cdot x\text{H}_2\text{O}$ ^{135, 136} and $M_2^{\text{II}}(\text{dpm})(\text{N}_3)_4$ ^{138–140}. The double lines indicate the bridging oxalate or azide anions connecting the metal ions into chains, which are, in turn, linked by the bridging bipyrimidine ligands into layers.

2. Azides

The above approach to the synthesis of layered polymeric compounds based on mixed-ligand complexes of metal oxalates with bipyrimidine, but with the use of azide ligands instead of oxalate ones, has been developed further.^{138–140} The authors succeeded in synthesising and studying a series of layered polymeric complexes with composition $M_2(\text{N}_3)_4(\text{dpm})$, where $M = \text{Co}^{\text{II}}, \text{Fe}^{\text{II}}$ and Mn^{II} . The structural motif of polymeric honeycomb-like layers in $M_2(\text{N}_3)_4(\text{dpm})$ is exactly the same as that in $M_2^{\text{II}}(\text{dpm})(\text{ox})_2 \cdot x\text{H}_2\text{O}$ (see Fig. 2) with only one difference: the role of a bridge is played by two bridging μ -(1,1)-azide ligands instead of the oxalate anion, *i.e.*, according to the systematics accepted, the $M_2(\text{N}_3)_4(\text{dpm})$ complexes correspond to the $M_3(1)M'$ class. The authors believed that the introduction of the azide anion into polymeric structures would be expedient for obtaining polymers with exchange interactions alternating in sign (ferromagnetic – antiferromagnetic). As a rule, strong antiferromagnetic exchange interaction (-200 to -400 cm^{-1}) predominates in exchange clusters linked by a bridging oxalate anion or bipyrimidine.^{13, 141, 142} However, it is known that in binuclear exchange clusters linked by azide following the μ -(1,3) pattern, the exchange interaction is antiferromagnetic,¹⁴³ while in those linked following the μ -(1,1) pattern, it is ferromagnetic.^{144, 145–162}



Experimental studies of the magnetic properties of the $M_2(\text{N}_3)_4(\text{dpm})$ complexes have shown that competition between ferro- and antiferromagnetic exchange interaction channels does exist in them, and at low temperatures ($< 12 \text{ K}$) these compounds behave as metamagnets with high critical magnetic fields ($> 2 \text{ T}$).¹³⁸ It should be noted that the ferromagnetic character of exchange in μ -(1,1) type binuclear azide exchange clusters was confirmed by quantum-chemical studies of the $[\text{M}(\mu\text{-}1,1\text{-N}_3)_2\text{M}]$ and $[\text{M}(\mu\text{-}1,1\text{-N}_3)_3\text{M}]$ fragments, where $M = \text{Cu}^{\text{II}}, \text{Ni}^{\text{II}}, \text{Mn}^{\text{II}}$ (see Ref. 146). For example, for the copper complex, the results of

calculation for the distribution of spin density qualitatively agree with the experimental results of a polarised neutron diffraction study. The spin density distribution obtained in the calculated model is a superposition of the electron delocalisation and spin polarisation effects: delocalisation of unpaired electrons from the $d_{x^2-y^2}$ orbitals to the donor atom of the ligand decreases in the series $\text{Cu} > \text{Ni} > \text{Mn}$, while spin polarisation in the same series increases because of the increase in the number of unpaired electrons.¹⁴⁶ It was also found that the exchange is hardly affected by deviations of the uncoordinated azide ligand from the plane of the $\text{M}(\mu\text{-N})(\mu\text{-N})\text{M}$ fragment, which opens the possibilities for a more flexible and versatile design of highly dimensional structures with the μ -(1,1) bridging azide.

In the synthesis of a layered polymer $\text{Ni}(\text{N}_3)_2\text{L}$, where L is 2,2-dimethylpropane-1,3-diamine,^{163, 164} advantage was taken of the diversity of coordination capabilities of the N_3^- ligand known for polynuclear complexes with azide ligands.^{147–157} The bidentate ligand was shown not to participate in the formation of bridging bonds. The layered polymeric structure is formed by only the azide anions, some of them serving as μ -(1,1) bridges and others as μ -(1,3) bridges. The magnetic ordering temperature for $\text{Ni}(\text{N}_3)_2\text{L}$ was found to be rather high ($T_c = 55 \text{ K}$), although the residual magnetization at 4.2 K is very low ($6 \times 10^{-3} \mu_B$). Below the critical temperature, this compound behaves as a weak ferromagnet, but the reason why the weak ferromagnetism appeared (antisymmetric exchange^{165–168} or *g*-factor anisotropy of the nickel ion¹⁶⁹) remains obscure.

Similar magnetic behaviour has been recorded for a series of layered polymeric coordination compounds $\text{Mn}(\text{N}_3)_2\text{L}_2$, where L stands for monodentate ligands, *e.g.*, pyridine, 3-acetylpyridine, 4-acetylpyridine, 4-cyanopyridine or ethylisonicotine.^{170–172} In polymers with exclusively μ -(1,3) bridging function of the azide ligand, antiferromagnetic exchange interactions between the manganese ions occur, whereas in polymers with alternating μ -(1,1) and μ -(1,3) bridging azides, alternation of ferromagnetic and antiferromagnetic channels of exchange interaction is observed. At low temperatures ($< 16\text{--}40 \text{ K}$) the ESR signal from polycrystalline specimens broadens and compounds behave as weak ferromagnets with small magnetic moments.¹⁷²

3. Dicyanamides

The first reported molecular ferromagnets^{173–178} were based on polymeric dicyanamide derivatives of transition metals $(\text{ML}_2)_\infty$, where $\text{L} = \text{N}(\text{CN})_2^-$; $M = \text{Co}, \text{Ni}$. In solid $(\text{ML}_2)_\infty$, each ligand has tridentate bridging coordination (Fig. 3a).

Each $\text{N}(\text{CN})_2^-$ bridging ligand is bound to metal ions through two terminal nitrogen atoms of the nitrile groups and the central amide nitrogen atom. In turn, each metal ion is bound to six different $\text{N}(\text{CN})_2^-$ ligands, four of which are coordinated by the nitrile nitrogen atoms and two are coordinated by the amide nitrogen atoms. This results in a framework structure similar to that of rutile. These compounds undergo magnetic phase transition into the ferromagnetic state at 9 K (Co) and 20 K (Ni). An important result of these studies is that no ordering effects were detected down to 2 K for the isostructural compound $(\text{CuL}_2)_\infty$ characterised by the pronounced Jahn–Teller effect, which is inherent in Cu^{II} . $(\text{CuL}_2)_\infty$ behaves as a usual paramagnet over the entire measurement range. In our opinion, this behaviour is due to a considerable elongation of the bonds between the copper ions and the amide nitrogen atoms in the structure of $(\text{CuL}_2)_\infty$,¹⁷³ *i.e.* the magnetic structure consists of the chains $[\text{—Cu—}(\text{N}\equiv\text{C—N—C}\equiv\text{N})_2\text{—Cu—}(\text{N}\equiv\text{C—N—C}\equiv\text{N})_2\text{—}]_\infty$ with Cu^{II} ions that weakly interact through five bridging atoms (Fig. 3). As regards the magnetism, $(\text{CuL}_2)_\infty$ belongs to the M_5M' class rather than to M_3M' as is the case for $(\text{CoL}_2)_\infty$ and $(\text{NiL}_2)_\infty$. Band chains of this type with weakly interacting manganese ions, $[\text{—Mn—}(\text{N}\equiv\text{C—N—C}\equiv\text{N})_2\text{—Mn—}(\text{N}\equiv\text{C—N—C}\equiv\text{N})_2\text{—}]_\infty$, have been reported.¹⁷⁹ They were detected for solid $\text{MnL}_2(\text{CH}_3\text{OH})_2$, which confirms the assumption stated above.

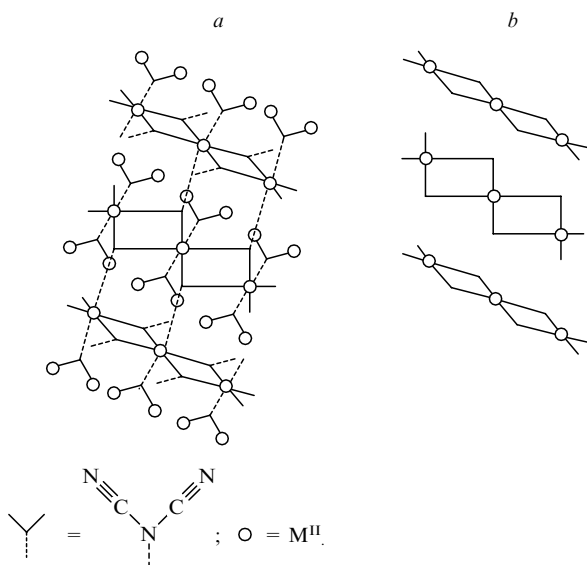


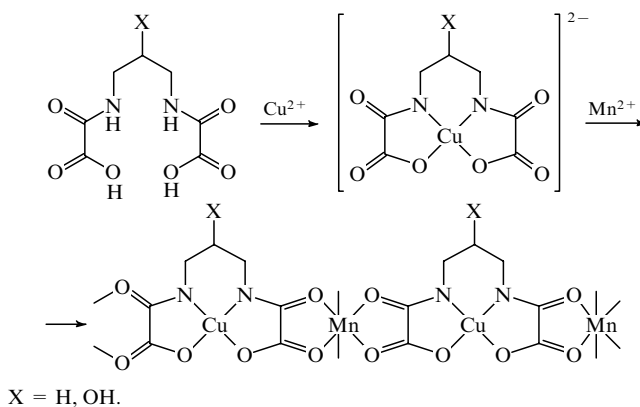
Figure 3. Scheme of decomposition of a three-dimensional framework structure of $(ML_2)_\infty$ (a) into separate chains (b) upon increase in the metal–amide nitrogen atom distance.

Experiments with the use of neutron diffraction on $(ML_2)_\infty$ powders ($M = Co, Ni, Mn$) and measurements of specific heat capacity of these compounds in the region of magnetic phase transition were carried out.^{176–178} It was possible to determine correctly the Curie temperatures for the ferromagnets, viz., cobalt (8.7 K) and nickel (19.7 K), the Neel temperature for an anti-ferromagnet $(MnL_2)_\infty$ (16 K), to determine the magnetic structure of the compounds and to establish that $(CoL_2)_\infty$ exists as two polymorphic modifications, one of which (α) can undergo ferromagnetic ordering below the critical temperature. In the studies of the magnetic properties of $(ML_2)_\infty$ ($M = Fe, Co, Ni$) and alloys $[Ni_{0.5}Co_{0.5}L_2]_\infty Ni(OH)_{2-x}L_x$, some unusual properties of these compounds were reported.^{180, 181} First, an increase in the pressure to 17 kbar makes it possible to increase the critical temperature of the phase by $\sim 10\%$; this is an important feature of molecular ferromagnets that rather commonly have a ‘loose’ structure. Second, anomalously high coercive fields are characteristic of the molecular ferromagnets studied: 710, 7975 and 17 800 G, respectively, for the nickel, cobalt and iron complexes.^{182–184} The latter value is not only the highest in the series of molecular ferromagnets but also exceeds the coercive fields for Sm–Co and Re–Nd–B alloys (the coercive field for classical magnetically hard materials reaches 10^3 – 10^4 G).¹⁸²

Thus, the examples presented above show that the organic dicyanamide anion can be efficiently used in the design of molecular ferromagnets.

4. Dioxamates

An original approach to the design of polymeric heterospin systems based on mixed-ligand complexes with polydentate ligands was developed.^{185–195} The construction of these systems is a multistage directed design of molecular ferromagnets starting from the synthesis of a specific polyfunctional ligand (various dioxamates) and allowing one to obtain a solid heterospin layered polymer with a strictly determined alternation of paramagnetic centres. In the first stage, a complex of Cu^{II} with a tetradentate ligand is formed, and then cross-linking of copper-containing fragments into a chain occurs through the formation of chelate complexes of Mn^{II} with the oxygen atoms of the oxamate groups. The Mn^{II} ion cannot compete with Cu^{II} for the donor nitrogen atoms, as its thermodynamic constants of complex formation with



$X = H, OH$.

nitrogen-containing ligands are much smaller than those for copper. As a result, a chain with regular alternation of Cu^{II} and Mn^{II} is formed.

Mutual arrangement of the paramagnetic centres belonging to different chains is an essential factor. It was found^{185–187} that in the case of N,N' -propane-1,3-dioldioxamate ($X = H$), the Cu^{II} ions in solid $MnCuL \cdot 5H_2O$ are arranged above Cu^{II} ions, while the Mn^{II} ions are above Mn^{II} ions; the magnetic moments of ions belonging to different chains are oriented oppositely (due to the predominant antiferromagnetic exchange interactions) and compensate each other (Fig. 4a). The magnetic moments in the copper and manganese sublattices generally tend to compensate each other. As a result, the compound is ordered antiferromagnetically at low temperature ($T_c = 2.2$ K).

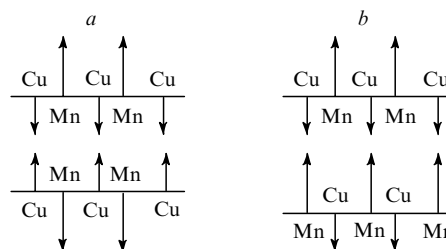
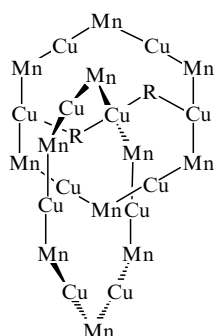


Figure 4. Antiferromagnetic spin ordering of neighbouring chains with resulting zero (a) and non-zero (b) magnetic moment.

In an attempt at changing the mutual arrangement of the metal ions, the authors synthesised the $MnCuL' \cdot 3H_2O$ complex, where L' is N,N' -(2-hydroxypropane-1,3-diyl)dioxamate ($X = OH$). In the solid phase of this compound, the chains $(\dots Cu \dots Mn \dots)_\infty$ are shifted relative to each other in such a way that the OH groups of one chain form hydrogen bonds with the water molecules coordinated by the Mn^{II} ions of the other chain. As a result, a staggered arrangement of the Cu^{II} and Mn^{II} ions appears (Fig. 4b). The magnetic moments of ions from different chains tend to be oriented oppositely. However, in this case each Cu–Mn pair forms a difference magnetic moment, and on the whole, uncompensated magnetic moment of the manganese and copper sublattices appears, as inside these sublattices all spins are oriented in the same way. As the temperature is decreased, the $MnCuL' \cdot 3H_2O$ structure is ordered ferromagnetically ($T_c = 4.6$ K). A series of molecular ferromagnets with the Curie temperatures of 5–22 K were obtained using this approach.^{188–193} The antiferromagnetic character of exchange interaction between the neighbouring Cu^{II} and Mn^{II} ions in these compounds was confirmed by polarised neutron diffraction.¹⁹⁴

A method for the synthesis of the multispin compound $R_2Mn_2(CuL)_3(DMSO)_2 \cdot 2H_2O$, where R is the 2-imidazoline 1-oxyl 3-oxide-containing radical cation; L is the *o*-phenylene-

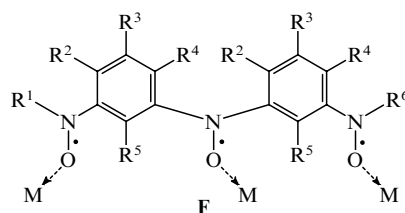
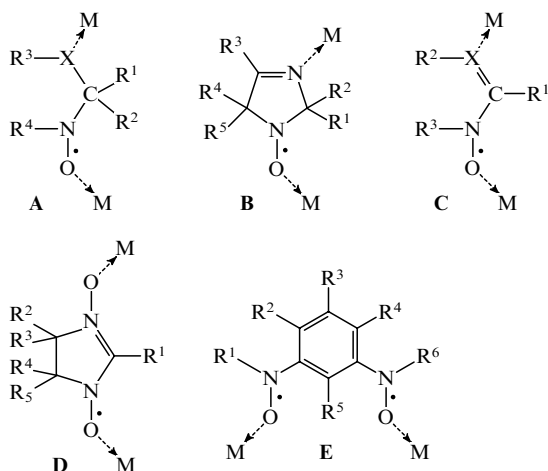
dioxamate anion, was developed.^{196,197} The structure of the compound consists of a system of almost perpendicular (73°) interlocked networks analogous to those of layered polymeric oxalates (see Fig. 1a), the only difference being that the vertices of each hexagon are occupied by the Mn^{II} ions, while the midpoints are Cu^{II} ions.



The tetradentate ligands L play the role of bridges connecting Mn^{II} and Cu^{II} . Each of the oxygen atoms of the nitronyl nitroxide is coordinated by Cu^{II} ions from different networks, which results in the formation of additional polymeric chains in the crystal; the compound is ordered as a ferrimagnet below 22.5 K. Using this approach, the authors obtained a series of molecular ferromagnets $(\text{R-Rad})_2\text{M}_2(\text{CuL})_3$, where R-Rad is the 2-(4- N -alkylpyridinium)-4,4,5,5-tetramethyl-2-imidazoline 1-oxyl-3-oxide cation, $M = \text{Mn}^{\text{II}}, \text{Ni}^{\text{II}}, \text{Co}^{\text{II}}$, with critical temperatures in the range of 22–37 K.¹⁹⁸

V. $\text{M4M}'$, $\text{M5M}'$ and $\text{M7M}'$ systems

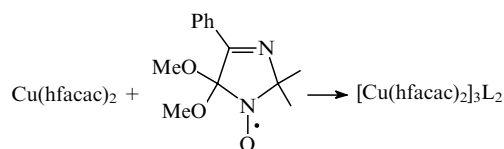
In the Introduction, we discussed the importance of involvement of synthetic organic chemistry in the design of molecular ferromagnets. However, in the classes of compounds considered above, it is not always possible to attach additional functional groups to the bridging ligand atoms. Besides, simple elongation of the hydrocarbon chain will result in a sharp decrease in the energy of exchange interactions between the unpaired electrons of the paramagnetic centres. To resolve the situation, one can use stable nitroxides; the methods for their synthesis and modification are well developed (see, *e.g.*, Ref. 11). The bridging heterospin structures are shown below. Depending on the nature of the group X , these systems can contain a minimum of four atoms in the bridge. Fragments of bridging structures representing derivatives of stable 2-imidazoline^{199–214} and 3-imidazoline^{215–227} nitroxides and acyclic polynitroxyls linked through benzene or heterocyclic rings are also shown.^{12, 228–231}



Substituents R^n in nitroxides may be varied over a broad range. The presence of one or several $\geq \text{N} \cdot \text{O}$ groups (preferably, with the greatest possible delocalisation of spin density over the bridging organic fragment) makes it possible to maintain efficient exchange interactions between the unpaired electrons of the metal ions and the nitroxyl radicals.

A group of chain polymers based on mixed-ligand complexes of Mn^{II} and Ni^{II} hexafluoroacetylacetonates with nitronyl nitroxides (structure D) and capable of ferrimagnetic ordering at $T < 8$ K has been reported for the first time in Refs 232–235. The solid phases formed by polymeric chains of $[\text{Mn}(\text{hfacac})_2\text{L}]_\infty$, where hfacac is hexafluoroacetylacetonate and L represents polynitroxyls, are characterised by similar ordering.^{236,237} Studies of these subjects led to the conclusion that, despite the strong intrachain exchange (the integral of exchange interaction is greater than 250 cm^{-1}),²³⁴ one cannot hope to obtain ferromagnets with high Curie temperatures from these compounds due to the very low energies of intermolecular exchange interactions. However, the design of molecular magnets makes it possible to pass from chain structures to structures with higher dimensionality.

In particular, synthesis of a series of triradicals with structures of the F type has been developed. High conformational mobility of acyclic nitroxyl fragments linked by single bond to an aromatic ring enabled the realisation of a framework structure in the complex $[\text{Mn}(\text{hfacac})_2]_3\text{L}_2$ (L is a triradical; $R^2, R^4, R^5 = \text{H}$; $R^1, R^3, R^5 = \text{Bu}^t$), which is ordered as a ferrimagnet at 46 K.^{238–240} Each coordination matrix $[\text{Mn}(\text{hfacac})_2]$ is bound to two ligands, whereas each ligand is surrounded by three different $\text{Mn}(\text{hfacac})_2$ units. Nevertheless, it should not be thought that a framework polymer is always formed at the stoichiometric ratio $\text{M}(\text{hfacac})_2 : \text{nitroxyl} = 3:2$. We found that this composition can also be observed for specific trinuclear molecules with radicals²⁴¹ which are formed particularly often in the synthesis of mixed-ligand complexes of $\text{Cu}(\text{hfacac})_2$ with nitroxides (Fig. 5).^{204, 209, 219, 221, 242}



If the compounds have the same composition, one has to pay special attention to the possibility of formation of polymorphic modifications, as their magnetic properties can differ considerably.^{199, 222, 232, 243, 244}

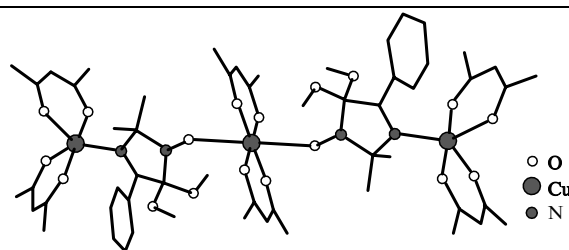
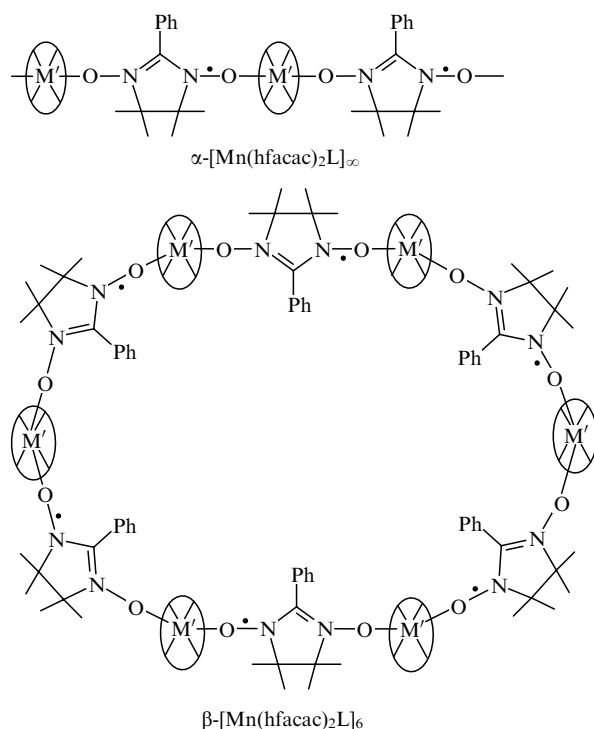


Figure 5. Molecular structure of the complex $[\text{Cu}(\text{hfacac})_2]_3\text{L}_2$.

Scheme 2



Scheme 2 shows that *trans*-coordination of the bridging 2-imidazoline nitronyl nitroxyl ligands in Mn(hfacac)_2 results in the formation of polymeric chains (α) in the solid which undergoes three-dimensional magnetic ordering below 6 K.²³² *cis*-Coordination of radicals results in hexanuclear separate molecules (β) due to closure of a 36-membered macrocycle formed by the manganese atoms and the O–N–C–N–O fragments of the paramagnetic ligand.¹⁹⁹

The ground state of hexanuclear molecules is that with $S = 12$ in the temperature range from 5 to 300 K; the β -modification behaves as an ordinary paramagnet.

The bischelate of divalent nickel with acetonyl 3-imidazoline nitroxide derivative NiL_2 (Fig. 6) also exists as two polymorphic modifications (α and β).²²² Both modifications have layered polymeric structures. The goffered layered structure of the solid is formed owing to coordination of the nitroxyl oxygen atoms of the neighbouring bischelates by the nickel ion. The coordinated oxygen atoms of the nitroxyl groups are *trans*-coordinated in the α -modification and *cis*-coordinated in the β -modification. In solid $\alpha\text{-NiL}_2$, the antiferromagnetic exchange interactions between the unpaired electrons of the paramagnetic centres in the $\text{>N}\dot{\text{O}}\text{--Ni}^{\text{II}}\text{--O}\dot{\text{N}}\text{<}$ fragments predominate, and μ_{eff} approaches zero as the temperature is lowered. In $\beta\text{-NiL}_2$, the antiferromagnetic ($J \approx -115 \text{ cm}^{-1}$) and ferromagnetic ($J \approx 10 \text{ cm}^{-1}$) exchange compete, which results in antiferromagnetic ordering at $T_c = 14 \text{ K}$ (Fig. 7).

Taking into account the stereochemical non-rigidity of bischelates of the NiL_2 type, it is possible, by selecting the crystallisation conditions, to obtain modifications having either a molecular structure incapable of cooperative magnetic ordering or a layered polymeric structure that displays a tendency towards cooperative magnetic ordering.^{243, 245}

Perhaps, the only factor that limits the possibilities of the design of molecular ferromagnets from complexes with nitroxyl radicals is that the $\text{>N}\dot{\text{O}}$ group, which results from the oxidation of the corresponding hydroxylamine, is a weak donor of electron density. However, coordination of the nitroxyl group or any other way of its inclusion in the network of polymeric exchange channels are necessary for cooperative magnetic ordering.²²⁰ Therefore,

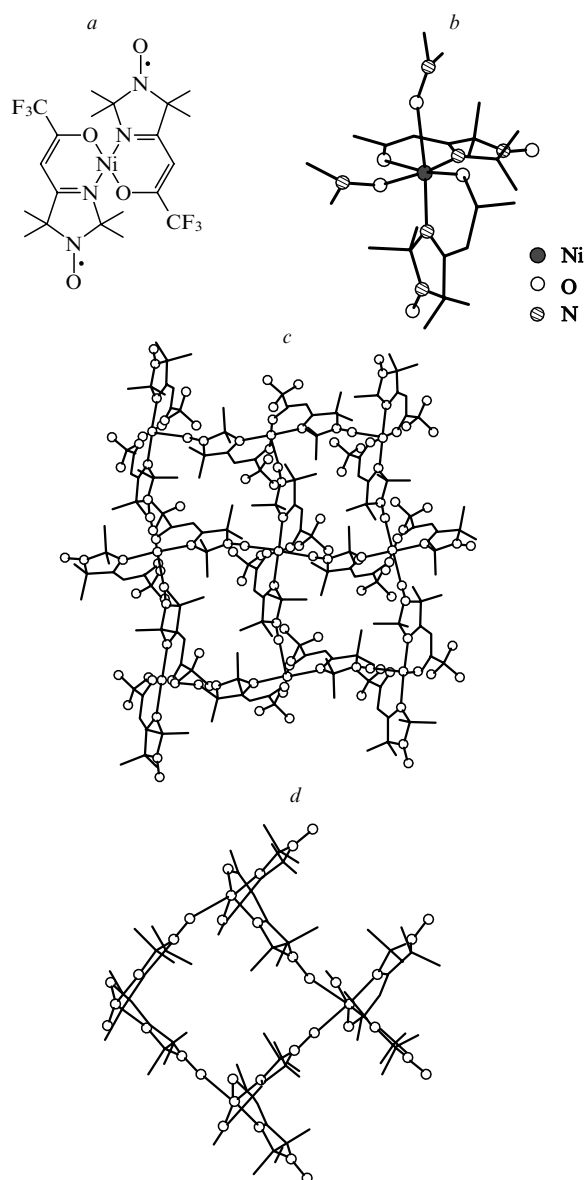


Figure 6. Fragments of layered polymeric structures of α - and β - NiL_2 ; (a) NiL_2 complex; (b) coordination of the Ni atom in $\beta\text{-NiL}_2$; (c) layered polymeric structure of $\alpha\text{-NiL}_2$; (d) layered polymeric structure of $\beta\text{-NiL}_2$.

metal hexafluoroacetylacetonates have mostly been used as acceptor matrices in early studies of heterospin systems based on complexes of transition metals with stable nitroxides.^{7, 11} It was shown²⁴⁶ that fluorinated carboxylates of metals can be used instead of hexafluoroacetylacetonate matrices; heterospin compounds capable of magnetic ordering at 21–24 K were obtained from mixed-ligand complexes of manganese bis(pentafluorobenzoate) with 2-imidazoline nitroxide.

It is possible in principle to get rid of the ‘ballast’ diamagnetic anionic ligands, such as hexafluoroacetylacetonate or carboxylate, if the organic radical is originally constructed in such a way that it can play both the roles of a bridge and an anion. We succeeded in synthesising a vast group of molecular ferromagnets of this type with layered polymeric or framework structure (Table 3). Scheme 3 illustrates the formation of polymeric layers in heterospin bischelates based on complexes of transition metals with derivatives of the stable 3-imidazoline nitroxide.

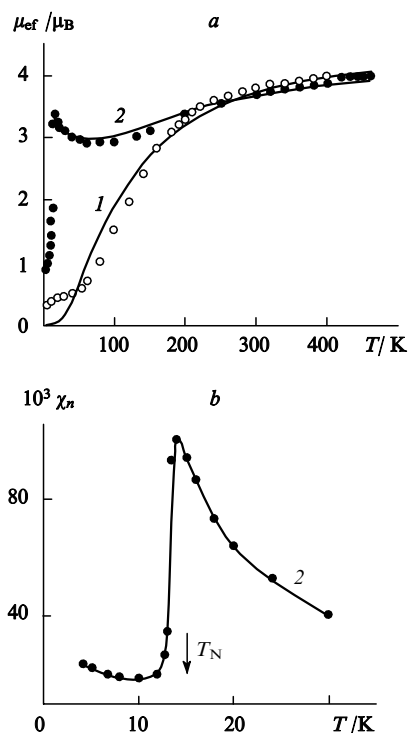
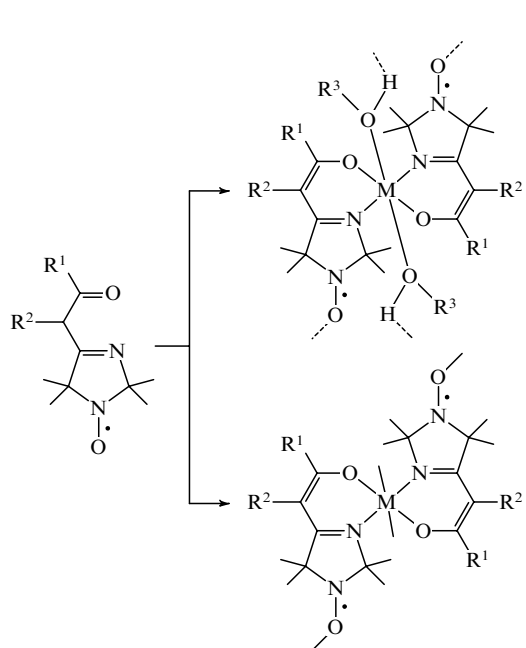


Figure 7. Temperature dependences of the effective magnetic moment for α - (1) and β -NiL₂ (2) (a) and the specific magnetic susceptibility (χ_n) for β -NiL₂ (b).

Table 3. Magnetic ordering temperatures for complexes with 3-imidazoline nitroxyl radicals.

Compound	T_c /K	Structure dimensionality	Ref.
$R^1 = CF_3, R^2 = H$			
NiL ₂ (MeOH) ₂	6.5	2D	247, 250
NiL ₂ (H ₂ O) ₂	—	2D	72
NiL ₂ (EtOH) ₂	5.3	2D	247, 250
NiL ₂ (C ₃ H ₅ OH) ₂	6.2	2D	248
NiL ₂ (Pr ⁿ OH) ₂	6.0	2D	248
NiL ₂ (Bu ⁿ OH) ₂	5.9	2D	249
NiL ₂ (Bu ⁱ OH) ₂	4.8	2D	249
NiL ₂ (n-C ₅ H ₁₁ OH) ₂	6.3	2D	248
NiL ₂ [HO(CH ₂) ₄ OH]	6.8	3D	247
NiL ₂ [HO(CH ₂) ₅ OH]	4.0	3D	247
CoL ₂ (MeOH) ₂	7.1	2D	251
CoL ₂ (EtOH) ₂	8.1	2D	11, 248
CoL ₂ [HO(CH ₂) ₄ OH]	4.0	3D	249
CuL ₂	—	molecular	254, 255
$R^1 = CF_3, R^2 = Cl$			
NiL ₂ (MeOH) ₂	5.0	2D	252
CoL ₂ (MeOH) ₂	7.1	2D	252
CuL ₂	5.0	2D	253
$R^1 = CF_3, R^2 = Me$			
NiL ₂ (MeOH) ₂	5.8	2D	252
$R^1 = COOEt, R^2 = H$			
CuL ₂	4.2	2D	253
$R^1 = COOMe, R^2 = H$			
CuL ₂	5.0	2D	253
$R^1 = COOEt, R^2 = Br$			
CuL ₂	4.3	2D	253



$R^1 = CF_3, COOMe, COOEt$; $R^2 = Me, H, Cl, Br$; $M = Cu, Ni, Co$.

High-quality single crystals of intracomplex chelates can be obtained from various organic solvents; therefore, it was possible to determine the crystal and molecular structures for all of the heterospin compounds listed in Table 3. A distinctive feature of the composition of the compounds studied is the presence of non-crystallisation molecules of alcohols in the crystal. In the solid phase, the metal ion coordinates the oxygen atoms of the OH groups belonging to two ROH fragments, then the ROH–ML₂–HOR groups are linked by hydrogen bonds ROH...O–N< with two neighbouring ROH–ML₂–HOR units. As a result, the bridging alcohol molecules ‘cross-link’ the

ML₂ fragments to form polymeric layers (monohydric alcohols) or a three-dimensional framework (dihydric alcohols), *i.e.* the two- or three-dimensional structure is formed by hydrogen bonds.^{247, 248, 250–253}

It should be noted that a separate metal ion in ML₂(ROH)₂ is surrounded by a large number of ‘organic’ atoms (C, H, N, O). For example, there are 90 C, H, N and O atoms altogether per each Ni^{II} ion in NiL₂(n-C₅H₁₁OH)₂; in spite of this, the compound is capable of cooperative magnetic ordering at low temperature. Removal of the alcohols and transition to layered polymeric structure in solid ML₂ leads to the loss of its ability to undergo ferromagnetic ordering.^{222, 248} At first glance, this seems paradoxical, as the transition from ML₂ to ML₂(ROH)₂ is accompanied by an abrupt increase in the fraction of the organic component in the compound, and hence, a decrease in the number of paramagnetic centres per unit volume of the solid phase of the complex. Nevertheless, it is such changes that determine the ability to undergo magnetic phase transition typical of weak ferrimagnets.²⁴⁷

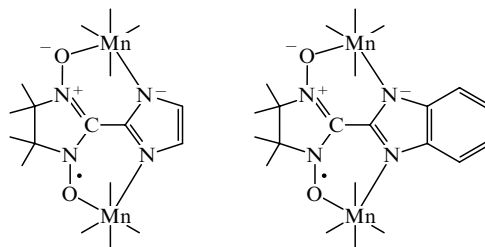
It was found by comparison of the magnetic properties of the isostructural complexes NiL₂(ROH)₂ and NiL₂(H₂O)₂ (see Ref. 72) that the introduction of water molecules in the exchange channel >N–O...HOH–M^{II}–HOH...O–N< results in a sharp decrease in the exchange interaction energy and, hence, the loss of ability to undergo magnetic phase transition, despite the structural identity of the exchange channels in NiL₂(H₂O)₂ and NiL₂(ROH)₂. The high kinetic stability of complexes with alcohols, especially dihydric ones, was noted. For example, no changes in the composition and properties of NiL₂(MeOH)₂ and

$\text{NiL}_2[\text{HO}(\text{CH}_2)_4\text{OH}]$ were recorded upon their storage under normal conditions for 10 years. Large single crystals (with sizes from several millimetres to two centimetres) of many compounds of this series are also storage-stable. The possibility of obtaining complexes of transition metals with nitroxyl radicals in the form of sufficiently large single crystals makes them convenient subjects for studying the anisotropy of the magnetic properties^{233–235, 238, 245, 247} and the spin density distribution using polarised neutron diffraction.^{256–259} For example, Fig. 8 shows the results of a study of the magnetisation anisotropy for $\text{NiL}_2(\text{MeOH})_2$ and $\text{NiL}_2(\text{EtOH})_2$ and demonstrates the relation between the direction of easy magnetisation axis for single-crystal $\text{NiL}_2(\text{EtOH})_2$ as a macrosubject and the direction of the second-order crystallographic axis of the crystal microstructure. The coincidence of these directions is a prerequisite (within the framework of the classical magnetism concept) for single crystals belonging to the space group $P2_1/c$.¹⁶⁸

It was established in systematic studies of transition metal complexes with stable 3-imidazoline nitroxides that the structural dimensionality of a solid can be controlled by varying the substituents R^1 and R^2 in the side chain of the ligand. If R^1 is not an electron density acceptor (alkyl, aryl), the solid phase of the complex has a molecular structure with a square or tetrahedral environment of the metal ion. If R^1 is a strong electron density acceptor (for example, CF_3 , COOEt), the central metal ion

coordinating the donor atoms of the neighbouring molecules also becomes a strong acceptor. The coordination number of the central ion is completed to 6 and a layered polymeric structure is formed.^{72, 260} In the case where the acceptor ability of a metal ion attained only due to the introduction of an electrophilic substituent R^1 is insufficient to implement a two-dimensional solid state structure, the introduction of additional acceptor groups, for example, halogen atoms, as the substituent R^2 is effective.²⁵³

In the examples of heterospin complexes discussed above, the 3-imidazoline nitroxyl radical plays the role of a tridentate bridge. Recently, heterospin layered polymers with deprotonated nitronyl nitroxyl radicals (NIT) containing an imidazole (Im) or benzimidazole (BzIm) substituent at position 2 of the paramagnetic heterocycle were described.^{261, 262}



Such substituents perform the tetradentate bridging function ($\text{M53M}'$ systems). Complexes with composition $[\text{Mn}_2(\text{NITIm})_3] \cdot \text{ClO}_4$, $[\text{Mn}_2(\text{NITBzIm})_3] \cdot \text{ClO}_4$ and $[\text{Mn}_2(\text{NITIm})_3] \cdot \text{BF}_4$ ordered as weak ferromagnets at 1.4, 40 and 3.6 K, respectively, deserve special attention.²⁶²

The layered polymeric structure of these complexes with honeycomb motif is the same as that of the layered polymeric oxalate (see Fig. 1a) or azide complexes (see Fig. 2). This fact agrees completely with the general requirement for the arrangement of a layered polymeric structure with a metal:bridging radical ratio of 3:2 with alternating chiral (Λ and Δ) fragments formed by the metal ions. This indicates that molecular ferromagnets of this structural type have a common architecture. A systematic study of magnetic-structural relationships only for compounds of this structural type will make it possible to obtain a series of molecular ferromagnets with different magnetic characteristics (critical temperatures, spontaneous magnetisation, coercive fields).

Like for oxalate molecular ferromagnets,^{125, 263} the critical temperature of heterospin layered polymers was found to depend on the nature of uncoordinated anions (ClO_4^- , BF_4^-);^{261, 262} varying the latter serves as an additional means for affecting the magnetic parameters of the solid phase. In addition, the interlayer distances in the imidazole complex $[\text{Mn}_2(\text{NITIm})_3] \cdot \text{ClO}_4$ increase as the temperature is decreased, which decreases the critical temperature of this complex in comparison with the benzimidazole complex $[\text{Mn}_2(\text{NITBzIm})_3] \cdot \text{ClO}_4$.

VI. The problem of organic ferromagnets

The general problem of the creation of molecular ferromagnets was intensely fed 15–20 years ago by theoretical studies^{264–269} and experiments^{270–275} aimed at the synthesis of the so-called high-temperature, purely organic ferromagnets, *i.e.*, compounds the solid phase of which has no metal-containing components at all. Experimental results on the synthesis of purely organic ferromagnets have not been confirmed in many aspects and are subject to criticism.^{276–281} In the review¹ where the results of studies on organic ferromagnets were generalised and analysed in detail, it was noted that a most complex problem in the creation of such compounds is that the intermolecular exchange interactions in solid organic paramagnets are rather weak because of the large distances between the paramagnetic centres. In fact, the Curie temperatures for the purely organic ferromagnets known to date do not exceed 1–2 K.^{282–303}

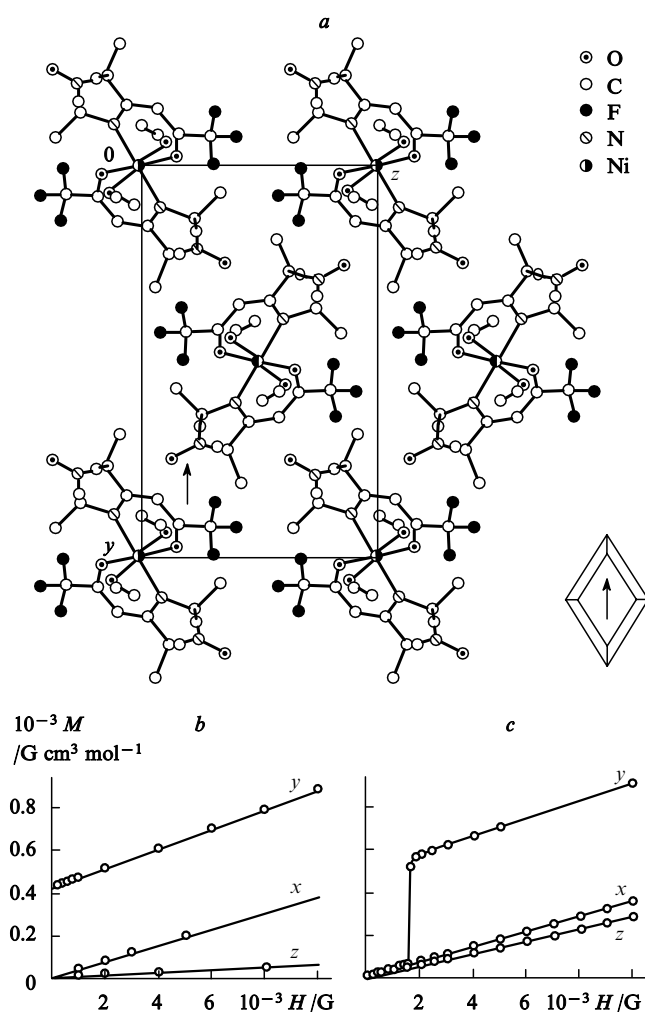
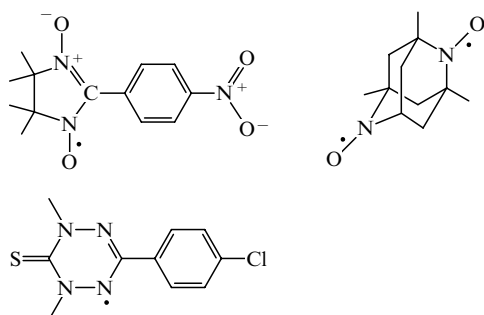
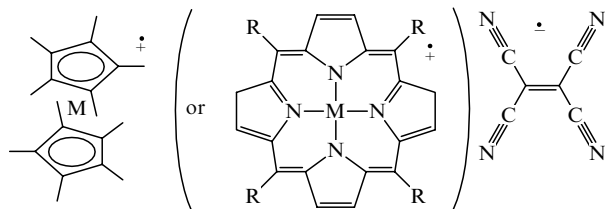


Figure 8. Scheme demonstrating the coincidence of the directions of the twofold symmetry axis (arrow inside the cell) and the direction of the easy magnetisation axis in the single crystal (arrow inside the crystal) for $\text{NiL}_2(\text{EtOH})_2$ (a) and dependences of $\mu(H)$ showing the magnetisation anisotropy of single crystals of $\text{NiL}_2(\text{MeOH})_2$ (b) and $\text{NiL}_2(\text{EtOH})_2$ (c).²⁴⁷



Perhaps, the only exception is the value of 16.1 K recorded for the adduct of C_{60} fullerene with tetrakis(dimethylamino)ethylene (TDAE) with composition $C_{60}(TDAE)_{0.86}$ (see Ref. 304). However, the nature of the ferromagnetism of $C_{60}(TDAE)_{0.86}$ remains unclear, although there was no doubt that the adduct did not contain ferromagnetic admixtures.

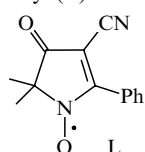
A series of molecular organometallic ferromagnets based on salts of sandwich radical cations of decamethylferrocenium type with radical anions of such π -acceptors as tetracyanoethylene or tetracyanoquinodimethane have been synthesised and studied.^{3–6, 305–316}



The solid phases of these compounds involve molecular packing with alternating paramagnetic donors and acceptors (... $D^{+\bullet}A^{-\bullet}...$... $D^{+\bullet}A^{-\bullet}...$). The reasons for the bulk magnetic ordering in them became the subject of extensive theoretical studies.^{1, 6, 317–319} The compounds have critical temperatures from 2.3 to 8.8 K and are stable only in an inert atmosphere.

A similar series of donor-acceptor systems capable of magnetic ordering at 3–13 K was obtained from derivatives of porphyrin or phthalocyanine macrocyclic complexes with organic radical anions.^{320–325} Judging by the temperature of bulk magnetic ordering, compounds of metals with the tetracyanoethylene radical anion (TCNE) with composition $M(TCNE)_2(CH_2Cl_2)_y$ [$M = Mn^{II}$ ($T_c = 75$ K), Fe^{II} ($T_c = 75$ K)]^{326, 327} and especially the vanadium compound $V(TCNE)_x(CH_2Cl_2)_y$, where $x \approx 2$ and $y \approx 0.5$, are prominent among these subjects. The latter compound behaves as a ferromagnet up to the temperature of thermal decomposition (> 350 K).^{6, 328, 329} Unfortunately, the compound is extremely unstable in contact with air, and its structure could not be elucidated.

Nevertheless, it is substantiated that a phase which is saturated with an organic component and contains solvate molecules of dichloromethane (tetrahydrofuran or acetonitrile)³²⁹ is capable of magnetic ordering at high temperatures. This means that, in principle, it is not forbidden to obtain purely organic ferromagnets with high critical temperatures in which the exchange interactions between the paramagnetic centres are sufficiently strong. Recently, we found in a study of the first stable vinyl-nitroxyl (L)³³⁰



that antiferromagnetic exchange chains with an exchange energy of $J/k \approx 100$ K are formed in this solid. Due to such a high antiferromagnetic exchange energy, the magnetic moment of the

radical L does not reach the theoretical value ($1.73 \mu_B$) even at room temperature and equals $1.49 \mu_B$, *i.e.* high exchange interaction energies can also occur in compounds with a molecular structure. On the other hand, as already noted, mutual orientation of magnetic orbitals in the solid phase of L is such that the exchange interactions between the paramagnetic centres are antiferromagnetic, and the magnetic moment approaches zero as the temperature is lowered. However, examples of organic radicals are known in the solid phases of which the intermolecular exchange interactions are ferromagnetic^{297, 298, 331–333} and even ferromagnetic chains are formed.³³⁴ Besides, antiferromagnetic exchange is not an insurmountable obstacle to cooperative ordering, because a ferrimagnet can be obtained²⁶⁷ by using heterospin bi- or polyradicals³³⁵ or by cocrystallisation of mono- and bi- or polyradicals.²⁶⁷ It is possible that a purely organic ferromagnet, maybe even one with a molecular structure and with a sufficiently high critical temperature (exceeding the boiling point of liquid helium) will be synthesised.

VII. Conclusion

This review analyses the main classes of chemical compounds for which the basic methods for designing high-dimensionality multi-spin systems which tend to cooperative magnetic ordering have been discussed. The development of any method for designing molecular ferromagnets is undoubtedly a laborious and lengthy process. About ten years ago, the determination of the first approaches to the design of various classes of molecular ferromagnets had only started. To date, vast and valuable experimental material has been accumulated: critical temperatures above room temperature (315–330 K) have already been achieved for molecular ferromagnets;^{336, 337} compounds with anomalously high coercive fields have been synthesised;^{180, 181} a number of compounds have been obtained as single crystals stable under ordinary conditions.^{8, 247} The prospects of the practical application of molecular ferromagnets in various electronic and magnetic devices as well as for data recording, magnetic visualisation and protection against low-frequency magnetic fields are under discussion.^{3, 6, 24} An original photomagnetic device with a cyanide molecular ferromagnet as a working element was shown at the XXXIIIrd International Conference on Coordination Chemistry.³⁵

The prospects of progress in the area of molecular ferromagnets are difficult to predict. However, it is doubtless that these compounds are promising, as they represent light, transparent and mainly dielectric materials obtained under mild conditions, with specific properties commonly not typical of the classical magnetic materials.³³⁸

We did not dwell upon details of analysis of the magnetic properties of molecular ferromagnets, as this has been done exhaustively in several monographs,^{13, 339–342} and a detailed discussion of the diversity of magnetic properties of molecular ferromagnets might be an independent topic of a separate review. Let us just note that the authors often introduce a large number of exchange parameters (J_1, J_2, J_3 etc.) in the spin-Hamiltonian when analysing the experimental temperature dependences $\chi(T)$ or $\mu(T)$ for complex multi-spin systems with various channels of exchange interactions. If this approach is used, it should be taken into account that the introduction of additional parameters improves the fitting of the experimental curves, but the errors of the model in the determination of the parameters can increase to such an extent (by several orders) that these additional parameters would be utterly uncertain.³⁴³ The reliability of the exchange parameters obtained from the experiment is extremely important for the subsequent quantum-chemical analysis of the mechanisms of exchange interaction between the paramagnetic centres.

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The problem of oxidation state stabilisation and some regularities of a Periodic system of the elements

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Abstract. The general principles of the concept of oxidation state stabilisation are formulated. Problems associated with the preparation and provision of the highest valent forms of transition elements are considered. The empirical data concerning the synthesis of new compounds of rare-earth elements and *d* elements in unusually high oxidation states are analysed. The possibility of occurrence of the oxidation states + 9 and + 10 for some elements (for example, for iridium and platinum in tetraoxo ions) are discussed. Approaches to the realisation of these states are outlined and it is demonstrated that solid phases or matrices containing alkali metal cations are the most promising systems for the stabilisation of these high oxidation states. Selected thermodynamic features typical of metal halides and oxides and the regularities of the changes in the extreme oxidation states of *d* elements are considered. The bibliography includes 266 references.

I. Introduction

According to traditional concepts, chemical compounds contain elements in definite oxidation states (OS). These concepts form the basis of, for example, authoritative handbooks on inorganic and coordination chemistry.^{1,2} A hypothesis for the stabilisation of the oxidation states has been offered rather long ago. The theoretical and experimental aspects of this hypothesis were discussed in the early 1960s (see, for example, Refs 3–7). More recently, the experimental aspect of the problem of the existence and OS stabilisation was repeatedly considered in connection with the discovery of noble gas compounds,⁸ studies of chemical properties of transactinides^{9,10} and the preparation of compounds of Np^{VII}, Pu^{VII},¹⁰ Am^{VII},^{11–14} Cm^{VI},¹⁵ Rn^{VI},¹⁶ Cf^V,¹⁷ Cm^V,^{15,18} Au^V,¹⁹ Ag^V,²⁰ Es^{IV},¹⁸ Cu^{IV},²¹ Tm^{IV},²² and lanthanides and actinides in the lowest oxidation states.^{23–29} Worthy of mention are investigations that have demonstrated the similarity

of the properties of heavy actinides and lanthanides, the discovery of the specificity of the so-called tetrad effect in lanthanide compounds,^{23,29,30} the preparation of Fe^{VIII} (see. Refs 31 and 32) and the detection of Co^{VI} in a cesium ferrate matrix.^{33,34} Studies of the properties of elements with atomic numbers 104, 105 and 106, *viz.*, rutherfordium, dubnium and seaborgium,^{35,36} and the possibility of generation of Hg^{IV} (see Refs 37 and 38) are also worthy of note.

Recently, new aspects of the problem under consideration became apparent to researchers in connection with the development of novel techniques for the stabilisation of oxidation states. With this in mind, Yatsimirskii^{39,40} and Parry⁴¹ examined the OS stabilisation upon coordination based on the original data. Previously, we have considered different aspects of this problem. In particular, we have discussed the stability of the highest OS of lanthanides in fluoride systems,^{29,42} the effect of outer-sphere cations on the stability of coordination compounds,⁴³ the ways of attaining high OS in the oxidative fluorination reactions,⁴⁴ procedures for the identification of the valent forms of transition elements⁴⁵ and some problems associated with the concept of valence,⁴⁶ in particular, some aspects of the problem of OS stabilisation in the solid phase⁴⁷ and the possibility of generation of high valent forms ($\geq +8$) of the heaviest transition elements (Ir, Pt, Au and Hg).⁴⁸ The validity of the principles reported in Ref. 48 was confirmed by direct quantum-chemical calculations.⁴⁹

In the present review, we consider some problems of OS stabilisation in relation to new evidence on their stability and touch on the problem of the extreme valent possibilities of transition elements. The concept of 'oxidation state stabilisation' is useful in this discussion because it provides ideas and mechanisms which allow researchers not only to perform experimental studies but also to interpret the results obtained. Let us formulate the general principles of this concept.

II. A concept of oxidation state stabilisation

It is generally assumed that chemical compounds contain elements in certain OS, which are stabilised by various forces. The character of chemical processes which result in a change in the oxidation state depends on the properties of the ion to be stabilised and the corresponding coordination environment.^{7,50,51} In the studies of OS stabilisation, the possibility of formation of compounds of a particular element in the particular OS and their stability are determined and the conditions for the synthesis of these com-

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pounds are searched for, *i.e.*, techniques and procedures for the preparation of compounds with the predetermined property, *viz.*, OS, are developed and factors that affect the stability of OS are revealed (for example, phenomenologically).

Quite apparently, it is impossible to reveal the stabilisation factors without considering the problem of stabilisation of coordination polyhedra and crystalline phases. The strength of the corresponding chemical bonds and the stability of OS can be enhanced by stabilising coordination polyhedra.^{52–56}

Within the framework of the concept under consideration, it is assumed that the OS stabilisation implies an increase in the lifetime of the oxidised (reduced) form in an oxidant–reductant dynamic system compared to the standard. This system is characterised by certain thermodynamic and kinetic parameters (for example, by the Gibbs potential, vapour pressure, the activation energy, the reaction order, *etc.*). To stabilise OS, one can vary these parameters or change the ‘thermodynamics’ and/or ‘kinetics’ for those that are more favourable for the increase in the lifetime of the oxidised (reduced) form.

Let us consider the following transformation:



The $\text{Pr}_{\text{aq}}^{\text{IV}}$ aqua ion exists in aqueous media for ~ 200 ns,^{57, 58} whereupon this ion is transformed into the $\text{Pr}_{\text{aq}}^{\text{III}}$ aqua ion. When phosphotungstic acid is introduced into this dynamic system, a Pr^{IV} heteropolycompound [containing an ion of the probable composition $\text{Pr}^{\text{IV}}\text{W}_{12}\text{O}_{40}^{5-}$ (see Ref. 59)] is formed and the lifetime of the ‘oxidised’ form containing Pr^{IV} is increased to 10–15 min. Consequently, a change in the coordination environment about the Pr^{IV} ion is accompanied by a change in its stability. We do not consider the kinetic characteristics of redox processes in the absence and in the presence of heteropolyacids. However, it is evident that a change in the nearest environment of the central ion in the complex is reflected in the kinetic parameters.

The problem of stabilisation has two aspects. The first aspect is associated with the ways of attaining the desired oxidation state. The second aspect concerns the stability of this state. It is the provision of the stability of the OS over a period of time which is sufficient for its formation, identification and utilisation of the properties that receives primary attention.

The stability of chemical compounds with respect to decomposition into elements is determined by the total energy of the ligand–central atom system:

$$E_{\text{tot}} = \sum E_i + E' + E'' + E_c, \quad (2)$$

where E_i is the bond energy of the i th molecular orbital of the isolated complex formed upon interaction of the electron system of the central atom with the ligand, E' is the energy of stabilisation due to loss of degeneracy, E'' is the energy of repulsion between the ligands and E_c is the energy of stabilisation due to establishment of the long-range order (crystal lattice).⁵¹

Analysis of Eqn (2) demonstrates that the stability of compounds is governed by a combination of properties of the central atom and the ligand environment as well as by the crystal structure. Many researchers have reached this conclusion in an empirical consideration of the problem (see, for example, Refs 4 and 5).

The factors that affect the stability of OS are diverse in nature and generally act simultaneously and competitively.⁵ However, these factors can be, though rather arbitrarily, divided into thermodynamic (the first group) and kinetic (the second group) factors. The factors of the first group determine the possibility of formation of a particular ligand environment about the central atom (the formation of the short-range or long-range order). The factors of the second group affect the rate of formation of the desired environment. Taking into account the aforesaid, the following ways of stabilising OS can be distinguished.

1. Stabilisation through coordination. This stabilisation is realised in the chemical process owing to the formation of the nearest environment of the central atom in the complex, which is

more stable than those in free ions in the gaseous state or in solvated ions in solution. In this case, the ligands, the geometry, *etc.* are selected.⁷

2. Stabilisation by the crystal lattice, which is realised due to an increase in the coordination saturation of the central atom in the course of formation of crystals compared to the coordination saturation of ions in the gaseous state or in solution.^{7, 47}

3. Kinetic stabilisation due to minimisation of kinetic barriers that appear in the course of formation of the thermodynamically more favourable nearest environment of the central atom.⁷

A particular technique for the stabilisation should be chosen taking into account the properties of both the reagents and the expected reaction products containing the ion (atom) to be stabilised. Thus, the stability of compounds in which the coordination polyhedron about the ‘highly oxidised central atom’ is formed from the most stable F^- and O^{2-} ions, which are the strongest, difficultly oxidisable and difficultly deformable, are generally a maximum. Probably, only these ligands in the nearest coordination sphere of the central atom are suitable for stabilisation of the high and the highest unstable OS. Therefore, compounds with oxide and fluoride coordination polyhedra are generally considered in studies on the stabilisation of the highest OS.

Direct and inverse problems can be distinguished in the analysis of problems associated with the stability of valent forms.

The problem is said to be direct if physicochemical characteristics of an oxidant–reductant system, for example, redox potentials, are determined experimentally or calculated. The problem is said to be inverse if the conclusion about the stability of the oxidation state is made from a change in the selected parameters (properties) which can be related to OS in some series of compounds.

These problems can in principle be solved because rather simple correlations exist between the energy characteristics of the ions to which particular valent forms are assigned.

Actually, the quantum-mechanical parameters which characterise the electron density distribution and which are calculated taking into account only the electrostatic interactions between nuclei and electrons (the first-order perturbation theory) directly correlate with the oxidation states of the elements. This can be exemplified by the linear equation for the chemical shifts in the Mössbauer spectra (Fig. 1).^{32, 60, 61}

$$\delta = a + bx,$$

where δ is the chemical shift, $a = 1.834$, $b = -0.456$ and x is OS.

There are rather simple correlations between the enthalpies of formation of halides MHal_n and the enthalpy increments of M^{n+} ions calculated according to the additive schemes.⁶² These correlations can be interpreted in a different way (see, for example, Ref. 63) because of the ambiguity of the approaches used by chemists or, more precisely, due to the fact that none of approaches can be extended indiscriminately to all compounds.

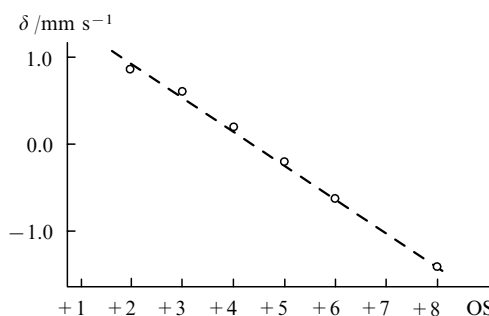


Figure 1. Dependence of the chemical shift relative to sodium nitroprusside on OS of the metal for iron derivatives.^{32, 60, 61}

In the general case, the direct and inverse problems cannot be solved. This is associated with many factors but the main reason is that M_{aq}^{n+} aqua ions that exist in solutions are known only for a limited number of elements (generally, in the lowest OS). As the atomic number of the element is increased, the covalence of the M–L bond and the role of relativistic effects, including spin-orbital interactions, are increased, which is accompanied by the enhancement of the characteristic features of the ions more complex than aqua ions (for example, of actinyl ions⁶⁴). An analogous situation is observed as the OS is increased.

The definition of the notion 'oxidation state' is the key in the analysis of the problems associated with the concept under consideration. This problem, which is directly related to the 'problem of valence,' is intricate. In particular, the problem of the relationship between the valence number, the effective charge and OS is still topical, although it has been discussed many times. This aspect of the chemical structure theory turned to be so contradictory that it has been suggested,⁶⁵ without going into terminological details, to consider the valence only as a number, to retain its classical content and to give up attempting to treat all modern discoveries in the field of chemical bonds in the context of this notion. However, more recently (see, for example, Refs 66 and 67) attempts to calculate the valence numbers have been undertaken. No consideration is given to these and other calculation procedures in the present discussion, but it should be noted that none of the available procedures is versatile.

The measure of the valence or OS can be most readily determined by the number of gram-equivalents of the oxidising or reducing agent per gram-atom of the element (metal or metalloid) which is either consumed or acquired when the element is transformed to the compound or vice versa. It is advantageous to take a one-equivalent oxidation or reduction process as the standard process, the choice of a particular one-equivalent conversion being of no importance. The above-described determination of the valence number[†] is convenient because it is based on experimental grounds and is invariant with respect to the model of the electronic structure of the compound.

We emphasise that the positive or negative value of OS does not imply that the corresponding charge is located on the atom. The determination of the valence on the basis of the number of gram-equivalents means the thermodynamic relations from which neither the spatial arrangement of the atoms nor characteristics of the bonds (for example, the bond order, which cannot be determined spectroscopically) can be directly obtained. The gram-equivalent is a complex parameter, which covers all interactions in the compound, and it cannot be represented either as a charge or as a number of bonds.

The valence (or OS) is a classification notion used in crystal chemistry or for systematising educational data on inorganic chemistry. For example, Kossel's views were consistently used in the monograph⁶⁹ for tetrahedral systems. Chemical compounds of the element in the same oxidation state can be characterised by different electron density distributions, coordination polyhedra and the bond character. This is not surprising because specific electronic properties of atoms, which can be judged from the results of physical methods, are nothing more than a consequence of the manifestation of a particular valence. The above-considered determination of the valence number does not contradict the notions⁷¹ of the electronic state fluctuation, processes of electronic ordering and, consequently, fractional OS for transition elements. These are the properties of the element which exists in a

particular OS or possesses a definite valence. These properties should be specially studied and systematised.

The results of calculations of the enthalpies of formation of inorganic halides and oxides according to additive schemes provide certain support for the above approach to the determination of the valence.^{62, 72–75}

Calculations of the enthalpies (energies) of inorganic halides and oxides are based on the classical structure theory, which has been conceptually refined by Tatevskii.^{76, 77} According to the known approximation of this theory, the macrocharacteristic, such as the self-energy, can be represented as a sum of increments (E_j) that characterise contributions of the so-called effective j th atoms with the valence number (n), $j^{(n)}$:

$$\Delta U = \sum E_{j^{(n)}}. \quad (3)$$

The application of this equation to inorganic subjects is limited. Equation (3) cannot be directly used even in the seemingly simple case, *viz.*, in the case of compounds of various metals of the same stoichiometry, because one has to solve a system of k equations of the type

$$\Delta U_{A_x B_y} = x E_{A^{(n)}} + y E_{B^{(n)}} [E_A = \Phi(n), E_B = \text{const}] \quad (4)$$

in $k + 1$ unknowns. One more equation is required to obtain a solution. We found an equation of relationship,^{62, 73, 78} which is an empirical correlation between the enthalpy of formation of compounds MX_n and the enthalpy of the following type:

$$H_{M^{(n)}} \equiv \frac{\sum I_i}{I_1} \Delta_s H_M,$$

where I_i are stepwise ionisation potentials and $\Delta_s H_M$ is the enthalpy of sublimation of the metal.

The equation takes the form of the following additive four-membered equation:

$$\Delta_f H_{MX_n}^0 = H_{M^{(n)}} + n H_X + n H_{M^{(n)}-X} + y H_{X-X}, \quad (5)$$

where $H_{M^{(n)}}$ is the enthalpy corresponding to the contribution of the central atom, H_X , $H_{M^{(n)}-X}$ and H_{X-X} are the enthalpies corresponding to the contributions of the ligand X and of the $M^{(n)}-X$ and $X-X$ bonds, respectively. Examples of selected dependences of the enthalpies of formation of chlorides and fluorides on the first term of Eqn (5) are given on Fig. 2 and in Table 1.

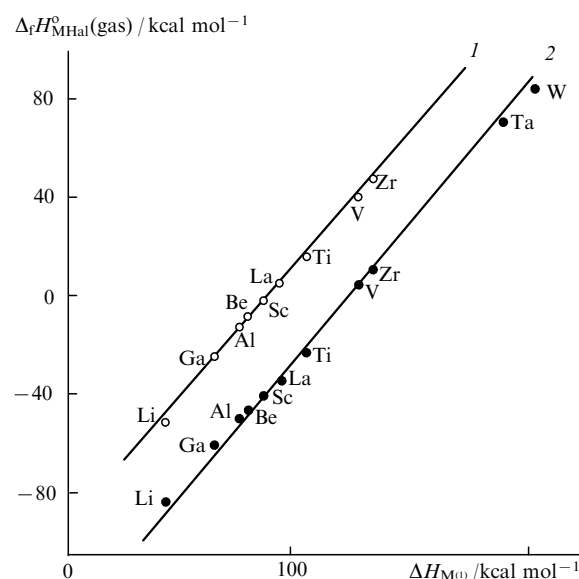


Figure 2. Dependence of the enthalpy of formation of gaseous monohalides on the partial enthalpy $H_{M(0)}$; (1) chlorides; (2) fluorides.

[†] In this approach, the valence numbers coincide with the so-called Jorgensen's formal OS (or the Russian term 'degrees of oxidation'). The application of the latter is improper because of the absence of charges on atoms. Crystal-chemists use 'formal charges' on atoms in calculations^{68, 69} and reject the reality of these charges by introducing the notion 'effective charges.' The valence balance or valence strengths would be more properly used (this approach was used, for example, in Ref. 70).

Table 1. Coefficients of the linear dependence $\Delta_f H^\circ = A + BH_{M^{(n)}}$ for gaseous metal halides.

Halide	Metal	A	B
MF	Na, K, Rb, Cs, Ag, Tl	−112.7	1.636
	Li, Be, Al, Sc, Ti, V, Ga, Zr, Ta, La–Lu	−117.4	0.970
	Ca, Sr, Ba, Cr, Mn, Fe, Co, Ni, Cu, In	−126.3	1.479
	Zn, Cd, Hg, Sn, Pb, Zr, Hf, Y	−26.0	0
MF ₂	Mg, Ba, Ra, Zn, Cd, Hg, Yb	115.0	−1.930
	Be, Cr, Mn, Fe, Co, Ni, Ga, Mo, Tc, Ru, Rh, Pd, Ag, In, Sn, Ta, W, Re, Os, Ir, Pt	−193.6	0.328
	Sn, Pb, Zr, Hf	−89.9	−0.0999
	Sr, Sc, La–Lu	−217.9	0.252
	Cu, Zn, Pb, Ru, Rh, Pd, Os, Ir, Pt	−141.8	0.252
	Al, Ti, V, Ga, Y, Nb, Mo, Tc, La, Ta, W	−340.1	0.486
	Al, Ga, In, Tl, Mn	−44.1	−0.280
	Al, Ti, Zr	−345.5	0.0841
MF ₃	Sc, Y, La–Lu	−302.7	0
	Na, K, Rb, Cs, Ag, Tl, Mg, Ca, Sr, Ba	−87.1	1.636
	Li, Al, Be, Sc, Ti, V, Ga, Zr, Ta, La–Lu	−84.9	0.970
	Cr, Mn, Fe, Co, Ni, Cu, In, Sn	−100.3	1.479
MCl	Zn, Cd, Hg, Sn, Pb, Zr, Hf, Y	5.0	0
	Mg, Ba, Ra, Zn, Cd, Yb	105.1	−1.930
	Cr, Mn, Fe, Co, Ni, Mo, Tc, Ru, Rh, Pd, Ag, In, Re, Os, Ir, Pt, Au, Tm	−129.5	0.328
	Sn, Pb, Hf, Hg	−26.0	−0.0999
MCl ₂	Be, Al, Sc, Ti, V, Ga, Y, Ca, Sr, Ba, Zr, Nb, Mo, Tc, Ru, Ag, La, Hf, Ta, W, Re, Ce–Lu	−144.4	0.252
	Cu, Zn, Rh, Pd, Os, Ir, Pt, Pb	−77.3	0.252
	Al, Ga, In, Tl	57.8	−0.280
	Cr, Mn, Fe, Ir	−233.6	0.239
MCl ₃	Sc, Y, La–Lu	−170.2	0

Note. The characteristic groups, *i.e.*, the sets of compounds of elements of the corresponding vertical groups in the short version of the Periodic system, are given in boldface type.

$$\Delta_f H^\circ = A + BH_{M^{(n)}}.$$

A similar situation is also observed for other halides and oxides.

The so-called characteristic sets of compounds can be distinguished in these linear dependences. The Group I elements are characteristic for monohalides (see Fig. 2), the Group II elements are characteristic for dihalides, *etc.* In other words, the characteristic sets of compounds of elements with the *i*th valence are comparable with the lists of the elements in the vertical groups of the short version of the Periodic system.

Taking into account the additive equation (5) and the linear dependences of the enthalpies of formation of gaseous halides on the enthalpies $H_{M^{(n)}}$, it can be concluded that grouping of compounds is dictated by the argument, while the character of the change in the function is determined by the remaining terms of the additive sum in Eqn (5).

The relationship between the enthalpy increments is such that the first terms of the sum (5) have the maximum values. This makes it possible to construct the hierarchy which defines the energetics of compounds and which is based on the classical structure theory.^{76,77}

This theory assumes the application of the model of pairwise interactions. A certain energy increment can be related to each pairwise interaction (the procedure is described in the monograph⁷⁶). The values of the increments depend on the following characteristics: chemical individuality, sort, type, kind and variety. On the whole, these characteristics comprise a 'tree' of chemical states. The first characteristic is determined by the position of the element in the Periodic system. The second characteristic is associated with the valence. The third characteristic is connected with the geometry of the nearest environment of

the central atom. The last two mentioned characteristics reflect finer details of the structure, for example, geometrical or optical isomerism.

The characteristics of the sort (valence), which determine, in particular, clustering of halides (or oxides) in the dependences analogous to those shown in Fig. 2, can be assigned to the parameter $H_{M^{(n)}}$. As a consequence, the valence is determined through the gram-equivalent, *i.e.*, through the thermodynamic relations.

The oxidation states can be determined by direct (chemical) and indirect (physical) methods. Oxidimetric and electrochemical techniques were referred to as the chemical methods in Ref. 45. Procedures for the analysis based on one-equivalent transitions of the types $I^- \rightarrow (1/2)I_2$ and $Ce^{III} \rightarrow Ce^{IV}$ as well as on processes described by a known number of equivalents ($MnO_4^- \rightarrow Mn^{II}$ and $Cr_2O_7^{2-} \rightarrow Cr^{III}$) are very popular. Of the above-mentioned procedures, iodometric techniques are most widely used because of their simplicity, availability and versatility.

For example, the applications of the iodometric analysis to fluoride-containing oxidants, which include compounds of *d* and *f* transition elements, and to platinum compounds were considered.^{79,80} Fluorides of Ln^{IV} , Cu^{II} , Cu^{III} , Ag^{II} , Ag^{III} , Ag^V , Au^V , Ni^{III} , Ni^{IV} , Mn^{III} , Mn^{IV} , Co^{III} , Fe^{III} , Fe^{IV} , Cl^{III} , Br^{III} , Br^V , Xe^{II} , Xe^{IV} , Xe^{VI} , *etc.* were analysed. The iodometric procedure was used in the analysis of alkaline solutions of iron derivatives in the highest oxidation states (Fe^{IV} , Fe^{VI} and Fe^{VIII}).⁸¹ In this case, not only the OS of iron but also the concentration of the metal in solution was determined.

The determination of the final state after titration is the key to oxidimetric (in particular, iodometric) procedures. Thus experiments with platinum compounds demonstrated⁸⁰ that $Pt^{2.3+}$ was the final state in the titration of iodide complexes, which does not prevent the analysis.

Evidently, the main drawback of oxidimetric procedures is the absence of selectivity. This calls for studies aimed at revealing reasons for redox transformations. For example, the analysis of alkaline solutions of iron in the highest oxidation state was accompanied by additional studies of solutions by Mössbauer spectroscopy, which have demonstrated that the iodometric data correspond to the valence transitions of iron.⁸¹

Much the same is true for electrochemical methods, *viz.*, for polarography and coulometry. Cyclic voltammetry in combination with coulometry is a convenient procedure for the determination of gram-equivalents in metal complexes.⁸² For example, two reversible one-electron waves corresponding to the $Ir^{VI} \rightarrow Ir^{V} \rightarrow Ir^{IV}$ transformations are observed in the cyclic voltammograms of reduction of the electrochemically oxidised hydroxo complexes of Ir^{IV} .^{83,84} Electrochemical methods can be applied not only to solutions but also to melts. For example, these procedures were used for revealing the nature of the processes in salt melts and for determining conditions for stabilisation of the highest transition-element OS in these melts.⁸⁵

Chemical methods for the OS determination are effective only in combination with physical methods. The most commonly used methods are magnetochemistry, ESR, electronic, Mössbauer and X-ray spectroscopy, X-ray photoelectron spectroscopy, X-ray diffraction analysis and methods of vibrational spectroscopy.⁴⁵ To answer the question about the element OS, it is necessary to know, first, the correlations between OS and the parameter observed and, second, the reasons for deviations from these correlations if these deviations are observed or expected. For example, the number of outer electrons withdrawn from the electronic configuration of the free atom often corresponds to the element OS. In addition, the number of gram-equivalents of the oxidising (reducing) agent consumed in the oxidimetric titration corresponds to the number of *d* (or *f*) electrons of the metal ion (for a series of important regularities, see Refs 86–88).

Below are considered procedures for the stabilisation of the highest OS of particular elements.

III. Rare-earth elements

The known OS^{89, 90} for rare-earth elements (REE, Ln) are listed in Table 2. For rare-earth elements, OS + 3 is generally realised in a rich variety of their compounds; OS + 2 belongs to the lowest OS and is not considered in the present paper because many studies were devoted to this problem and the results have been reviewed.²³

Table 2. Known oxidation states of rare-earth elements.^{89, 90}

OS	La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
+2	?	?	+	+	?	+	+	?	?	+	+	+	+	+	?
+3	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
+4		+	+	+		+			+	+			+		

Note. Hereinafter, the following notations are used: +, this OS exists; ?, indirect evidence is available and reliable proof is absent.

1. Complexes of Ln^{IV} with organic ligands

The problem of preparation of rare-earth complexes in high OS with organic ligands arose in the 20th century.^{91–93} These compounds are often characterised by high stability constants and are very promising, for example, for the separation of rare-earth elements and actinides.^{94–96} In the 1970s, it was established that intramolecular redox processes cannot be completely eliminated even in Ce^{IV} compounds (see, for example, Ref. 97), and the number of studies aimed at this particular application became fewer. However, it was reported⁹⁸ that the influence of these processes in rare-earth complexes with diphthalocyanines was a minimum, and it was concluded that these subjects contain Ln^{IV} ions throughout the entire lanthanide family. Nevertheless, a number of facts do not allow one to accept this interpretation of the data made in the work cited. In studies of transition metal complexes in the highest OS with carboxyl-containing chelating agents, hydroxy carboxylic acids, polydentate acyclic ligands, crown ethers and β -diketones, it was demonstrated that redox processes occur in all cases, though at different rates.⁹⁷ In other words, intramolecular redox interactions can only be partially suppressed (but not completely excluded) by choosing an appropriate ligand. Phthalocyanine can be readily reduced due to the presence of a large number of multiple bonds. Even if rare-earth complexes under consideration possess high stability, one cannot expect that intramolecular redox processes would be completely suppressed taking into account extremely high values of the redox potentials of the Ln^{III}/Ln^{IV} pairs (for example, the values of E° were estimated as equal to 2.83.0 V for Ln = Tb and Pr^{99, 100}). Apparently, additional supporting evidence for the existence of Ln^{IV} in diphthalocyanines is required.¹⁰¹

2. Complexes of Ln^{IV} with inorganic ligands

The data on the behaviour of Ln^{IV} (Ln = Ce, Pr, Nd, Tb and Dy) in aqueous media are limited mainly by those for Ce^{IV} compounds. The Ce^{IV} ion is a rather strong oxidant ($E^\circ_{\text{Ce}^{IV}/\text{Ce}^{III}} = 1.66 \text{ V}^{99, 100}$). These ions are formed in the reactions with the participation of oxidants such as bromate (see, for example, Ref. 102) and are stabilised by various inorganic ligands with different efficiency. Interestingly, Ce^{IV} compounds containing chloride ions in the nearest coordination sphere exist although Cl[−] ions are known as reductants. For example, a large series of hexachlorocerates(IV) M₂Ce^{IV}Cl₆ (M^I = NR₄⁺, PR₄⁺, AsR₄⁺, H₃O⁺, Rb⁺ and Cs⁺) were prepared and their structures and stabilities were studied.^{103–112} It was demonstrated¹¹³ that the anionic [CeCl₆^{2−}] complex exists in aqueous media for a rather long period of time and an excess of chloride ions even somewhat stabilises this complex. The cesium salt (air-stable below 300 °C) is a convenient gravimetric form in the chemical analysis and separation of alkali metal cations.¹⁰⁵

Data on the existence of Tb^{IV} and Pr^{IV} in aqueous media are scarce. Note that the information on the preparation of Pr^{IV} and Tb^{IV} acido complexes (nitrates, sulfates and chlorides) in aqueous solution was disproved.¹¹⁴ As mentioned above, reliable data on the Pr^{IV} ions were obtained by pulse radiolysis:^{57, 58} the short-lived absorption was assigned to the Pr^{IV} aqua ion. The Pr^{IV} ion is unstable due to the larger value of the Pr^{IV}/Pr^{III} pair redox potential. The preparation of aqueous solutions of Pr^{IV} phosphotungstate was reported.^{115–117} The possibilities of studying this deep coloured complex are limited since this complex exists in a solution for only several minutes even at low concentrations. As a consequence, detailed information on this complex is absent.

Tetravalent terbium ($E^\circ_{\text{Tb}^{IV}/\text{Tb}^{III}} \approx 2.8 \text{ V}$) is also stabilised in a salt of phosphotungstic acid.^{59, 117, 118} Its solutions can be stored at room temperature for several months. Phosphotungstic acid can be very efficiently used for stabilising strong oxidants, such as actinide ions, and the complexation leads to a decrease in the E° value by $\sim 1.0 \text{ V}$.^{118, 119} The evidence on the existence of Pr^{IV} and Tb^{IV} ions in these compounds suggests that the above conclusion is true for lanthanides as well.

While on the subject of aqueous media, Pr^{IV} and Tb^{IV} hydroxides should be mentioned. Treatment of alkaline suspensions of Tb^{III} hydroxide with such reagents as O₃, S₂O₈^{2−} and IO₄[−] is accompanied by the formation of Tb^{IV} hydroxide.¹²⁰ Treatment of binary and complex Pr^{IV} and Tb^{IV} fluorides with alkaline solutions also resulted in the isolation of hydroxides.¹²¹ Note that the yield of Ln^{IV} hydroxide decreases as the stability of Ln^{IV} ions decreases. Thus when the corresponding fluoride complex was treated with cold alkali, Tb^{IV}O₂·*n*H₂O was obtained in almost quantitative yield, the yield in the case of Pr^{IV} was substantially lower and Dy^{IV} hydroxide was formed only in trace amounts.¹²¹

To summarise, the stabilisation of Ln^{IV} in solutions is insufficiently efficient due to a limited number of inorganic ligands which are able to decrease the redox potential of the system to a reasonable value. The stability of Ln^{IV} is substantially higher in the solid state than in solutions, which is manifested not only in the higher thermal stability of the solid compounds compared to that of the complexes in solutions but also in the broad assortment of the corresponding tetravalent ions^{89, 122, 123} that occur in solid phases.

Solid fluoride complexes of Ce^{IV}, Tb^{IV}, Pr^{IV}, Nd^{IV}, Dy^{IV}, Tm^{IV} and Sm^{IV} (the data on the last two mentioned complexes were reported in Refs 22 and 29) and binary Ce^{IV}, Tb^{IV} and Pr^{IV} fluorides (the synthesis of pure PrF₄ was described for the first time in Refs 124 and 125) have been prepared to date. Binary oxides PrO_{2−*x*} and TbO_{2−*x*} (*x* < 0.5) and complex compounds were detected in oxygen-containing systems.^{126, 127} A large number of Ln^{IV} ions (Pr^{IV}, Tb^{IV}, Nd^{IV} and Dy^{IV}) are stabilised in BaCeO₃,^{128–130} which serves as a matrix. Stabilisation was performed under an atmosphere of oxygen at 1200–1400 °C.^{128, 129, 131}

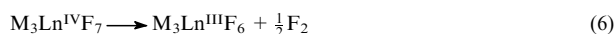
Therefore, the stability of a metal–ligand system in the solid phase (*i.e.*, in the presence of long-range order) is higher than that of this system in solution. The coordination effects that occur in the solid state diminish the intermolecular metal–ligand distances in the nearest coordination sphere about the central atom of the complex compared to the internuclear distances in the binary compounds,¹³² which also favours the stabilisation of the Ln^{IV} ions.

The currently available evidence allows one to consider the regularities of stabilisation of the highest OS of lanthanides. Analysis of the stability of Ln^{IV} compounds based on the published data^{29, 43, 133–137} allowed conclusions^{29, 137} that the efficiency of Ln^{IV} stabilisation can be judged from only two groups of data. The first group includes the data on redox potentials or ionisation potentials of lanthanide atoms. However, this information does not allow reliable conclusions about the stability of Ln^{IV} because $E^\circ_{\text{Ln}^{IV}/\text{Ln}^{III}}$ are calculated by empirical methods and only the data on Ce^{IV} derivatives provide trustworthy basis for these calculations. The experimental E° values

for other $\text{Ln}^{\text{IV}}/\text{Ln}^{\text{III}}$ pairs cannot be obtained due to the high oxidising capacity of Ln^{IV} , which does not allow one to construct an equilibrium electrochemical cell. The solution of the direct problem of the stability presents difficulties because the initial data are scarce. The series of the relative stabilities of oxidation states^{122, 123} obtained on the above basis reflect only roughly the actual situation. Therefore, an alternative method which consists in the solution of the above-mentioned inverse problem is used for obtaining data on the stability of Ln^{IV} .

The thermodynamic characteristics of Ln^{IV} fluorides with composition Cs_3LnF_7 were reported.¹³⁵ The thermal stabilities of the same fluorides were also studied by methods of non-isothermal kinetics. The thermodynamic values were determined according to procedures of differential thermal analysis,¹³⁸ which have been developed and tested in special experiments, with the use of a specially designed sealed nickel cell whose sensitivity is close to that of the cell of a differential scanning calorimeter.^{139–141} These procedures make it possible to obtain data on the enthalpies of fluorination reactions.

The most reliable values of the enthalpies and Gibbs energies of the reactions



for all rare-earth elements (Table 3) can be obtained on the basis of the available data^{135–137} and results of calculations of the Born–Haber cycle.^{135, 142–144}

Table 3. Results of calculations of the enthalpies of process (6) (kJ mol^{-1}) according to the Born–Haber cycle.¹³⁵

Ln	ΔU	$-\Delta_r H^\circ$	Ln	ΔU	$-\Delta_r H^\circ$
Ce	3608	331	Tb	3809	239
Pr	3656	164	Dy	3827	95
Nd	3730	90	Ho	3852	22
Sm	3753	31	Er	3904	58
Eu	3774	–68	Tm	3986	136
Gd	3793	–184	Yb	3998	47

It was confirmed^{135, 142–144} that in the LnF_4 series the cerium compound is the most stable one, this is followed by the terbium and praseodymium derivatives in order of decreasing stability. The thermal stability of the M_3LnF_7 complexes decreases in the following order: $\text{Ce} > \text{Tb} > \text{Pr} > \text{Dy}$.^{137, 145, 146}

The thermodynamic stability of the complexes with respect to elimination of fluorine according to reaction (6) decreases on going from Ce to Sm: $\text{Ce} > \text{Tb} > \text{Pr} > \text{Dy} > \text{Tm} > \text{Nd} > \text{Sm}$. The stability of the highest OS (+4) of lanthanides decreases in the same order.

The regularity which is observed in the lanthanide series and is referred to as the ‘tetrad effect’ has been refined.^{29, 137} In the series of the rare-earth elements, ‘nodal points’ exist in which the probability of changes in the composition, structure, the type of phase diagram and some other parameters is a maximum. The lanthanide family is divided into four segments (from whence the name ‘tetrad’ follows). This effect is most pronounced in the middle of the 4f series, which corresponds to the ‘gadolinium break’.^{29, 147, 148} This effect is most clearly manifested in the atomic properties (ionisation potentials, electron affinity, Gibbs energy, enthalpies of gaseous ions, *etc.*). The tetrad effect was attributed to the specific change in the electrostatic term of the exchange interaction of the f electrons in the Ln series.¹⁴⁵

The thermodynamic data (ΔH° and ΔG°) for Ln^{IV} fluorides reproduce the tetrad effect.^{29, 135} However, the distinguishing feature is that this effect is of different importance for the middle elements of each half of the series. This effect is more pronounced in the middle of the second half of the series. As a consequence, the

stability of Tm^{IV} is anomalously high compared to that of Sm^{IV} due to the effect of the condensed state.

Actually,^{137, 149} the difference between the lattice energies of $\text{Ln}^{\text{III}}\text{F}_3$ and $\text{Ln}^{\text{IV}}\text{F}_4$ or of $\text{M}_3\text{Ln}^{\text{IV}}\text{F}_7$ and $\text{M}_3\text{Ln}^{\text{III}}\text{F}_6$ (ΔU) and the differences between the corresponding enthalpies of formation (ΔH°) are related to the fourth ionisation potentials of the lanthanide atoms (I_4) by the following equation:

$$\Delta H^\circ + \Delta U + \text{const} = I_4.$$

The ΔU values in the lanthanide series change ‘smoothly’ (see Table 3) so that these values for the second half of the 4f series are substantially larger than those for the first one. Since the dependence of I_4 on the atomic number of the element is nonlinear and is governed by the tetrad effect, the ΔH° (ΔG°) values should be changed analogously. This implies that the enthalpies (Gibbs energies) of formations of Tm^{IV} compounds should be larger in magnitude than the corresponding values for the Sm^{IV} compounds.

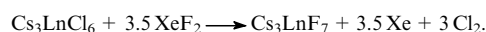
3. The effect of complexation

A large number of tetravalent rare-earth elements are stabilised in cesium fluoro complexes. The higher stability of the complexes compared to the corresponding binary compounds has been discussed many times (see, for example, Refs 29 and 42). In the solid phase, the stabilisation occurs due to the positive charge of the outer-sphere cation, which compensates for the negative charges on the complex anions.⁴³ The absence of the outer-sphere cations in the structure of a compound leads to a distortion of the coordination polyhedron of the central atom as a result of which the overall atomic system is destabilised. For example, the structure of AuF_5 is built of octahedra linked to each other and twisted into a helix.¹⁵⁰ In Au^{V} complex fluorides, there is no need for such twist and the anion has an octahedral shape.¹⁵¹

4. Valence possibilities of lanthanides

Efforts were made to extend the series of lanthanides which could be transformed into the highest OS and to reveal the possibilities of attaining OS higher than +4 by experimental methods.^{121, 124, 137, 140, 141}

In the solution of the first problem, reactions were found which are characterised by minimal kinetic barriers to processes of formation and the maximum possibility of the $\text{Ln}^{\text{III}} \rightarrow \text{Ln}^{\text{IV}}$ transformation.⁴⁴ The reaction that proceeds according to the following general equation:



is most suitable.

This reaction was successfully used for the preparation of Cs_3TmF_7 ; Tm^{IV} was identified by physicochemical methods. Experimental evidence (the data from differential thermal analysis) for the existence of Sm^{IV} was obtained.⁴⁴

The solution of the second problem was considered using praseodymium, which exhibits the most promise for preparing the highest valent forms, as an example.¹³⁷ Various high- and low-temperature fluorination reactions of binary and complex chlorides, fluorides, nitrates and sulfates under diverse reaction conditions (with variations of the temperature and the duration of the reaction, in the presence or in the absence of a solvent, *etc.*) were studied. The most powerful oxidants, including fluorine, krypton difluoride, *etc.*, were used. It appeared that in all cases fluorination afforded only Pr^{IV} compounds. Taking into account this fact and based on the theoretical grounds, it was concluded^{29, 137} that +4 is the extreme OS for 4f elements due to strong localisation of 4f states in the atomic core of lanthanides and the presence of serious energy hindrances to the subsequent ionisation. These 4f elements differ sharply from 5f elements.

In conclusion, it should be noted that OS +4 for the rare-earth elements are also stabilised in other solid systems, in particular, in perovskites BaTbO_3 , SrCeO_3 ,¹⁵² $\text{Ba}_{1-y}\text{Sr}_y\text{PrO}_3$, $\text{BaCe}_y\text{Pr}_{1-y}\text{O}_3$ and $\text{Sr}_y\text{Ba}_{1-y}\text{PrO}_3$,¹⁵³ oxide superconductors

$\text{Pb}_2\text{Sr}_2\text{Ce}_{1-x}\text{Ca}_x\text{Cu}_3\text{O}_8$ ¹⁵⁴ and $\text{Pb}_2\text{Sr}_2\text{RCu}_3\text{O}_8$ ($\text{R} = \text{Ce}, \text{Pr}, \text{Tb}$ or Am ¹⁵⁵) and manganites $\text{Y}_{1-x}\text{Pr}_x\text{Sr}_2\text{Cu}_{2.85}\text{Re}_{0.15}\text{O}_{7+\delta}$,¹⁵⁶ $\text{Pr}_{1-x}(\text{Ca},\text{Sr})_x\text{MnO}_3$,¹⁵⁷ $\text{Pr}_{0.6}\text{Ca}_{0.4}\text{MnO}_3$ ¹⁵⁸ and $\text{Pr}_{0.6}(\text{Ca},\text{Sr})_{0.4}\text{MnO}_3$.¹⁵⁹

IV. Transition elements

Of all transition metals, the Group VIII elements, silver, gold and mercury are of most interest because researchers faced serious problems when preparing their highest valent forms.

1. Highest valent forms of iron

Until recently, it was assumed that the maximum valence of iron is no higher than +6 and this fact was even substantiated theoretically. Quantum-chemical calculations for Fe, Ru and Os tetroxides¹⁶⁰ demonstrated that FeO_4 is characterised by high populations of the atomic states, which excludes the formation of strong Fe–O bonds. However, this fact does not necessarily indicate that this compound, though unstable, cannot be prepared. For iron, an OS of +5 was observed only in one compound, *viz.*, in $\text{La}_2\text{LiFeO}_6$, which was prepared at high pressure and was well studied.¹⁶¹ The seemingly well-known ferrates(VI) continue to attract the attention of researchers. For example, the mechanism of decomposition of ferrate(VI) was considered in Ref. 162. At the same time, Fe^{IV} compounds remain poorly studied.

The processes that occur in alkaline media upon anodic dissolution of metallic iron under conditions of high current density were studied in detail.^{31, 32, 163–178} The conditions for formation of ferrate(VI) were found,^{31, 32, 168–173} qualitative notions of the mechanism of this process were developed and explanations were offered for the decomposition of concentrated ferrate(VI) solutions to form iron(III) hydroxide. Abnormal properties of ferrate solutions were observed. The detailed studies of these properties allowed conclusions to be made about the existence of ferrates(IV) in alkaline media (previously, it was believed that these compounds are unstable in aqueous solutions) as well as about the occurrence of FeO_4 .^{31, 32} These compounds were identified by electronic spectroscopy of solutions, Mössbauer spectroscopy and some other methods. The justified assumptions were made that ferrate(VI) may undergo disproportionation and thermal stimulation of the latter afforded Fe^{VIII} and Fe^{IV} derivatives.

Iron tetroxide is very unstable. It can be isolated in a relatively pure form by extraction from solutions of ferrates in CCl_4 . The extracts were distilled at 30 °C to give products in yields no higher than 25%–30%. These properties were used in the preparation of highly pure iron.^{179–181} Solutions of Fe^{VIII} undergo autocatalytic decomposition to Fe^{III} hydroxide and can exist only when the concentration of iron is lower than 0.01 mol litre^{−1}. The Mössbauer spectra (77 K) of aqueous–alkaline systems containing Fe^{VIII} have a singlet line belonging (judging from the value of the chemical shift δ) to the highest valent form of iron.³²

Ferrate(VI) in an aqueous–alkaline medium is so stable that its solutions under normal conditions can be stored for at least two years. This compound is formed not only in the course of the above-mentioned disproportionation but also under prolonged action of oxygen on alkaline solutions of Fe^{III} hydroxo complexes.^{178–181}

The data on FeO_4 essentially supplement the known regularities of the Periodic system and, in addition, make it possible to establish a qualitative correlation between the stability of the compounds and the occupancies of the orbitals determined by quantum-chemical methods.

2. Copper, silver and gold

The data on OS of copper, silver and gold are given in Table 4. For this group of elements, OS $\geq +3$ are unstable, although, strictly speaking, even OS of +2 is unstable. For example, one of the manifestations of the effect of variable valence, *viz.*, the fluctua-

Table 4. Oxidation states of copper, silver and gold.

OS	Cu	Ag	Au
+1	+ (see ^a)	+ (see ^a)	+ (see ^a)
+2	+ (see ^{a, b})	+ (see ^{b, d})	? (see ^b)
+3	+ (see ^{c, d})	+ (see ^{c, d})	+ (see ^a)
+4	+ (see ^{c, d})	? (see ^b)	? (see ^b)
+5		+ (see ^d)	+ (see ^d)

^a Known in many compounds. ^b Undergoes disproportionation. ^c For oxides. ^d For fluorides.

tion of the charge state, is observed for Cu^{II} ions. Apparently, this results in such a value of the redox potential $E^\circ_{\text{Cu}^{\text{III}}/\text{Cu}}$ that the Cu^{II} ion can be considered as an oxidant.

The problem of the existence of the highest valent forms for Cu, Ag and Au is still not completely solved. This is particularly true for gold. The first Au^{V} compound, *viz.*, the fluoro complex with the bulky $\text{Xe}_2\text{F}_{11}^+$ cation, was prepared only in 1972.¹⁸² Since that time, some other Au^{V} compounds have been synthesised. In particular, AuF_5 and fluoro complexes with cations of alkali and alkaline-earth metals were prepared. However, no compounds with ligands other than fluoride were found.¹⁸³ The questions of whether Au^{IV} can be isolated and whether OS higher than +5 can be realised are still open. The same is true for silver compounds. Thus, only the Ag^{V} derivative with composition $\text{Cs}_2\text{Ag}_{1/2}^{\text{V}}\text{Ag}_{1/2}^{\text{III}}\text{F}_6$ is known.¹⁸⁴

These problems have been considered many times.^{150, 151, 185–197} New binary (AgF_3) and complex fluorides of Cu^{III} , Ag^{I} , Ag^{II} , Ag^{III} , Au^{III} , Au^{V} and $\text{Ag}^{\text{III, V}}$ with various outer-sphere cations were synthesised and studied. Many of the synthetic reactions of these compounds have been examined and the factors that affect the yields of the products and, consequently, the stabilisation of the corresponding OS have been revealed.¹⁹⁷ Finally, data which can be interpreted in the context of disproportionation of Au^{V} were obtained in studies of thermolysis products of Au^{V} fluoro complexes.¹⁵⁰ In fact, there is no direct evidence for the presence of a disproportionation product, *viz.*, of a fluoride more enriched with fluorine than AuF_5 , in the gaseous phase.

The data on the preparation of Cu^{IV} as Cs_2CuF_6 and Cu^{IV} oxide were reported in Refs 198 and 199, respectively. The latter experiments were carried out under high oxygen pressure. The oxide contains Cu^{III} and Cu^{IV} stabilised in the perovskite lattice with composition $\text{La}_{1-x}\text{Sr}_x\text{CuO}_3$ ($0 \leq x \leq 0.25$).

The formation of mixed-valence states is typical of Cu, Ag and Au both in the fluoride and oxide systems. In oxide superconductors and related compounds, these states of copper are of great importance. In superconductors, the OS of copper varies from +1 to +2.33. In this case, the π -orbitals of oxygen atoms make significant contributions to the corresponding molecular orbitals. The mixed-valence states^{200, 201} are responsible, for example,²⁰² for a ‘charge-stabilised’ distortion of $\text{NaBa}_2\text{Cu}_3\text{O}_6$. Of the recent works in this field, let us note Refs 203–205. The unusual properties of gold oxides in oxide films were described.^{206, 207} In this connection, recall the effects associated with the dynamics of the electron density in the solid phase.⁷¹ The unit cell can contain metal ions in different OS that occupy crystallographically non-equivalent positions, metal ions in different OS that occupy equivalent positions and, finally, metal ions in the so-called fluctuating state where fast oscillations (which are equivalent to electron transitions between different OS) of electron density occur at each lattice centre. The existence of the mixed-valence state is an indication of valence instability. This problem as well as the factors favourable for disproportionation were considered.⁴⁸ The existence of copper in the mixed-valence state ($\text{Cu}^{\text{III, IV}}$) in oxides is indicative of a decrease in the stability of OS +4 of copper compared to that observed in the fluoride due, apparently,

to the presence of the essential π -component of the metal–ligand bond in the oxide. Taking into account the existence of copper in the $\text{Cu}^{\text{III}}/\text{Cu}^{\text{IV}}$ state, it is believed that +4 is the extreme oxidation state for copper.

3. Heavy platinum elements

Difficulties emerge in the realisation of the highest OS for heavy 5d transition elements (Table 5). This is particularly true for Ir, Pt, Au and Hg. It can be seen that the maximum oxidation state attained for platinum metals is equal to +6, which is, apparently, far from the extreme value. The main and most reliable information on the properties of the strongly oxidised ions of the above-mentioned elements concern predominantly their fluorides, although scattered data on oxide systems have been recently reported.

Thus attempts were made to synthesise iridium compounds in the highest OS under high oxygen pressure (it is known^{211,212} that high pressure favours attainment of unusual OS of transition elements).^{208–210} The properties of a new series of oxides with the distorted K_2NiF_4 structure of composition $\text{A}_2\text{M}^{\text{VI}}\text{O}_6$ ($\text{A} = \text{Ba}$ or Sr ; $\text{M} = \text{Sr}$, Ca , Mg or Zn) containing iridium in OS of +6 were reported.^{208,209} The structural and magnetic properties of the $\text{Sr}_2\text{Rh}^{\text{IV}}\text{O}_4$ and $\text{Sr}_2\text{Ir}^{\text{IV}}\text{O}_4$ compounds, which are analogues of La_2CuO_4 , were studied.²¹³ X-Ray and neutron diffraction studies demonstrated the distortion of the ideal structure of the K_2NiF_4 type. Oxoplatinates with composition $\text{Ln}_2\text{M}^{\text{IV}}\text{O}_6$ ($\text{Ln} = \text{La}$, Pr , Nd , Sm , Eu or Gd ; $\text{M} = \text{Mg}$, Co , Ni or Zn) were prepared.²¹⁴

Note also the electrochemical studies of hydroxo complexes of iridium in OS of +4, +5 and +6^{83,84} and studies aimed at preparing platinum and iridium compounds in the highest OS in alkaline solutions.^{215–219} Solutions of hydroxo complexes of platinum and iridium were treated with ozone and the resulting compounds were studied by various methods, including ESR, electronic absorption spectroscopy, cyclic voltammetry and chemical analysis. It was established that the platinum hydroxo complexes afforded the previously unknown platinum superoxo complexes $[\text{Pt}(\text{OH})_5(\text{O}_2^-)]^{2-}$, $[(\text{OH})_5\text{Pt}(\mu\text{-O}_2^-)\text{Pt}(\text{OH})_5]^{3-}$ and $[(\text{OH})_4\text{Pt}(\mu\text{-O}_2^-)(\mu\text{-OH})\text{Pt}(\text{OH})_4]^{2-}$. In the case of iridium, hydroxo complexes of iridium in OS of up to +6 inclusive were detected in solution along with the peroxo and superoxo complexes of iridium of the $[(\text{OH})_5\text{Ir}^{\text{IV}}(\mu\text{-O}_2^-)\text{Ir}^{\text{III}}(\text{OH})_5]^{5-}$ {or $[(\text{OH})_5\text{Ir}^{\text{III}}(\mu\text{-O}_2^-)\text{Ir}^{\text{III}}(\text{OH})_5]^{5-}$ } type.²¹⁸ This suggests that OS of +6 for iridium can be attained even under rather mild conditions (in solution), which indicates that treatment of solu-

tions of hydroxo complexes with oxidants under more drastic conditions has considerable promise.

V. Matrix oxidation state stabilisation

Recently, the so-called method of matrix OS stabilisation has been developed. This method is based on the fact that the tracer atoms incorporated into the crystalline matrix are interchangeable with the metal atoms of the base upon heating. Thermal treatment is apparently one of a few procedures used in this case because the mechanism of transfer of the atoms is obviously of a diffusion character and the diffusion is enhanced at higher temperatures. The efficiency of the exchange reaction is associated with the possibility of the change in the size of tracer atoms or of a change in the electronic configuration (and, consequently, in OS) of the above-mentioned atoms, *i.e.*, with the lability of the corresponding electron cloud. The crystal field of the matrix ‘forces’ the doping ions to behave as the electron cloud in the crystal lattice, which is in some cases accompanied by charge transfer from one metal atom to another,²²⁰ *i.e.*, by a change in OS.

The geometrical criteria (ionic radii, local symmetry, *etc.*) are of great importance because they reflect the effect of the thermodynamics of the mixed matrix–tracer system. The stability of OS should be determined to a large extent by the isomorphism rules because the geometry of the vacancy into which a transition metal ion is inserted plays a great role in the stabilisation of the latter.

The effect of the matrix on the properties of the doping ions can be illustrated by a change in the colour of Cr^{III} ions placed at the matrix nodes with different local symmetry. In corundum ($\alpha\text{-Al}_2\text{O}_3$), beryl ($\text{Al}_2\text{Be}_3\text{Si}_6\text{O}_{18}$) and kyanite (aluminosilicate, Al_2SiO_5), the Cr^{III} ions are red, green and blue, respectively.²²¹ Shifts of the absorption bands in energy depend on various factors, including the coordination number, and the absorption bands corresponding to the charge transfer depend on the valence transitions or on the stability of OS. For example, a change in OS of cerium in the same matrix, *viz.*, in ZrO_2 (fianites), leads to a change in the colour from bright red-claret (Ce^{IV}) to yellow-orange (Ce^{III}).²²²

Many researchers use the matrix stabilisation of the highest OS in spite of the fact that the lattice contributions to the total energy are insignificant. This method was used for preparing laser crystals doped with transition metal ions (see, for example, Refs 223 and 224). However, note that it is difficult to obtain metal ions in high OS in these subjects because of their specificity.

Table 5. Known oxidation states of heavy transition elements.

OS	W	Re	Os	Ir	Pt	Au	Hg
+1		+ (see ^a)	+ (see ^a)	+ (see ^a)		+ (see ^c)	+ (see ^c)
+2	+ (see ^b)	+ (see ^b)	+ (see ^d)	+ (see ^a)	+ (see ^c)	+ (see ^{f,g})	+ (see ^c)
+3	+ (see ^d)	+ (see ^{a,b})	+ (see ^d)	+ (see ^c)	+ (see ^g)	+ (see ^{c,d})	+ (see ^j)
+4	+ (see ^{b,c})	+ (see ^c)	+ (see ^c)	+ (see ^c)	+ (see ^c)		
+5	+ (see ^c)	+ (see ^c)	+ (see ^d)	+ (see ^{e,f})	+ (see ^f)	+ (see ^{f,g})	
+6	E (see ^d)	+ (see ^d)	+ (see ^{e,f})	+ (see ^{e,f})	+ (see ⁱ)	? (see ⁱ)	
+7		E (see ^d)	+ (see ^d)			? (see ^{i,j})	
+8			E (see ^{e,h})				– (see ^j)
+9				? (see ^k)			
+10					– (see ^j)		

Note. The following notations are used: E, the highest OS, which is, apparently, the extreme one; ‘minus sign,’ this OS is absent.

^a Known, for example, in carbonyls and complex phosphines. ^b Known, for example, in halides and cyanides. ^c Known in many compounds. ^d Known in oxides and halides. ^e For fluorides. ^f For oxides. ^g Disproportionation occurs. ^h For hydroxo complexes. ⁱ A very unstable higher fluoride with an unknown composition formed upon heating of fluoro Au^{V} complexes. ^j See the discussion in the text. ^k The formation of this OS in a compound formed upon β -decay of $^{191}\text{OsO}_4$ was reported.

In matrices which are more suitable for stabilisation (for example, in $\text{BaM}^{\text{IV}}\text{O}_3$, where $\text{M} = \text{Ce, Th or Zr}$), Pr^{IV} , Tb^{IV} , Nd^{IV} and Dy^{IV} were obtained.^{128–130} Interestingly, it is possible to obtain Nd^{IV} in all the above-mentioned matrices, while Dy^{IV} was obtained only in $\text{BaCe}^{\text{IV}}\text{O}_3$. The Mn^{III} ,²²⁴ Cr^{IV} and Cr^{V} as well as Fe^{VI} ions^{225, 226} are stabilised in matrices of garnets, chromates and sulfates (the systems were prepared from solution) and Tb^{IV} ions are stabilised in $(\text{SrMgF}_4 : \text{Tb}^{\text{IV}})$ -phosphors (prepared in the solid phase).²²⁷

In studies of matrix oxide systems involving oxoferrates and oxoruthenates,^{33, 34, 228–236} the conditions for doping these matrices with Fe^{n+} and Co^{n+} ions (OS were established by Mössbauer spectroscopy with the use of ^{57}Fe and ^{57}Co isotopes) were found. Of the most interesting results, note the stabilisation of Co^{VI} ions in the ferrate $\text{Cs}_2\text{Fe}^{\text{VI}}\text{O}_4$ (see Refs 33 and 34) and the stabilisation of Fe^{VI} ions in the mixed-valence compound with composition $\text{Cs}_3(\text{Ru}_{1/2}^{\text{VI}}\text{Ru}_{1/2}^{\text{VII}}\text{O}_4)$.^{232, 235}

Attempts to attain the Fe^{VII} state are of particular interest. This OS can be realised for Fe. Thus it was concluded¹⁶⁵ that the disproportionation of FeO_4^{2-} ions (in alkaline media) occurs according to the following scheme:



Since a two-equivalent exchange occurs, the intermediate one-electron conversion with the participation of Fe^{VII} could be expected in accordance with Scheffer's principle. It was attempted to solve the problem of stabilisation of this OS by placing ^{57}Fe in the $\text{Cs}_3(\text{Ru}_{1/2}^{\text{VI}}\text{Ru}_{1/2}^{\text{VII}}\text{O}_4)$ matrix. In this ruthenate, the iron ion is stabilised primarily in the Fe^{VI} form. However, an unstable satellite was also observed in the slope of the intense line in the Mössbauer spectrum. The chemical shift value of this satellite corresponds to that expected for Fe^{VII} .^{232, 236} Unfortunately, there is no more convincing evidence for the presence of Fe^{VII} in this system. According to the data of Mössbauer spectroscopy (4 K),^{229, 237–241} the Fe^{VII} state can also be stabilised in the $\text{Na} - \text{Fe} - \text{O}$ system at a molar ratio $[\text{Na}]:[\text{Fe}] > 50:1$ (at lower ratios, only Fe^{IV} compounds are formed²⁴²).

Unlike other researchers, the authors of the publications^{229, 237–242} applied oxidation processes using sodium and cesium peroxides under rather mild conditions. The latter are suitable for the realisation of high OS if the strongest oxidants (Na_2O_2 and CsO_2) as well as an efficient stabilising agent (in particular, Cs^+ cations) are present in the reaction mixture.⁴³ In addition, peroxides as such can stabilise the highest OS of, for example, iron and cobalt on condition that their contents in the reaction mixtures are low.^{229, 241} Highly reactive reagents (precursors) which are formed, for example, upon ultrasonic treatment show promise. It is by this procedure that specimens of highly disperse Fe_2O_3 were prepared.²⁴³ The procedures for the preparation of the corresponding precursors have been summarised.²⁴⁴

VI. Valence possibilities of transition elements

It was hypothesised that the heaviest $5d$ elements can attain high OS,⁴⁸ which can be realised for Ir, Pt, Au and Hg in the tetrahedral oxo ions $\text{MO}_4^{\pm}$. Estimates of the energies of molecular orbitals which were obtained by the scattered wave X_α method for a series of tetraoxo anions $\text{M}^{\text{VII}}\text{O}_4^-$ of the third-row elements^{245, 246} indicate that rather stable compounds can be formed. Quantum-chemical and thermodynamic calculations were performed for the tetrahedral MO_4^q ions isoelectronic with OsO_4 ($\text{M} = \text{Ir, Pt, Au or Hg}$, $q = +1, +2, +3 \text{ or } +4$, respectively).⁴⁹ Quantum-chemical calculations were carried out with the use of quasirelativistic and relativistic pseudopotentials (*cf.* Ref. 247), which are believed to be very reliable.

Ab initio calculations for the $\text{Ir}^{\text{IX}}\text{O}_4^+$, $\text{Ir}^{\text{VII}}\text{O}_4^-$, $\text{Pt}^{\text{VIII}}\text{O}_4^0$ and $\text{Au}^{\text{VII}}\text{O}_4^-$ ions demonstrated⁴⁹ that the potential surfaces have minima. For the $\text{Pt}^{\text{IX}}\text{O}_4^{2+}$ and $\text{Au}^{\text{IX}}\text{O}_4^+$ cations, minima are also

observed but they are apparently too shallow to expect the formation of more or less stable compounds. An analogous conclusion can be drawn on the basis of the results of thermodynamic calculations. The main outcome of the study⁴⁹ was the conclusion that transition elements in very high OS (which have not yet been realised), up to $+10$ inclusive, can theoretically occur.

It was demonstrated⁴⁹ that the probability of the existence of $\text{Hg}^{\text{VIII}}\text{O}_4^0$ is distinct from zero because calculations gave a reasonable value for the internuclear $\text{Hg} - \text{O}$ distance of 2.12 Å (HgO_4^{2+} ions and all the more so, HgO_4^{4+} ions are unstable). Probably, mercury compounds in OS of lower than $+8$ are rather more stable.

For mercury and its analogues (Zn and Cd), $+2$ is still considered to be the highest OS. Note that the short-lived complex of trivalent mercury with composition $[\text{Hg}(\text{cyclam})](\text{BF}_4)_2$ was reported,²⁴⁸ although these data require additional proof. It was suggested that an unstable intermediate containing Hg^{III} is formed upon fluorination of organomercurials with xenon difluoride.^{249, 250} Based on the results of X-ray photoelectron spectroscopy of mercury copper–oxide superconductors with composition $\text{HgBa}_2(\text{Ca}_{0.86}\text{Sr}_{0.14})_2\text{Cu}_3\text{O}_{8+\delta}$, it was concluded that these superconductors contain Hg^{III} .^{251, 252} On the basis of the general regularities of the Periodic system, Jorgensen also believed that the possibility exists of attaining high OS for mercury.³⁷ He reasoned that the existence of $I(5d)$ of ~ 14 eV for mercury(II) fluoride may favour oxidation of Hg^{II} to Hg^{III} or Hg^{IV} , particularly taking into account that HgF_2 crystallises in the fluorite structure with a low lattice energy. The realisation of the $5d^8$ configuration and consequently of Hg^{IV} in the square-planar HgF_4 molecule is more probable than the $5d^9$ configuration and Hg^{III} .

In this connection, the publication³⁸ in which the molecular and electronic structure and the stability of HgF_4 , ZnF_4 and CdF_4 were compared is of fundamental importance. The possibility of stabilisation of HgF_4 upon anionic complexation was considered. Calculations were performed with the use of the same pseudopotentials as those used previously²⁴⁷ for HgF_2 . It was shown that the fluoride HgF_4 may well exist in the gaseous state.³⁸ To the contrary, the existence of CdF_4 and all the more ZnF_4 is highly improbable. In addition, it follows that complexation does not enhance stabilisation of Hg^{IV} with respect to Hg^{II} in anions.³⁸ The conclusion that complexation affects only slightly the stability of Hg^{IV} is unexpected because this is considered as one of the ways of stabilising the highest OS of f and d transition elements.^{39, 40} Since Hg^{IV} should exhibit the properties of d transition elements, the statement that the formation of the HgF_{4+x}^x anionic complexes has a favourable effect on the stability of Hg^{IV} should be fulfilled. The introduction of an equivalent amount of cations into the system containing anions decreases substantially the total energy of the system. In this case, the mutual cation–anion influence should occur and stabilisation should be realised through the electrostatic forces. In particular, this is consistent with the results of calculations of the electronic structures of the $\text{M}^{\text{V}}\text{F}_6^-$ ions ($\text{M} = \text{Hf, Ta, W, Re, Os, Ir, Pt, Au or Hg}$)²⁵³ by the spin-polarisation discrete variation X_α method. The change in electron affinity in the $\text{HfF}_6^- \rightarrow \text{HgF}_6^-$ series as well as the experimental data on the stability of the complex fluorides of Os^{V} , Ir^{V} , Pt^{V} and Au^{V} (compared to the data on the corresponding MF_5) indicate that the effect of complexation does exist. Thus the temperature of decomposition of complex fluoroaurates(V) is 100 °C higher than that of AuF_5 .^{45, 150, 192} Hence, the conclusion that coordination has no effect on the stability of higher mercury fluorides is questionable although it was not disproved (HgF_4 or other Hg^{IV} fluorides have not been obtained yet despite attempts, as can be judged from the published data,³⁸ aimed at their synthesis).

We emphasise that in the above-mentioned theoretical studies, only the presence of the minimum on the potential surface was noted, while the depth of this minimum can be determined only

experimentally. Thus derivatives of $\text{Cs}^{\text{III}}-\text{Cs}^{\text{IX}}$ and krypton oxides[‡] have not yet been obtained, although calculations predicted that they can exist.²⁵⁵ Apparently, this is also true for HgF_4 .

VII. Regularities of changes in the extreme oxidation states of transition elements

The highest OS of transition elements (according to the experimental data and results of quantum-chemical calculation)⁸⁹ are shown in Scheme 1. The extreme OS (E) are separated from the higher OS by a thick line, which assumes that the latter cannot be attained. It can be seen that the values of the extreme OS in the series of transition metals increase, reach a maximum and then decrease. This character of the change in the maximum OS is one of the main regularities of the Periodic system. For some OS, the experimental data are lacking but there is reason to hope that such information will be obtained. In relation to the aforesaid, it is necessary to make some comments.

For the first-row transition metals, the maximum OS is observed for iron (+8). The existence of Mn^{VIII} in tetraoxide MnO_4^0 , which is formed upon photodissociation of the MnO_4^- ion, is suggested on the basis of spectroscopic data.²⁵⁶ Probably, this conclusion is erroneous. For cobalt, +6 is the highest OS.^{33, 34} This state was identified by emission Mössbauer spectroscopy. The detection of OS by this method may indicate that it is highly unstable. In view of this fact, it is believed that +6 is the extreme OS for cobalt. For Ni, +4 is the highest OS attained. It is assumed that Ni^{VI} can be realised (handbooks even contain the E° value for the $\text{Ni}^{\text{VI}}/\text{Ni}^{\text{III}}$ pair). In our opinion, the existence of Ni^{VI} is still an open question. The preparation of Ni^{V} is more probable. Moreover, the identification of the OS in this case is a very complicated problem. The stability of Ni^{VI} and Ni^{V} derivatives should be rather low and probably the only suitable technique for observing OS is Mössbauer spectroscopy which can detect the chain of transformations $^{57}\text{Ni} \rightarrow ^{57}\text{Co} \rightarrow ^{57}\text{Fe}$.

The detection of particular OS in studies by emission Mössbauer spectroscopy [provided that radiative transitions (known as post-effects) are absent] is very revealing. In fact, for the $A \rightarrow B$ process where compound B has OS which can be observed by Mössbauer spectroscopy, $a_A \sim 1$ and $a_B = 10^{-8}$ (a is the activity). The latter value can readily be obtained on the assumption that the activity of the source was ~ 1 mCi (^{57}Co). Then $k_{\text{eq}} = a_B/a_A \sim 10^{-8}$ and $\Delta_r G^\circ = RT \ln k_{\text{eq}}$ is about 50 kJ mol^{-1} , i.e., it is impossible to obtain macroscopic amounts of a compound containing the desired OS.

For the second-row transition metals (see Scheme 1), the maximum OS is attained for Ru(+8). Compounds containing Rh^{VI} and Pd^{V} were described. On the basis of the published data,²⁴⁶ both states can hardly be assigned to the limiting states. In this connection, the question of whether higher OS are possible remains open. In the third-row transition elements, the maximum OS for iridium is +9^{48, 49} (apparently, this is the extreme OS), while OS +10 can be attained for platinum.⁴⁹ The probability of occurrence of the nona- and decavalent states for the elements is an open question.

According to Abegg's rule, each element may have a set of OS consisting of no more than 8 values. It is known³⁷ that this rule is fulfilled for the main-group elements and for the post-transition elements. Only four exceptions to this rule are known, namely, Mn, Ru, Re and Os, for which ten OS can be realised.³⁷ Assuming that OS of +10 and +9 can be attained for platinum and iridium, respectively, and thus postulating sets of 10 OS for these elements, we extend the series of the above 'exceptions.' Without consider-

Scheme 1

Metal	Oxidation state of the metal									
	2+	3+	4+	5+	6+	7+	8+	9+	10+	
Sc		E								
Ti			E							
V				E						
Cr					E					
Mn						E				
Fe							E			
Co					E					
Ni			H	??						
Cu			E							
Zn	E									
Y		E								
Zr			E							
Nb				E						
Mo					E					
Tc						E				
Ru							E			
Rh					H	??				
Pd				H						
Ag				E						
Cd	E									
La		E								
Hf			E							
Ta				E						
W					E					
Re						E				
Os							E			
Ir					H	??	??	?(see ^a)		
Pt					H		??	??	see ^b	
Au				H			see ^b	see ^b		
Hg	H	see ^c	see ^b				see ^b			

The following notations are used: H, the high OS is known, but it is unclear whether it is the extreme value; ??, the data are lacking, but there is the probability that this state can be attained.

^a The data were not confirmed. ^b According to the results of quantum-chemical calculations, this OS can be attained.⁴⁹ ^c The possibility of formation of derivatives upon fluorination of organomercurials at low temperature was reported.^{249, 250}

ing the nature of this phenomenon (which is, of course, governed not only by the electrostatics of metal–ligand interactions), we emphasise that the above 'exception' for transition elements is apparently the rule. Evidently, the presence of a particular set of OS for the element as well as the maximum valence are determined primarily by the principle of the arrangement of the Periodic system (the so-called 'Aufbau' principle; this follows from the ideology of the publication³⁷) which is based on thermodynamic factors, primarily on the energies of the detachment of electrons from the free atom. This can be judged, for example, from the values of the ionisation potentials^{257, 258} of atoms[§] realising that it is the differences between the ionisation potentials, which can characterise the tendency for OS stabilisation, rather than the absolute values of these potentials that are of importance. Analysis of the ionisation potentials demonstrated that it is necessary to overcome an energy barrier the value of which is

[‡] It was reported that a krypton compound with the orthotellurate ligand was presumably obtained though under cryogenic conditions.²⁵⁴ This compound exploded even under these conditions. More detailed data in support of the individuality of this compound and of the presence of the Kr–O bond are lacking.

[§] An analogous procedure was used in the analysis of the regularities of the changes in the ionisation potentials of atoms of the heavy transition elements.⁴⁸ Speculative conclusions obtained on this basis were subsequently confirmed by direct quantum-chemical calculations.⁴⁹

reflected in the stability of the OS, on going from one OS to another.

These barriers can be overcome in chemical (or in physical) processes. The latter is illustrated in the observation of a high OS for the metal atoms upon β -decay of ^{191}Os , ^{259}Am and ^{247}Bk in oxides,^{15, 16} which provides short-lived $\text{Ir}^{\text{IX}}\text{O}_4^+$, $\text{Cm}^{\text{VI}}\text{O}_2^{2+}$ and $\text{Cf}^{\text{VO}}\text{O}_2^+$ ions, respectively. In other words, the existence of OS +9 or +10 for some elements does not contradict the principles of construction of the Periodic system.

It was of interest to verify the regularities of the changes in the extreme OS and the observations of OS higher than the extreme values. On the one hand, the fundamental regularity as declared above seemingly does not allow for the formation of these OS. On the other hand, these OS are not theoretically forbidden and only energy barriers occur, which can be overcome in some cases, as demonstrated above.[¶] Presently, there is no point in going through all the details because the experimental data are lacking. However, attempts can, in principle, be undertaken to obtain this information, for example, in experiments on bombardment of solid and liquid targets with heavy highly charged ions. For example, calcium targets were bombarded with Ar^{12+} ions,^{262, 263} helium was treated with C^{6+} , N^{7+} , O^{8+} , Ar^{16+} , I^{16+} and Xe^{30+} ions²⁶⁴ and the recombination of Kr^{34+} ions on hydrogen molecules was considered.²⁶⁵ Evidently, the appearance of an almost bare nucleus in the matrix should cause a cascade of Auger electrons. These secondary processes are known and are being studied. For example, the manifestations of the secondary processes in the K_α spectra which were observed in experiments on bombardment of sulfur targets with Ar^{5+} and Xe^{8+} ions were analysed.²⁶⁶ Actually, the problem of OS stabilisation was not solved in the papers cited because ions and targets evidently were not optimum (in this context, the above-discussed studies on the matrix OS stabilisation are of importance). The questions are how long these superhigh OS live and whether these states can be detected by the available physical methods.

To summarise, the present review considers the state-of-the-art of the problem of the existence and stabilisation of the highest and extreme valent forms of transition elements. In the discussion of these problems, many authors (see, for example, Refs 23 and 29) attempted to reveal the relationship between the electronic structures of the atoms and the properties of the compounds. Evidently, this relationship can be also revealed in the present review. However, d transition elements (particularly, heavy elements) are characterised by a high degree of covalence, which makes these correlations poorly informative. Hence, we restrict ourselves to the discussion of the chemical evidence and the statement of empirical regularities. The advantage of the empirical method is its independence from the electronic structure and the inherent nature of the subjects under consideration. This is of particular importance when the data are scarce as in the case of elements in the highest unstable OS which are few in number. At the same time, the discussion of the general situation on the basis of the available reliable quantum-chemical and experimental data allows us to offer the hypothesis that superhigh and short-lived OS exist and to suggest the procedure for its verification.

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Synthetic diamond in electrochemistry

Yu V Pleskov

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Abstract. The results of studies on the electrochemistry of diamond carried out during the last decade are reviewed. Methods for the preparation, the crystalline structure and the main electrophysical properties of diamond thin films are considered. Depending on the doping conditions, the diamond behaves as a superwide-gap semiconductor or as a semimetal. It is shown that the 'metal-like' diamond is corrosion-resistant and can be used advantageously as an electrode in the electrosynthesis (in particular, for the electroreduction of compounds that are difficult to reduce) and electroanalysis. Kinetic characteristics of some redox reactions and the impedance parameters for diamond electrodes are presented. The results of comparative studies of the electrodes made of diamond single crystals, polycrystalline diamond and amorphous diamond-like carbon, which reveal the effect of the crystalline structure (*e.g.*, the influence of intercrystallite boundaries) on the electrochemical properties of diamond, are presented. The bibliography includes 99 references.

I. Introduction

Diamond is a material endowed with unique properties: it is a perfect dielectric characterised by extremely high atomic density and hardness. Historical records of intensive electrophysical, physicochemical and optical studies of diamond is only several-decade long.^{1,2} Its practical uses have diversified and embrace nowadays such fields as materials technology,³ microelectronics⁴ and other.

Depending on the doping level, diamond behaves as a superwide-gap semiconductor or as a semimetal. Owing to its exceptional chemical stability, semiconductor diamond is undoubtedly promising as an electrode material. However, in contrast with other carbon materials of long-standing use (graphite, glassy carbon and other), electrochemical studies of diamond were initiated approximately a decade ago. Until recently, such investigations have been seriously hampered by two circumstances: firstly, diamond remained an exotic, difficultly accessible mate-

rial; secondly, by its nature, diamond is an insulator and hence is unsuitable material for electrodes.

The situation has radically changed in connection with the achievements in the technology of manufacture of diamond thin films from the gas phase under subatmospheric pressure. Highly efficient methods have been developed for the growing of polycrystalline diamond films on non-diamond substrates; such films are relatively inexpensive when manufactured on a large scale. Doping with boron, as an acceptor admixture, allowed one to synthesise semiconductor films with good conductivity, while high doping levels led to quasimetallic films.⁵

The first studies on diamond electrodes have opened a new branch of electrochemistry of semiconductor materials⁶ known now as electrochemistry of diamond.

Formally, the first publication on diamond electrochemistry was that describing attempts to make an electrode from a dielectric diamond crystal.⁷ In order to make electroconducting at least the thin outer layer of the specimen, the authors implanted Ar^+ ions into the diamond crystal. Argon is not a doping impurity for the diamond and does not change its conductivity, but as the result of such an ion implantation the external diamond layer becomes amorphous (*e.g.*, see Refs 8, 9). A noticeable conductivity arises because of the destruction of the diamond crystalline lattice and the appearance of a large number of carbon atoms with the sp^2 -hybridisation of their orbitals.¹⁰ For this reason, strictly speaking, the study of Iwaki *et al.*⁷ dealt with the electrochemistry of non-diamond (amorphous) carbon and not with the diamond proper.

In fact, the electrochemistry of diamond was started with the study reported in Ref. 11. In this work, the $I-V$ characteristic was derived for the first time and the differential capacitance at the diamond/electrolyte solution interface was measured; photosensitivity of diamond electrodes was also revealed and related to the semiconductor properties of diamond. A few years later, these investigations of Russian researchers were followed by studies carried out by electrochemists in Japan, Israel, France, USA and other countries. For the last three years the number of publications devoted to diamond electrodes has increased dramatically.

This review generalises the most important results from studies of electrochemical properties of synthetic semiconductor diamond and application of electrochemical methods for the determination of characteristics of diamond films and outlines perspectives of the development of this new branch of electrochemistry.

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II. Preparation of diamond thin-film electrodes

Since the work reported in Ref. 11 until now the subjects of virtually all studies have been diamond films prepared by the method of chemical vapour deposition (CVD). The studies by Derjaguin *et al.*¹² carried out in the 1970s were an important stage in the development of this method. The CVD method relies on the deposition under subatmospheric pressure from an activated gas phase consisting of a volatile organic substance and hydrogen.^{3, 13} The gas phase activation is required in order to create sufficiently high concentration of active carbon-containing species. These particles, by colliding against the surface of a heated substrate, disintegrate and release carbon atoms from which the crystalline lattice of diamond is formed. In the temperature and pressure ranges used, the diamond is metastable; the stable form is another allotropic carbon modification known as graphite. The gas phase activation should lead to the appearance of a reagent suppressing the deposition of non-diamond forms, *viz.*, graphite and amorphous carbon. Atomic hydrogen is such a reagent; in its atmosphere graphite 'burns out', while diamond remains unaltered.

Current practices rely basically on the use of thermal and electric (sometimes, chemical and photochemical) methods of gas activation. In the case of thermal activation, a reactor for vapour deposition of diamond films is used (Fig. 1). Above the substrate, on which diamond is supposed to grow, an activator is suspended in the form of wire made of a high-melting metal (W, Ta). This wire is heated to incandescence ($\sim 2000^\circ\text{C}$) at which temperature the H_2 molecules dissociate at a sufficiently high rate. The gas phase is a mixture of carbon-containing gases (methane, acetone or methanol vapour, *etc.*, usually at concentrations of up to 5%) with hydrogen. Their contacts with the activator surface yield, along with the hydrogen atoms, excited carbon-containing molecules and radicals that are transferred towards the substrate surface, where deposition of diamond film takes place.

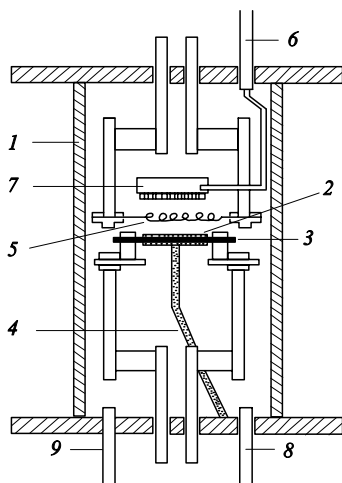


Figure 1. Scheme of a reactor for the chemical vapour deposition of diamond films under thermal activation;³

(1) reactor body; (2) substrate; (3) substrate heater; (4) thermocouple; (5) heated tungsten wire; (6) gas input; (7) diffuser; (8) pipe-line to a vacuum pump; (9) pipe-line to a manometer.

Electrical activation is induced using various forms of electric (arc, glow) discharge with the use of constant and alternating current (high frequency, ultra-high frequency, pulse mode). Each version of the electric method has its own advantages and disadvantages. For example, the electric arc discharge permits high deposition rates ranging from tens to hundreds of micrometers per hour. Under the ultra-high-frequency activation, the plasma ensures homogeneous conditions for the deposition over a large surface area of the substrate.

Depending on the aim of particular studies, the role of the substrate is played by metals (W, Mo), silicon (wafers with a mirror-polished surface that are frequently used in microelectronics), glassy carbon, *etc.* Crystallisation is primed by diamond microcrystals seeded on the support surface. Later, the silicon substrate can be easily etched to obtain the so-called free-standing films. If the substrate is a diamond single crystal (natural or synthetic), then epitaxial growth takes place: the growing film repeats the crystalline structure of the substrate and forms a single crystal (such films are called homoepitaxial). Usually, the film thickness is a few micrometers, but in some cases it may reach several millimetres. The area covered with a diamond film reaches 10×10 cm and more, though the electrochemical studies usually use electrodes $\sim 1 \times 1$ cm in size.

As noted above, in order to make a diamond film electroconducting, one should dope it (usually in the process of its growth) with boron. For this purpose, the gas phase is supplemented with a volatile boron compound, *e.g.*, trimethyl borate, in the concentration ranging from 10 to 10 000 ppm. Alternatively, a solid source of boron is placed near the activator and the substrate. In the latter case, the boron is transferred into the gas phase as a result of the activation. It has been established empirically that the content of boron in the growing film is approximately proportional to its content in the gas phase.¹⁴ The specific resistance of diamond depends on the content of boron in the film: it can vary, *e.g.*, from 10^4 Ohm cm (at a content of boron atoms in diamond of $\sim 10^{18} \text{ cm}^{-3}$) to tenth and even thousandth fractions of Ohm cm (at a content of boron atoms in diamond $\sim 10^{21} \text{ cm}^{-3}$). As its resistivity decreases, the dielectric diamond acquires successively the properties of a semiconductor, a degenerate semiconductor and then of a semimetal.

The energy of boron ionisation in diamond is great compared with the thermal energy (kT). At room temperature, the activation energy is 0.37 eV and decreases appreciably at high boron concentrations.¹⁵ Hence, the concentration of the majority charge carriers (holes) is 2–3 orders of magnitude lower than that of the boron atoms (acceptors).

It should be pointed out that the methods of chemical and physical vapour deposition are widely used for the preparation of not only crystalline (diamond) films but also films of amorphous hydrogenated carbon a-C:H¹⁰ in which there is no long-range ordering of the C–C bonds (hence, there is no crystalline structure), but the short-range ordering exists. Of a wide diversity of amorphous carbon films, one can conditionally distinguish graphite- and diamond-like films. Hybridisation of the carbon atom orbitals is predominantly of the sp^2 -type in the former and of the sp^3 -type in the latter. The graphite-like films are characterised by a small width (< 1 eV) of the gap and have high electric conductivity. The diamond-like films have a wider (2–4 eV) gap and are appreciably less conductive; certain properties of these films are similar to those of diamond (and this explains their name).

In addition to thin films, individual diamond crystals grown at high temperature and high pressure can also be used as electrodes. Such crystals are obtained from a carbon solution in molten metals (*e.g.*, Ni–Fe–Mn) in the pressure and temperature ranges corresponding to the region of thermodynamic stability of diamond; diamond crystals are doped with boron during their growth.

III. Crystal structure and basic electrophysical characteristics of diamond films

1. Crystal structure

Polycrystalline films consist of crystallites the size of which increases with the film growth approximately proportionally to its thickness and reaches a few micrometers. Facets of crystallites usually form a characteristic faceted morphology of the film surface.

The perfection of the crystalline structure of deposited films is monitored by recording their Raman spectra. A typical spectrum of a diamond film is shown in Fig. 2. The crystalline diamond is characterised by a narrow peak at 1332 cm^{-1} due to the first-order scattering on the crystal lattice. Two blurred bands at ~ 1350 and $\sim 1550\text{ cm}^{-1}$ correspond to the non-diamond carbon form with the predominant sp^2 -hybridisation. When comparing the diamond peak and the maximum determined by the sp^2 -carbon in the spectrum, one should bear in mind that the magnitude of Raman signal on the ordinate (Fig. 2) is 50 times more sensitive to the non-diamond carbon form than to the crystalline diamond.¹⁶ In the best specimens employed as electrodes, the admixture of the non-diamond form did not exceed 1% (as confirmed by independent electrochemical measurements). According to Hashimoto *et al.*,¹⁷ the admixture content decreases in the film substrate surface direction. Nevertheless, modern physical techniques (Raman and Auger spectroscopy, atomic-force microscopy) do not provide sufficiently exhaustive characterisation of non-diamond carbon inclusions in polycrystalline diamond films. It is by electrochemical measurements that these inclusions are revealed.¹⁸

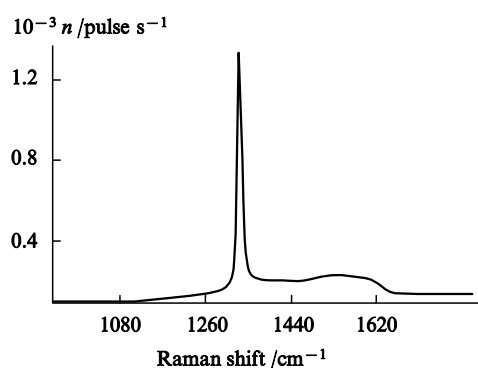


Figure 2. Raman spectrum of a polycrystalline diamond film.

In polycrystalline diamond films, the non-diamond form is represented primarily by a disordered carbon of intercrystallite boundaries, the outcrops of which on the diamond surface were observed using high-resolution electron microscopy.¹⁹ The thickness of the intercrystallite boundaries in diamond films reaches a few nanometers. In addition, the crystal lattice of films has various defects. In some instances, a thin (about several nanometers) non-diamond layer coating the diamond film was revealed. This layer is often formed in the latest (poorly controlled) stages of film growth after cessation of the gaseous phase activation. To remove it, samples are heated in air to $520\text{ }^{\circ}\text{C}$ or boiled in concentrated HClO_4 , dichromate-sulfuric acid mixture or solutions of other strong oxidants. Such a treatment of the non-diamond carbon form results in its oxidation to CO_2 .

2. Electroconductivity of films

Specific resistance of diamond films is determined not only by the concentration but also by the mobility of free charge carriers. Usually, the mobility of the holes in polycrystalline films is not high; it is lower than that in natural single crystals (usually, of the magnitude of $1\text{ cm}^2\text{ V}^{-1}\text{ s}^{-1}$).^{20–22} although in some cases it reaches tens and hundreds of $\text{cm}^2\text{ V}^{-1}\text{ s}^{-1}$ (see, *e.g.*, Refs 23 and 24). The mobility of the holes in single-crystal (homoepitaxial) films is 1–2 orders of magnitude higher than that in polycrystalline films grown under the same conditions.²² In films of amorphous diamond-like carbon, the mobility is several orders of magnitude lower than that in crystalline diamond.²⁰

The character of conductivity of doped polycrystalline films and its relation to the crystal structure were studied by the method of impedance spectroscopy.²⁵ The results obtained have made it

possible to describe a conducting polycrystalline film using a simple model of a heterogeneous medium. According to this model, the medium consists of regularly distributed well-conducting crystallites of the same size separated by poorly conducting intercrystallite boundaries, which form a continuous matrix. Undoubtedly, such a model simplifies the structure of a real film in which crystallites are distributed over its thickness with regard to their size, while individual acicular crystallites penetrate through the entire film thickness. Nevertheless, this model is applicable in the studies of moderately doped diamond films. The theory of complex conductivity of a heterogeneous medium²⁶ developed for the model described has made it possible to determine the bulk proportion of the boundary phase in the film ($\sim 5\%$, which in order of magnitude correlates with the above-mentioned results of Raman spectroscopy) and to estimate conductivities of crystallites[†] and intercrystallite boundaries as 10^{-4} and $10^{-7}\text{ Ohm}^{-1}\text{ cm}^{-1}$, respectively.

Similar conclusions about the character of conductivity of polycrystalline films were made by Sokolina *et al.*²⁷ Subsequent studies devoted to thorough investigation of the frequency dependence of the impedance of polycrystalline films^{28–30} have shown that at high temperatures the electric conductivity due to the motion of free holes in the valence band should be supplemented with a component determined by the jump-over of holes between localised traps (possibly, associated with the intercrystallite boundaries).

IV. Synthetic diamond films as electrodes: resistance to corrosion and background current – potential curves

In the assessment of novel electrode materials used in electrolysis, electroanalysis and manufacture of electrochemical sensors and other devices, the main attention is paid to the magnitude of background current and the width of the potential range in which this current remains sufficiently low and does not interfere with measurements as well as to the corrosion resistance and stability of materials. The diamond electrode meets all of these criteria.

Let us consider the current-potential curves in solutions of indifferent electrolytes as the initial characteristic of the electrode behaviour of diamond.^{31–33} It is these curves that form the ‘background’ against which the kinetic, impedance, photoelectrochemical and electroanalytical characteristics of diamond electrodes are manifested.

An advantage of diamond electrodes is a wide potential range of weak background currents, which is sometimes called the range of ideal polarisability. It is obvious in comparison with other materials, which are widely used as electrodes (platinum, glassy carbon, graphite, *etc.*).

Figure 3 shows characteristic polarisation curves recorded using a solution of an indifferent electrolyte ($0.5\text{ M H}_2\text{SO}_4$) in the potentiodynamic mode of potential cycling on the polycrystalline diamond thin-film electrodes and the electrodes from platinum and highly oriented pyrographite which are traditionally applied in electrochemistry.

According to Martin *et al.*,³² all the diamond films used as electrodes may be divided into ‘good’ and ‘bad’ films, depending on the width of the ideal polarisability range. For the ‘good’ films, this range reaches $\sim 3\text{ V}$ at the current density j of several mA cm^{-2} and at least about 1.5 V for the j values making up a few decimal fractions of $1\text{ }\mu\text{A cm}^{-2}$ (Fig. 3a). For the ‘bad’ films, the range of ideal polarisability is appreciably narrower (Fig. 3b); there is a noticeable hysteresis, which naturally restricts their

[†] In the studies reported in Refs 11 and 25, the conductivity of diamond films was associated not with the boron incorporation but rather with the presence of unidentified admixtures and/or defects due to specific conditions of deposition (in particular, an elevated temperature of the substrate).

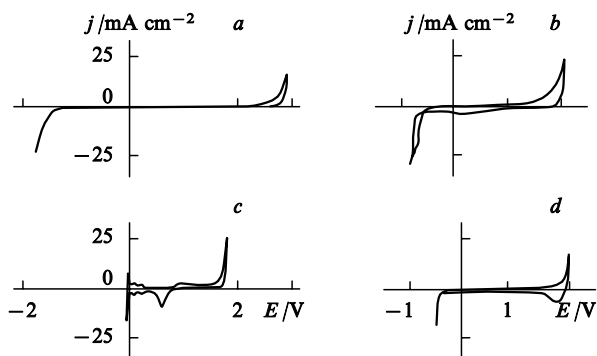


Figure 3. Polarisation curves of the electrodes made of polycrystalline diamond (*a*, *b*), platinum (*c*) and highly oriented pyrographite (basal plane) (*d*) in 0.5 M H₂SO₄.³³ (*a*) 'good' film; (*b*) 'bad' film; potential was measured relative to the normal hydrogen electrode (NHE).

applicability as electrodes. Martin *et al.*³² did not give any accurate definition of 'good' films but indicated that they were obtained at a low content ($\sim 1\%$) of a carbon-containing gas (methane) in the reaction system (the 'bad' films are formed at a methane content of $\sim 4\%$).

Comparison of the background currents for diamond and glassy carbon has shown that this current is 10 times as low on diamond.³⁴

As regards its resistance to corrosion in aggressive media and under extreme potentials, the diamond demonstrates it in full measure. Multiple cycles of potential variation on the diamond electrode from the potential of hydrogen evolution on the cathode to the potential of oxygen evolution on the anode in the aggressive solution 1 M HNO₃ + 0.1 M HF had no effect on either the surface morphology of diamond (according to electron microscopy data) or the ratio of diamond and non-diamond carbon forms on the electrode surface (according to Raman spectra). Under the same conditions, the electrodes from glassy carbon and pyrographite underwent strong degradation.³⁵ A similar study was conducted in the solution 1 M HNO₃ + 0.1 M NaCl under the potentials of the chlorine evolution on the anode.³⁶ But in this case too, X-ray photoelectron spectroscopy showed that neither the morphology of the diamond surface nor the content of admixtures on it were altered.

On the other hand, prolonged 'cycling' of the diamond electrode potential in concentrated (15%) KOH solution can lead to corrosive degradation of the diamond surface. The extent and character of this degradation depend on the conditions of diamond growth, although this dependence has not been clearly established. The intercrystallite boundaries composed of the non-diamond carbon undergo the strongest degradation.³⁷

In some cases (probably, in the presence of latent flaws in the film), prolonged polarisation of the diamond electrode in solution leads to the appearance in it of pinholes through which the electrolyte penetrates to the substrate.^{38–40} On the electrode surface, some inactive sites may appear⁴¹ as the result of local detachment of diamond films from the substrate or possibly because of a non-uniform doping of diamond with boron. The well-prepared films prove to be not only resistant to corrosion themselves but also to protect the metal substrate.^{39, 42, 43}

If a diamond film was obtained in a hydrogen atmosphere, its surface is covered by a hydrogen monolayer and displays hydrophobic properties. This type of surface is also obtained after treatment of diamond in a hydrogen plasma.⁴⁴ On the contrary, an oxidised diamond surface contains the hydroxy groups and hence is hydrophilic.^{32, 45} These two types of surface can also be obtained by electrochemical treatment consisting, respectively, in the cathodic or anodic polarisation in an aqueous electrolyte solution.⁴⁶

In conclusion, let us consider properties of the electrodes made of diamond-like carbon. Here, the data are scarce and are somewhat contradictory. For example, Howe⁴⁷ has reported that even thin films (50-nm thick) are well resistant to corrosion, while Sakharova *et al.*^{48, 49} have pointed out that such films proved to be permeable to the electrolyte, which by penetrating to the metal substrate resulted in its corrosion and led eventually to the film peeling. Films from diamond-like carbon of submicron thickness were found to be more resistant. Their background current – potential curves resemble analogous curves for the diamond electrode (Fig. 3*a, b*) but have a narrower range of ideal polarisability.⁵⁰

V. Impedance spectroscopy and semiconductor properties of diamond electrodes

1. Linear impedance. Equivalent circuits

Measurement of frequency characteristics of electrochemical systems makes it possible to derive information on their microscopic structure, as well as on the nature and kinetics of the charge transfer processes that occur in them. Linear impedance can be measured if a harmonic electrical signal with the frequency f is applied to the cell and then the real (Re Z) and imaginary (Im Z) components of the impedance Z are determined by analysing the spectrum of the system response with an appropriate device.

In studies of the impedance of diamond electrodes, the greatest attention is paid to the following peculiarities: the semiconductor character of diamond (for moderately doped films) and a special type of the frequency dependence of the impedance characteristic of the overwhelming majority of films.

In its general form, the impedance of a thin-film electrode may be represented by the three equivalent circuits shown in Fig. 4. The circuit depicted in Fig. 4*a* includes two RC -chains, one of which belongs to the diamond film itself and the other relates to the diamond/electrolyte solution interface. In the first chain, R_s is the ohmic resistance of the diamond film and C_g is the geometrical capacitance of the film; in the second chain, C_{sc} is the differential capacitance of the space charge region at the diamond/solution interface and R_F is the differential resistance to the process of charge transfer at this interface (the so-called Faraday resistance).

The geometrical capacitance of most films is low (of the order of 10^{-9} F cm⁻²); as regards the order of magnitude, the corresponding impedance is larger than the film resistance R_s (except for very lightly doped films), and hence the latter may be neglected. In this case, we obtain a simple equivalent circuit with three elements (Fig. 4*b*) which is known as the Randles – Ershler circuit.⁵¹ It is essential that all the elements of the above circuits are independent of signal frequency. The circuit represented by Fig. 4*c* includes a frequency-dependent, constant phase-shift element (CPE) (see below).

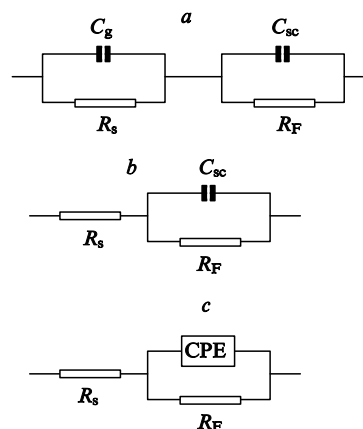


Figure 4. Equivalent circuits of the impedance (see text).

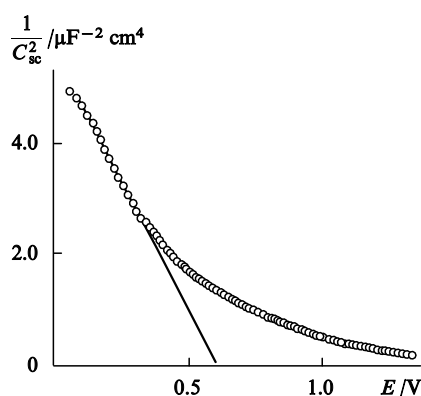


Figure 5. The Mott–Schottky plot for a boron-doped polycrystalline electrode with frequency-independent capacitance in 0.5 M H₂SO₄.⁵²

In certain cases, the impedance spectra of diamond electrodes are well described by the equivalent circuit (Fig. 4b) with a virtually frequency-independent (in the range of 1–10⁵ Hz) capacitance.⁵² Figure 5 presents the Mott–Schottky plot, which expresses the dependence of the squared reciprocal capacitance C_{sc} on the polycrystalline diamond electrode potential E in 0.5 M H₂SO₄. Physically, it reflects the dependence of the space charge layer thickness in a semiconductor on potential.⁶ The space charge arises because the near-surface region of semiconductors is depleted in mobile charge carriers (the so-called depletion layer). Extrapolation of the linear segment until its intersection with the abscissa provides the value of flat-band potential of the electrode E_{fb} , while the slope of this line can be used for calculating the concentration of non-compensated acceptors in a semiconductor by the formula

$$N_a = -\frac{2}{e\epsilon_0\epsilon} \left[\frac{d(C_{sc}^{-2})}{dE} \right]^{-1}, \quad (1)$$

where e is the electron charge, ϵ and ϵ_0 are the dielectric constants of diamond and vacuum, respectively. Formula (1) was derived under assumptions that, first, the potential drop during polarisation takes place in the space charge region (and, *e.g.*, not in the Helmholtz layer at the interface); second, there is no ionisation of ‘deep’ acceptors; third, the measured capacitance is that of the space charge region C_{sc} (and does not include, *e.g.*, the capacitance of surface states, adsorption capacitance, *etc.*). For the electrode under discussion (see Fig. 5), $N_a \approx 3.1 \times 10^{18} \text{ cm}^{-3}$.

The depletion layer is usually formed in a doped wide-bandgap semiconductor which is in contact with another phase (metal, electrolyte solution or vacuum). The potential barrier associated with the depletion layer formation (in particular, upon contact with the conducting phase) is called the Schottky barrier. The contact of polycrystalline diamond films with certain metals (Au, Pt, Pd) manifests a rectifying effect (see, *e.g.*, Refs 53 and 54), while its capacitance characteristics resemble those of the diamond/indifferent electrolyte contact.

However, specimens with a frequency-independent capacitance represent an exception rather than the rule. Usually, the capacitance of diamond films depends on frequency. Figure 6 features a characteristic electrode impedance spectrum presentation on a complex plane.⁵⁵ At high frequencies (1–100 kHz), the complex-plane plot forms a straight line that does not pass through the origin of coordinates (see Fig. 6a). A similar impedance feature was observed in a series of studies (see, *e.g.*, Refs 56–59). At low frequencies, the $-\text{Im}Z$ vs. $\text{Re}Z$ plot is curved due to the presence of the Faraday resistance in the equivalent circuit (Fig. 6). Under the anodic or cathodic polarisation, the curvature becomes more appreciable due to the decrease in R_F , and the shape of the low-frequency segment of the curve approaches a semicircle.

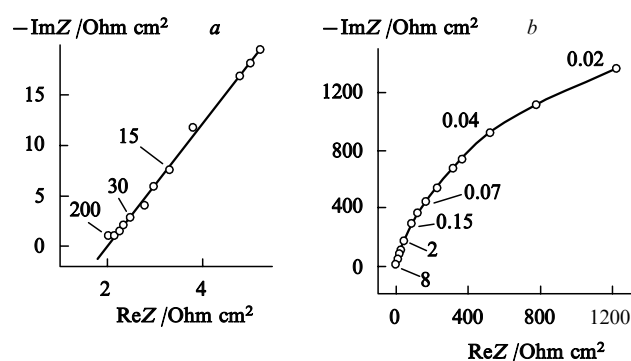


Figure 6. High-frequency (a) and low-frequency (b) segments of the complex-plane plot of the impedance of a single-crystal electrode in 0.5 M H₂SO₄ under a steady-state potential.³⁵ Numerals at the curves indicate the signal frequencies /kHz.

Such a characteristic type of the frequency dependence suggests that the equivalent circuit of the electrode includes the so-called constant phase element (CPE) with its impedance equal to

$$Z_{CPE} = \sigma^{-1}(i\omega)^{-a}, \quad (2)$$

where the frequency-independent parameter σ has the dimensionality $\text{F}^a \text{ Ohm}^{a-1} \text{ cm}^{-2}$, the index a determines the character of the frequency dependence, i is the imaginary unity, $\omega = 2\pi f$ is the angular frequency of the alternating current. Analysis of the impedance spectra is based on the equivalent circuit (Fig. 4c) derived from the Randles–Ershler circuit by replacing the frequency-independent capacitance with CPE. The elements of the equivalent circuit are usually calculated by the least-squares method with minimisation of the standard deviation of the logarithm of the impedance modulus measured at different frequencies from the logarithm of the impedance modulus calculated for the equivalent circuit using the corresponding computer programme.⁶⁰

Typical σ and a values, film resistance R_s , calculated diamond resistivity ρ and the Faraday resistance R_F are listed in Table 1 for the polycrystalline and single-crystal (thin-film and compact) diamond electrodes and the electrode made of amorphous diamond-like carbon.^{50,61} Comparison of the data presented in

Table 1. Parameters a , R_s (Ohm cm²), σ ($\mu\text{F}^a \text{ Ohm}^{a-1} \text{ cm}^{-2}$), ρ (Ohm cm) and R_F (Ohm cm²) found in the studies of the impedance of polycrystalline and single-crystal diamond films in 0.5 M H₂SO₄ solution.

Electrode	Substrate	Film thickness /μm	a	R_s	σ	ρ	R_F
Polycrystalline film	W	2.4	0.92	1.5	1–1.5	0.7×10^4	10^4 – 10^7
Single-crystal film	synthetic diamond single crystal	10	0.96	32	2.7	0.1	10^6 – 10^8
Single crystal ^a	—	—	0.92	2.8	2.5	30	10^6
Amorphous diamond-like film	glassy carbon	0.07	0.9	—	0.05	0.8×10^5	10^6

^a A single crystal grown under high pressure and high temperature.

Table 1 suggests that in both the qualitative respect (the equivalent circuit form and the presence of CPE in it) and the quantitative respect (typical a and σ values) the polycrystalline and single-crystal electrodes are virtually the same: a varies within a narrow range 0.9–0.96, $\sigma \approx 1\text{--}3 \mu\text{F}^{a-1} \text{ Ohm}^{a-1} \text{ cm}^{-2}$, $R_F \approx 10^4\text{--}10^8 \text{ Ohm cm}^2$ (in an indifferent electrolyte solution under a stationary potential). Assuming that the measured integral impedance parameters a and σ characterise the double electrical layer on diamond electrodes, it may be concluded that the structure of this layer is approximately the same in the polycrystalline and single-crystal specimens. Furthermore, on the whole, the structure of the double electrical layer is identical in the diamond and wide-bandgap diamond-like carbon electrodes.

Rather high values of the Faraday resistance R_F reflect the above-mentioned low background currents and the negligibly small corrosion of diamond in aqueous solutions. Larger values of σ in comparison with those in other semiconductor electrodes are indicative of a relatively high doping level of the diamond films studied (the acceptor concentration $N_a \geq 10^{18} \text{ cm}^{-3}$).

Note that according to different authors, the flat-band potential (E_{fb}) values determined by the extrapolation of the Mott–Schottky plots are in the range from 0.5 V (Ref. 52) to 1.2 V (Ref. 55) [relative to the saturated calomel electrode (SCE)]. Such a spread of data can in part be explained by different degrees of diamond surface oxidation (resulting from pretreatment of samples). It is known⁶ that the anodic and cathodic oxidation of numerous semiconductors shifts their flat-band potentials toward positive and negative regions, respectively. This is largely due to an appreciable extent to the dipolar potential drop associated with the oxygen monolayer adsorbed on the electrode surface and determined by the polarity of the C–O bonds.

Note in conclusion that in the CPE-containing equivalent circuit of the electrode, no separate frequency-independent capacitance was revealed that could be attributed to the space charge region in diamond.⁶² This means that it is the CPE [with its dependence on potential which is characteristic of semiconductor electrodes (see Section V.2 for more detail)] that describes the properties of the space charge region.⁶²

Recently, the diamond crystals grown under high pressure and high temperature have been used for the first time as electrodes. Their impedance characteristics proved to be close to those of thin-film electrodes (see Table 1).^{63, 64}

2. On the nature of the frequency dependence of the differential capacitance of diamond electrodes

Naturally, the dependence of capacitance on frequency that follows from the impedance complex-plane plot (see Fig. 6) determines the slope of the straight line in the Mott–Schottky plot.⁶⁵ The researchers investigating the frequency dependence of the differential capacitance of diamond electrodes must answer two major questions, *viz.*, what processes lead to the appearance of this dependence and what is the most convenient manner of its formal presentation.

The nature of the frequency dependence of the slope of the Mott–Schottky plot for the semiconductor electrodes has been subject to discussion for over three decades (see, *e.g.*, Refs 6 and 66). Possible reasons for its appearance are believed to be the dependence of dielectric relaxation on frequency in the space charge region,⁶⁷ roughness of the electrode surface,⁶⁶ slow ionisation of deep donors (acceptors) in the space charge region of semiconductors⁶⁸ and the influence of the surface states.

Evstefeeva *et al.*⁶⁹ investigated the dependence of capacitance on frequency in its application to the diamond electrode assuming that the electrode surface roughness should not necessarily lead to the appearance of CPE in its impedance.⁷⁰ The hypothesis⁵⁹ of slow ionisation of atoms with a deep-lying energy level (*e.g.*, boron) in the space charge region of diamond crystals has been assumed for a tentative explanation of the frequency dispersion of the Mott–Schottky plots of diamond electrodes. This explanation is supported by the fact that the magnitude of σ varies regularly

with changes in the thickness of the space charge layer (in conformity with Schottky's theory), whereas the magnitude of a is virtually independent of both the potential and the solution dilution, *i.e.*, the factors influencing the electrode surface state. Therefore, it has been concluded that the observed dependence of capacitance on frequency is not associated with the surface states but is determined by the process occurring in the space-charge region of diamond.[‡]

Let us consider different forms of the Mott–Schottky plots when they are frequency-dependent using the diamond electrode as an example. As noted above, this situation is typical of the electrochemistry of various semiconductor electrodes. Figures 7 and 8 illustrate three ways of presentation of such plots. The first pattern is a 'sheaf' of C^{-2} – E straight lines plotted from the capacitance values measured directly at a given frequency (a series of frequencies) and potential (see Fig. 7). The second one is the plot C_{calc}^{-2} – E (see Fig. 8, curve 2). When plotting this curve, the real equivalent electrode circuit (see Fig. 4c) was replaced by a simpler circuit (see Fig. 4b) including the frequency-independent capacitance instead of CPE. In its essence, the C_{calc} is the capacitance C_{sc} averaged over the entire range of the alternating current frequencies studied. As this step uses the body of experimental data for the whole frequency range, the value of C_{calc} obtained may be regarded formally as the frequency-independent one. Finally, the third pattern (for the cases where the equivalent circuit contains CPE) is the σ^{-2} – E plot (see Fig. 8, curve 1). Note that $\sigma \rightarrow C_{\text{calc}}$ at $a \rightarrow 1$.

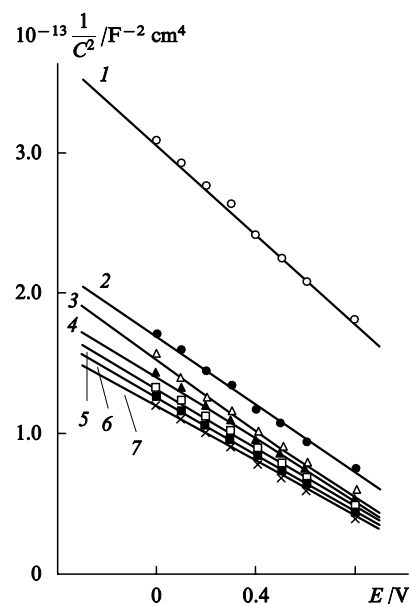


Figure 7. The Mott–Schottky plot for a boron-doped single-crystal electrode with a frequency-dependent capacitance in 0.5 M H_2SO_4 . Frequency/Hz: (1) 21 544; (2) 10 000; (4) 4642; (5) 2154; (6) 1000; (7) 215; (3) the curve is calculated for C_{calc} ;⁶⁹ the potential values were measured relative to the Ag/AgCl electrode.

When comparing the above-listed patterns, one should pay attention to the fact that the plot σ^{-2} vs. E is frequency-independent, since σ is the frequency-independent parameter by definition [see formula (2)]. It may be considered as the most general case and be used for comparing results of different experiments, since in this case the contribution from the intrinsic frequency-dependent element is ruled out. However, taking into

[‡] It is unclear until now why the differential capacitance of some diamond electrodes is independent of frequency.

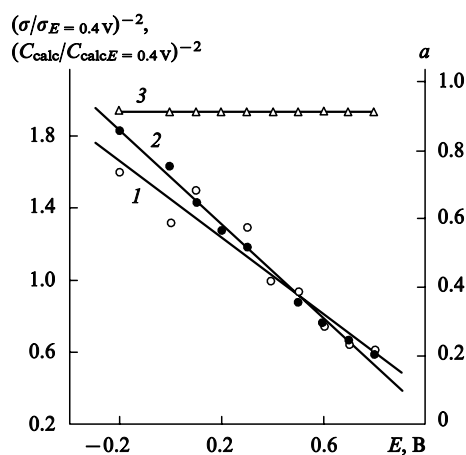


Figure 8. Dependence of $(\sigma/\sigma_{E=0.4\text{ V}})^{-2}$ (1), $(C_{\text{calc}}/C_{\text{calc},E=0.4\text{ V}})^{-2}$ (2) and a (3) on potential for a single-crystal electrode (calculated using the data of Fig. 7).⁶⁹ Potentials were measured relative to the Ag/AgCl electrode.

account the dimensionality of σ , correct comparison of the calculated data with the published results of direct capacitance measurement on diamond electrodes seems questionable.

The use of the $C_{\text{calc}}^{-2}-E$ dependence removes the dimensionality problems, although a somewhat formal character of the C_{calc} parameter is a disadvantage of this form of the Mott–Schottky plot presentation.

The sheaf of $C^{-2}-E$ straight lines may be interpreted as manifestation of a slow process (e.g., the above-mentioned ionisation of the deep acceptor) occurring in the space charge region of a semiconductor. Unfortunately, the nature of the dependence of differential capacitance on frequency is unknown; therefore, one should consider as approximate the literature data on the concentration of acceptors in diamond calculated on the basis of Schottky's theory for an arbitrary frequency of the measured signal. Nonetheless, it appears more convenient to use the dependence $\sigma^{-2}-E$ (especially for the cases when the exponent a is close to 1) or $C_{\text{calc}}^{-2}-E$ for qualitative comparison of electrodes made of the same semiconductor material.

VI. Kinetics of the electrode reactions

1. Kinetics of outer-sphere reactions. Metal-like diamond electrodes

It is common practice to divide electrochemical reactions into outer-sphere (occurring without cleavage of interatomic bonds in the reacting molecule) and inner-sphere ones (occurring with the cleavage or formation of such bonds). An example of outer-sphere reactions is the electron transfer in the $\text{Fe}(\text{CN})_6^{3-/4-}$ system, while the inner-sphere reactions may be exemplified by the oxidation and reduction of water molecules with the evolution of O_2 and H_2 , respectively. Let us start discussion of the kinetics of reactions on the diamond electrode with the former type of reactions.

A number of outer-sphere reactions were investigated by the method of potentiodynamic curves with a linear potential sweep. This method proved to be convenient for both qualitative and quantitative characterisation of the electrode behaviour. The theory of this method has been considered in textbooks.^{71, 72}

Typical cyclic voltammograms recorded for four redox systems are presented in Fig. 9. The outer-sphere reactions occur in solutions of $\text{Fe}(\text{CN})_6^{3-/4-}$, $\text{Ru}(\text{NH}_3)_6^{2+/3+}$ and $\text{IrCl}_6^{2-/3-}$, while the inner-sphere reaction occurs in the quinone/hydroquinone system. A characteristic shape of all curves with peaks of anodic and cathodic currents demonstrates that in all cases the stage of charge transfer at the interface is rather fast; the reaction is hampered due to the insufficiently rapid reagent mass transfer in solution toward the electrode surface. Similar curves were

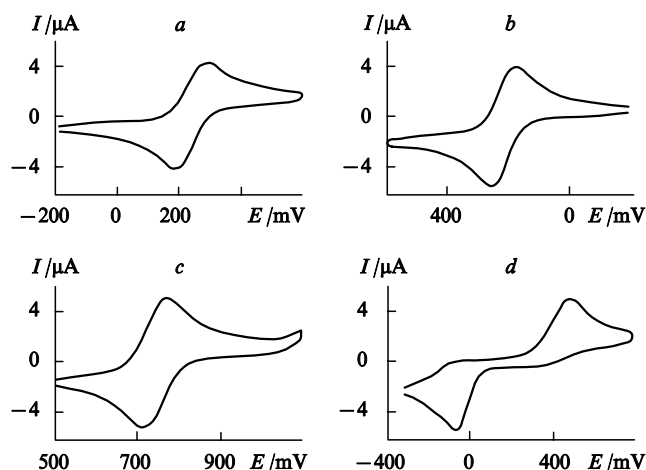


Figure 9. Cyclic voltammograms in 10^{-4} M solutions of $\text{Fe}(\text{CN})_6^{3-/4-}$ (a), $\text{Ru}(\text{NH}_3)_6^{2+/3+}$ (b), $\text{IrCl}_6^{2-/3-}$ (c) against the background of 0.1 M KCl and quinone/hydroquinone (d) against the background of 0.1 M HClO_4 .⁷³ Potentials were measured relative to the SCE.

obtained in a series of studies of the ferrocyanide/ferricyanide⁷⁴ and quinone/hydroquinone systems,⁷⁵ Ce^{3+} ions (see Ref. 76), etc.

Analysis of these curves makes it possible to determine the following characteristics of the diffusion and interphase charge transfer: diffusion coefficient, transfer coefficients of the cathodic (α) and anodic (β) reactions and the rate constant (k^0). Quantitatively, the larger the difference between the potentials of the cathodic and anodic peaks the less reversible the electrode reaction. According to the theory of electrode kinetics,^{71, 72} for a reversible one-electron reaction at room temperature, $\Delta E_p = 56$ mV irrespective of the reagent concentration and the rate of potential sweep. For the systems, the voltammograms of which are shown in Fig. 9a–c, the values of ΔE_p are 88, 72 and 65 mV, respectively.⁷³ Consequently, on a relatively strongly doped polycrystalline electrode, the processes under consideration occur in the mode of a quasi-reversible reaction. On the contrary, the electrode reaction is markedly irreversible in the quinone/hydroquinone system: $\Delta E_p = 560$ mV. These qualitative estimates correlate with the values of rate constants determined for the above-listed redox systems.⁷⁷

Reagent	$\text{Fe}(\text{CN})_6^{3-/4-}$	$\text{Ru}(\text{NH}_3)_6^{2+/3+}$	$\text{IrCl}_6^{2-/3-}$	quinone/hydroquinone
$k^0/\text{cm s}^{-1}$	9×10^{-4}	3×10^{-3}	4×10^{-3}	$< 10^{-6}$

The rate constants strongly depend on both the level of diamond doping with boron (see below) and the prior preparation of the electrode surface; these data are presented here for the purpose of illustration. On the whole, based on the studies of a series of systems [including methyl viologen; $\text{FeL}_3(\text{ClO}_4)_2$, where L is *o*-phenanthroline; 1,1'-dimethoxyferrocene, etc.], the following qualitative inferences have been made:^{78, 79} the outer-sphere reactions are closer to reversible reactions than the inner-sphere ones; the reactions in the systems with a positive equilibrium potential are closer to reversible reactions than those in the systems with a negative potential;[§] on the heavily doped metal-like diamond the reaction rate is higher than on the moderately doped electrodes characterised by semiconductor properties. But even on the metal-like diamond electrodes the reaction rate is appreciably lower than that on the metal electrodes with high electrocatalytic activity, e.g., platinum. Consequently, upgrading

[§] This regularity is invalid for the $\text{Ce}^{3+/4+}$ system (see Ref. 75) which is discussed in more detail in the next section.

of electrocatalytic properties of diamond electrodes intended for practical applications is a topical problem. First experiments have shown^{80,81} that the deposition of microquantities of platinum onto the diamond electrode surface reduces the overvoltage of the cathode reactions.

2. Semiconductor properties of diamond and the electrode kinetics

The systems $\text{Fe}(\text{CN})_6^{3-/4-}$, quinone/hydroquinone[¶] and $\text{Ce}^{3+/4+}$ have been investigated quantitatively.^{75, 80, 82} The dependences of the potentials of the anodic and cathodic current peaks E_p in the potentiodynamic curves on the logarithm of the rate of potential sweep v were determined experimentally; the data characterising the quinone/hydroquinone system are shown in Fig. 10.⁷⁵ The transfer coefficients of the anode and cathode reactions were calculated from the slope of the straight line (Fig. 10 c) using the theory of the method of potentiodynamic curves.⁷²

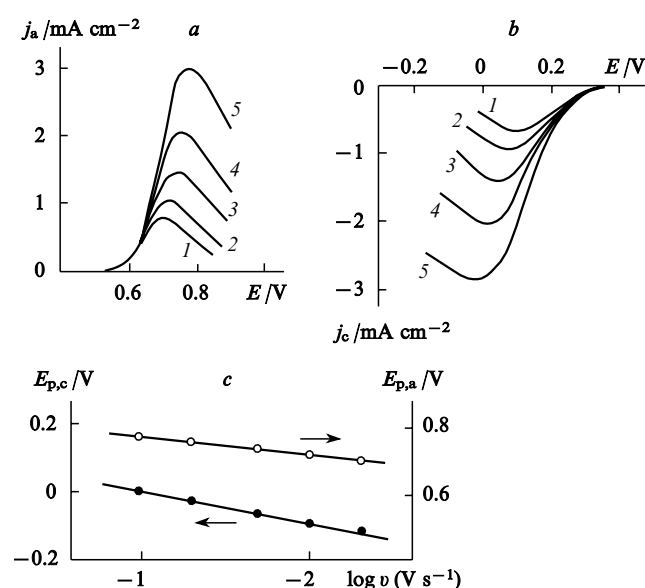


Figure 10. Potentiodynamic curves recorded during the linear potential sweep in the course of hydroquinone (0.01 M) oxidation (a) and quinone (0.01 M) reduction (b) in 0.5 M H_2SO_4 on a polycrystalline diamond electrode, and dependences of the potentials of the cathodic ($E_{p,c}$) and anodic ($E_{p,a}$) current peaks on the logarithm of the sweep rate (c).⁷⁵ The rate of potential sweep $v/\text{V s}^{-1}$: (1) 0.005; (2) 0.01; (3) 0.02; (4) 0.05; (5) 0.1. Potentials were measured relative to the Ag/AgCl electrode.

Table 2 presents the measured α and β values typical of the single-crystal and polycrystalline thin-film electrodes and a single crystal (grown under high pressure and high temperature) in Ce^{3+} and Ce^{4+} solutions. For the $\text{Ce}^{3+/4+}$ system (as for the two other systems, viz., $\text{Fe}(\text{CN})_6^{3-/4-}$ and quinone/hydroquinone), the transfer coefficients are less than 0.5, especially for the cathodic reaction, and the sum $\alpha + \beta$ proves to be less than unity. According to the theory of the electrochemical kinetics on semiconductors,⁶ in the case of an 'ideal' p -type semiconductor electrode, the transfer coefficients for the reactions occurring with the participation of holes should be as follows: $\alpha = 0$, $\beta = 1$; $\alpha + \beta = 1$. In practice, however, the ideal case is extremely rare even for single-crystal semiconductor materials (silicon, gallium arsenide, etc.) that are prepared using much more advanced technologies than the technology for the preparation of polycrystalline CVD-diamond. The reason for the deviation from 'the ideal situation'

Table 2. Kinetic characteristics of diamond electrodes in a 0.01 M Ce^{3+} (or Ce^{4+}) + 0.5 M H_2SO_4 solution.

Electrode	α	β	$k^0/\text{cm s}^{-1}$
Polycrystalline film ⁵⁵	0.16	0.46	6×10^{-9}
Single-crystal film ⁵⁵	0.2	0.43	6.5×10^{-7}
Single crystal grown under high pressure and high temperature ⁶³	0.33	0.27	4.4×10^{-6}

appears to lie in the fact that during the electrode polarisation, part of the interphase potential drop is lost in the Helmholtz layer (e.g., due to a high density of the surface states). As a result, the transfer coefficients α and β have the values intermediate between those characteristic of semiconductors (0 or 1) and metals (~ 0.5).

Extrapolation of the impedance complex-plane plot until its intersection with the $\text{Re}Z$ axis (Fig 6a) gives the diamond film resistance R_s from which the diamond resistivity ρ can be calculated. The dependences of R_F on ρ for two redox systems are presented in Fig. 11. It is seen that, first, the reaction rate in the $\text{Fe}(\text{CN})_6^{3-/4-}$ system is approximately three orders of magnitude higher than that in the quinone/hydroquinone system, which is consistent with the above-cited rate constants; second, R_F is observed to be directly proportional to ρ over a wide range of diamond resistivity. The existence of such a dependence for diamond electrodes was first reported by Modestov *et al.*⁸⁰ It reflects the fundamental law of the kinetics of reactions on semiconductor electrodes: the rate of an electrochemical reaction is proportional to the concentration of free carriers on the electrode surface. Indeed, the concentration of holes in the diamond bulk p_0 is inversely proportional to its resistivity ρ .[†] The concentration of holes on the electrode surface p_s is related to p_0 by the Boltzmann equation⁶

$$p_s = p_0 \exp\left(-\frac{e\phi_{sc}}{kT}\right),$$

where ϕ_{sc} is the potential drop in the space charge layer.

If the chemical interaction of diamond with the solution and hence the potential distribution over the diamond/solution interface is assumed to be independent of the level of diamond doping with boron, then at the given electrode potential which is set by the redox system the value of $e\phi_{sc}$ is the same for all electrodes. Consequently, the reaction rate ($\sim 1/R_F$) should be proportional

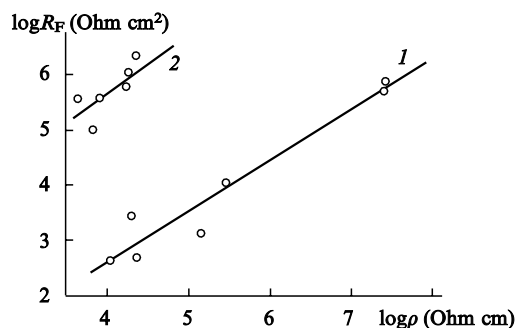


Figure 11. Dependence of the Faraday resistance under equilibrium potential in the $\text{Fe}(\text{CN})_6^{3-/4-}$ (1) and quinone/hydroquinone (2) systems on the film resistivity.⁸³

¶ Note that the reactions occurring in the quinone/hydroquinone system are inner-sphere ones.

† In the discussion of the relation between the concentration of holes in specimens and their resistivity, it is assumed that the mobility of holes is independent of the boron concentration in specimens.

to the diamond conductivity, which is in fact observed in experiments.

3. Crystal structure and the electrode kinetics: comparison of electrodes from single-crystal and polycrystalline diamond and amorphous carbon

Polycrystalline diamond films are heterogeneous systems consisting of diamond crystallites and disordered carbon of intercrystallite boundaries (see Section III. 1). In this context, the following question arises: to what extent do the intercrystallite boundaries influence the electrochemical properties of polycrystalline diamond electrodes? In order to answer this question, one should compare the electrochemical behaviour of crystalline diamond with that of diamond-like carbon, which may be arbitrarily regarded as a model for the material of intercrystallite boundaries in the polycrystalline diamond.

Such a comparison shows that the kinetic characteristics (α and β) of single-crystal and polycrystalline diamond electrodes are similar. In solutions of redox systems, both types of diamond electrodes possess electrocatalytic activity (though not very great, which is characteristic of semiconductor electrodes).

The properties of amorphous carbon vary within very wide limits. In their electrode properties, the 'graphite-like' thin-film electrodes resemble conventional carbonaceous materials (*e.g.*, glassy carbon); redox reactions occur on them at high rates. On the contrary, in the case of 'diamond-like' electrodes there are no peaks of oxidation and reduction currents in such systems as $\text{Ce}^{3+/4+}$, $\text{Fe}(\text{CN})_6^{3-/4-}$ and quinone/hydroquinone; the currents measured do not differ from the background current. The fact that the diamond-like carbon proved to be electrochemically inactive suggests that the intercrystallite boundaries make no practical contribution to the electrode behaviour of polycrystalline diamond; it is totally determined by diamond crystallites. This conclusion relies on the results of comparison of the impedance (Table 1) and kinetic (Table 2) characteristics of polycrystalline and single-crystal diamond films and seems to be valid at least in the range of moderate electrode polarisation.⁵⁵

On the other hand, at high anode potentials (+1.7 V relative to the NHE, just before the beginning of oxygen evolution) a small peak is observed in the polarisation curve of a polycrystalline electrode in an indifferent electrolyte solution (similar to that shown in Fig. 3a).³² Its height is as small as $\sim 1 \mu\text{A cm}^{-2}$; therefore, it can hardly be seen in Fig. 3a (and other similar graphs). As to the quantity of electricity passed corresponding to this current peak, it may be concluded that within one such 'passage' of the curve, $\sim 0.05\%$ of the monolayer substance of the electrode surface takes part in the reaction. This current peak is better expressed for the diamond films with a relatively high content of non-diamond carbon, but it is not observed on single-crystal electrodes. According to Martin *et al.*,³² this peak is due to the oxidation of the non-diamond carbon of the intercrystallite boundaries, which is less resistant to oxidation than the crystalline diamond. No other peculiarities of the electrode behaviour of diamond, which could be attributed to the intercrystallite boundaries, have been revealed.

Note in conclusion that the wide-bandgap diamond-like carbon a-C:H which is usually electrochemically inactive acquires an electrode activity after the incorporation of a sufficiently large quantity ($\sim 10\%$) of platinum into the bulk of film (in the course of its deposition). In the shape of their potentiodynamic curves and the values of kinetic parameters, the a-C:H/Pt electrodes thus obtained resemble qualitatively the polycrystalline (boron-doped) diamond electrodes. For example, in the redox system $\text{Ce}^{3+/4+}$ no current peaks in the curves are observed at the Pt level ranging from traces to 1%, but they become well expressed at 12% of platinum; coefficients α and β being equal to 0.13 and 0.18, respectively. The redox reactions are irreversible; they occur under a mixed diffusion-kinetic control and have a moderate overvoltage.⁶¹

The results obtained point to the possibility of creation of fairly active electrodes from corrosion-resistant carbonaceous materials, *viz.*, synthetic diamond and diamond-like carbon, by incorporating into their bulk rather small quantities of metal catalysts such as platinum.

Platinum can be distributed in a carbon material in the form of individual atoms or clusters depending on the mode of its incorporation.⁸² An essential feature is that platinum is not a doping admixture in a-C:H in the sense of this term as used in the physics of semiconductors. Impedance measurements have shown that the Pt admixture does not virtually change the material resistivity. Therefore, it may be suggested that the effect of platinum is of a purely catalytic nature: its atoms on the electrode surface play the role of active sites on which the adsorption and the electrode reaction proceed at high rates.^{50, 61}

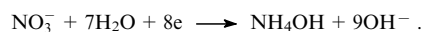
4. Kinetics of inner-sphere reactions. Diamond electrodes in preparative electrolysis and electroanalysis

The evolution of oxygen from water on the anode and hydrogen on the cathode are regarded as the inner-sphere processes. Potentials of these processes restrict the region of 'ideal polarisability' in aqueous solutions of electrolytes (see Fig. 3a,b). Overvoltage of these reactions increases with higher quality of electrode films. For the anodic evolution of oxygen, the exchange current is $5 \times 10^{-11} \text{ A cm}^{-2}$, transfer coefficient $\beta = 0.25$; for the hydrogen evolution on the cathode the exchange current is $10^{-10} \text{ A cm}^{-2}$ and $\alpha = 0.30$ (see Ref. 32).

The region of 'ideal polarisability' may be restricted by decomposition potentials of not only the solvent but also dissolved electrolyte, *e.g.*, halides. The reactions of anodic oxidation of Cl^- , Br^- and I^- ions with the evolution of the corresponding halogens proceed irreversibly and are accompanied by a much higher (by 1 V for Cl^-) overvoltage than on the platinum or graphite electrodes. Most probably, this is associated with low adsorbability of intermediate products (chlorine, bromine and iodine atoms) on the diamond surface, which thus proves to be passive.⁷⁸ (The outer-sphere reactions discussed in Section VI.1 occur without adsorption of reagents or intermediate products on the electrode; for this reason, they are insensitive to the poor adsorption capacity of the diamond surface.)

In addition to the above-mentioned processes, the inner-sphere reactions also include oxidations of numerous organic compounds, in which the interphase charge transfer is accompanied by transformations of organic molecules. Polycrystalline diamond electrodes have been used to investigate the anodic oxidation of chlorpromazine,⁴¹ ascorbic acid,⁸⁴ anthraquinone-2,6-disulfonate⁸⁵ and several amines.⁸⁶

One of the most efficient and promising applications of the diamond electrodes is their use for the electroreduction of compounds that are difficult to reduce. For example, the reduction of nitrate and nitrite ions to ammonium has been investigated.^{87–89} In an alkaline solution of NO_3^- , the following reaction takes place on a heavily doped electrode (with N_a up to 10^{21} cm^{-3}) under anodic polarisation:



At a potential of -5 V , the current density reaches 300 mA cm^{-2} but no corrosion of diamond is observed even after a few days of continuous electrolysis.

The most striking feature of this process is that the anodic current efficiency exceeds several-fold the theoretical limit calculated by the equation for the reaction! Attempts were undertaken to rationalise this fact by the occurrence of the conjugated oxidation of silicon (the diamond film was prepared by deposition on a silicon substrate), *e.g.*, through pinholes in the film. However, special experiments on a free-standing diamond film (see Section II) have shown that the current efficiency, though being somewhat decreased, still remained higher than its theoretical level. The reason of this effect is still unclear.

The electrodeposition of metals (Li, Ag, Cu, Pb, Pt, Hg) leading to the formation of a new phase stands somewhat apart. Data on such processes are scanty and rather contradictory. Lead and mercury are deposited as islets a few micrometers in diameter predominantly over the intercrystallite boundaries.⁸¹ According to Li *et al.*,^{18,90} lithium is deposited in the same mode with concomitant intercalation into the non-diamond carbon. Observation of the lithium intercalation–deintercalation may be used as a technique for revealing non-diamond inclusions on the surface of diamond films. Finally, there is indirect evidence that the electrodeposition of copper, the first stages of which follow the ‘underpotential deposition’ mechanism, also takes place on the intercrystallite boundaries.⁸

Electroanalytical methods have been developed on the basis of certain electrochemical reactions on diamond electrodes. Judging from the results of relevant studies,^{8,81} the diamond electrode is well-suited for use in the commonly accepted anodic-stripping analysis of solutions for low concentrations of metal ions, which consists in the cathodic deposition of small quantities of metals on an inert working electrode with their subsequent anodic dissolution.

A flow-type thin-layer cell with a diamond electrode has been devised^{85,91,92} for the determination of ethylamine, ethylenediamine and other amines, as well as azide ion N_3^- . Such determinations are carried out by injecting a microportion of the solution under study into the electrolyte flow with subsequent recording of the current jump induced by the oxidation of the compound under analysis (Fig. 12). The electrode function is linear in the concentration range of 10^{-2} – 10^{-5} M; the detection limit, *e.g.*, of azide ion, is 8 nmol l^{-1} (see Ref. 92).

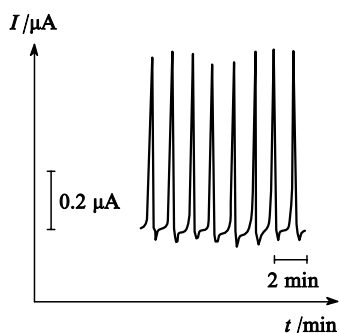


Figure 12. Chronoamperogram in the determination of ethylamine concentration by injecting an aliquot (20 μl of 0.25 mM solution) into a flow-type cell with 0.1 M carbonate buffer; solution flow rate, 0.5 ml min^{-1} (see Ref. 91).

VII. Photoelectrochemistry of diamond

Like any other semiconductor, the diamond demonstrates a photoelectric effect due to photogeneration of free charge carriers upon illumination. An increase in the concentration of charge carriers affects the current across the diamond contact with another conducting phase or the interface charge. In the potentiostatic regime, a photocurrent is recorded and a photopotential is recorded in the galvanostatic and coulombostatic regimes.

Starting from the first study,¹¹ the photoelectrochemistry of diamond has been investigated by illuminating electrodes with light with quanta energy $h\nu$ smaller than the bandgap ($E_g \approx 5.5 \text{ eV}$); this energy is insufficient for the transition of excited electrons from the valence band to the conduction band. Free carriers were apparently formed due to ionisation of some unidentified photosensitive sites in the bandgap of diamond, *viz.*, admixtures or structural defects (the so-called extrinsic or impurity photosensitivity). Curves of photocurrent in the diamond electrode elicited by band-to-band electron transitions (the so-

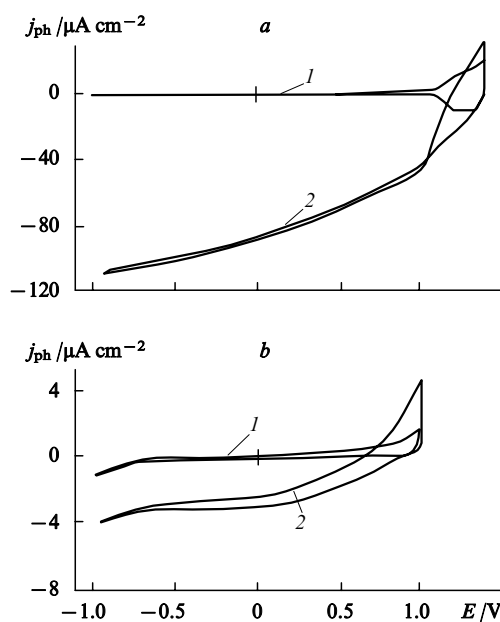


Figure 13. Dependence of dark current (1) and photocurrent (2) upon illumination of a polycrystalline diamond electrode in 0.1 M KH_2PO_4 under intrinsic (a) and impurity-related (b) photoexcitation. The quanta energies were 6.4 eV (a) and 5 eV (b). Density of illumination power was 80 mW cm^{-2} (Ref. 93); the potential values were measured relative to the SCE.

called intrinsic photosensitivity⁹³) have been derived quite recently using an excimer laser with a wavelength of 193 nm (which corresponds to quantum energy $h\nu = 6.4 \text{ eV}$) as the high-energy light source. Figure 13 illustrates well the differences in the photocurrent density j_{ph} in the intrinsic and impurity-related photoexcitations. In the impurity-related excitation the quantum yield of photocurrent was $\sim 0.01\%$,⁹⁴ whereas in the intrinsic excitation it reached 34%.⁹³

The absolute magnitude of photocurrent is increased with increase in cathodic polarisation. This effect may be understood by examining Fig. 14 showing the square of photocurrent as a function of the potential.¹¹ This plot is equivalent to the Mott–Schottky plot (see Fig. 5) because, like the latter, it reflects the variation of the width of the space charge layer in the semiconductor diamond as a function of the potential. Upon illumination of this semiconductor, the light-generated charge carriers with opposite signs are separated by an electric field in the space charge region. The minority carriers drift in the electric field

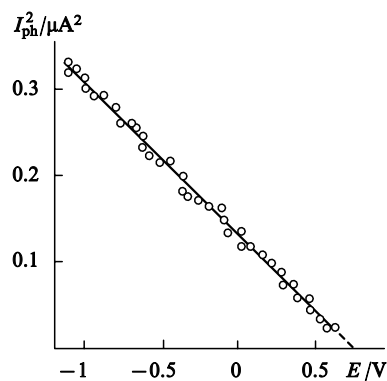


Figure 14. Dependence of the squared photocurrent on the diamond electrode potential in 1 M KCl;¹¹ the potential values were measured relative to the SCE.

toward the interface, where they are 'captured' by the electrochemical reaction or they charge (in the coulombostatic regime) the electrode, whereas the majority carriers migrate into the bulk of diamond and then, through the ohmic contact, to the external circuit of the electrochemical cell. Therefore, the thicker the space charge layer from which the minority carriers are 'harvested' the stronger the photocurrent. By extrapolating the straight line in Fig. 14 until its intersection with the potential axis, one can determine the flat-band potential in the same way as when using the Mott–Schottky plot; both methods give consistent values for the same electrode (see Section V.1).

In a series of studies^{11,93,95} the photocurrent was measured in the steady-state mode upon illumination of the electrode with light of constant intensity. Later,^{94,96,97} pulsed illumination was used; the photopotential and dynamics of its decay were measured after the application of a light pulse. The current of photogenerated minority charge carriers charges the electrode capacitance and thereby determines the potential shift. The analysis conducted with the aid of a somewhat more complex version of the Randles–Ershler circuit (see Fig. 4b)[‡] afforded a satisfactory description of the dynamics of photopotential decay.

A typical spectrum of the cathodic photocurrent I_{ph} of a diamond electrode is shown in Fig. 15a. Processing of such spectra in the coordinates $(I_{ph}h\nu)^{1/2}$ vs. $h\nu$ (see Fig. 15b) provided values of threshold energies of indirect electron transitions that determine the photogeneration of charge carriers (for more details, see Ref. 6). In some cases, the spectra include two regions and give, respectively, two values of threshold energy. The problem of the elucidation of the physical nature of the energy levels in the bandgap of diamond which participate in such transitions is still far from its solution. Some transitions with a threshold energy close to 4 eV have been identified with the photoexcitation of electrons of the valence band on the energy levels of N^+ ions in the bandgap of diamond localised ~ 1.7 eV below the conduction band.⁹⁴

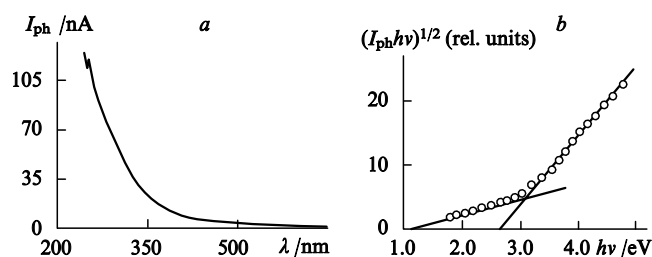


Figure 15. Spectrum of the cathodic photocurrent of a boron-doped polycrystalline diamond electrode in 0.5 M H_2SO_4 under a potential of 0.05 V (relative to NHE) (a) and its presentation in the $(I_{ph}h\nu)^{1/2}$ vs. $h\nu$ coordinates, which is convenient for the spectrum processing for the threshold energy determination.⁹⁴

The photocurrent–potential curves and the photocurrent spectra were also recorded for the films of amorphous diamond-like carbon.^{48,49,98} Processing of the spectra similar to that described above has made it possible to determine the width of the mobility gap in the disordered structure of this material. Upon illumination, the diamond-like carbon displays properties characteristic of intrinsic semiconductors.

Photoelectrochemical measurements make it possible to derive certain characteristics of the semiconductor diamond. Thus comparison of the spectra of light absorption coefficient and open-circuit photopotential allowed determination of the

diffusion length ($2-4\ \mu m$) of the minority carriers in polycrystalline diamond films.⁹⁹

VIII. Conclusion

About ten years have passed since the first studies in the field of diamond electrochemistry. This decade has witnessed the development of a somewhat schematic but rather comprehensive system of concepts of diamond as a novel electrode material. Investigations of diamond electrodes have afforded better understanding of the relationship between the crystal structure of solids and their electrode behaviour.

It is most likely that further studies on diamond electrochemistry will develop both extensively (a wider range of studied reactions, search for new applications of diamond electrodes in fundamental and applied electrochemistry) and intensively (a deeper insight into the relationship between the semiconductor and structural properties of carbon allotropes and their electrochemical behaviour). In the near future, the corrosion-resistant diamond film electrodes may be expected to replace (at least in part) the conventional dimension-stable electrodes based on the platinum group metals, which are used nowadays for the electrochemical synthesis and analysis.

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[‡] The Randles–Ershler circuit was supplemented with a branch which included a capacitance and a resistance connected in series and modelled the process of charging the surface states.

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^b — *Russ. J. Electrochem. (Engl. Transl.)*

^c — *Dokl. Chem. Technol., Dokl. Chem. (Engl. Transl.)*

Cationic molecular rearrangements of natural terpene compounds in superacidic media: reality and predictions

V A Barkhash, M P Polovinka

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Abstract. The main factors affecting the pathways of multistep cationic molecular rearrangements of natural terpenes and their analogues are considered. Methods for predicting the most probable pathways of cationic rearrangements are proposed. The bibliography includes 85 references.

I. Introduction

Carbocationic reactions play a prominent role in molecular rearrangements of organic compounds. The regularities of these reactions are most efficiently studied by modelling methods based on 'direct visualisation' of ion conversions in hypernon-nucleophilic superacidic media at superlow temperatures. Specially synthesised simple organic compounds are normally used as subjects for the investigation. The use of this approach in a particular field of organic chemistry in which cationic molecular rearrangements play a central role (*e.g.*, terpene chemistry) seems to be highly efficient. The study of regularities of carbocationic reactions of terpenoids and their analogues pursues three main goals:

1. Elucidation of regularities of molecular rearrangements of complex polycyclic cations.
2. Broadening of the range of available natural compounds suitable for the preparation of novel substances.
3. Chemical proof of validity of biogenetic schemes.

II. Conformational control of reactions

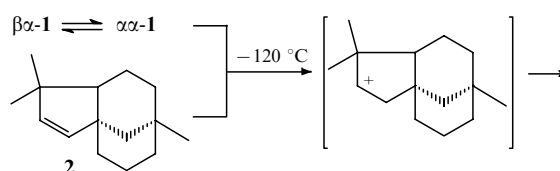
Polyfunctionality and conformational mobility are the most characteristic features of terpenes. Studies of conformational mobility and its effect on the reactivity of terpenes at low temperatures have generated an entirely new field of research, *viz.*, the

chemistry of conformationally controlled carbocationic reactions. In synthetic organic chemistry, conformational control is usually restricted to deamination of aliphatic amines and related compounds, but it plays a prominent role in biogenetic reactions of carbocationic cyclisation. The discovery of conformationally controlled reactions of stable ions derived from terpenes at low temperatures has made it possible to fill the gap between the biogenetic and chemical processes and provided a way for experimental realisation of biogenetic reactions.

Conformational control can be manifested both in initial steps of reactions and in subsequent transformations of the intermediate carbocations. The former can be exemplified in rearrangements of a sesquiterpene diene, *viz.*, caryophyllene (**1**). According to ^{13}C NMR spectral data, which are consistent with the molecular mechanics (MM2) calculations, compound **1** may exist in four stable conformations, *viz.*, $\beta\alpha$, $\alpha\alpha$, $\alpha\beta$ and $\beta\beta$.^{1,2}

Con- former				
	$\beta\alpha$ - 1	$\alpha\alpha$ - 1	$\alpha\beta$ - 1	$\beta\beta$ - 1
ΔH_f° (MM2), /kcal mol ⁻¹	12.6	14.2	17.3	12.4
Content (MM2) (%)	39	3	0	58

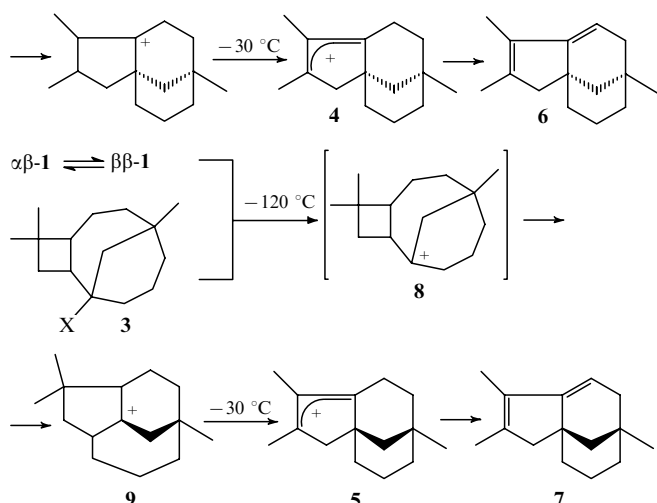
The experimental barrier to the transition between the pairs $\beta\alpha \rightleftharpoons \alpha\alpha$ and $\alpha\beta \rightleftharpoons \beta\beta$ (16.25 kcal mol⁻¹) cannot be virtually overcome at temperatures employed for the ion generation ($\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$, from -120 to -100 °C). Indeed, the ratio of reaction pathways of two conformers, *viz.*, $\alpha\alpha$ and $\beta\beta$, the transannular cyclisation of which gives radically different intermediate carbocations and different reaction products, correlates with the ratio of the above conformers.



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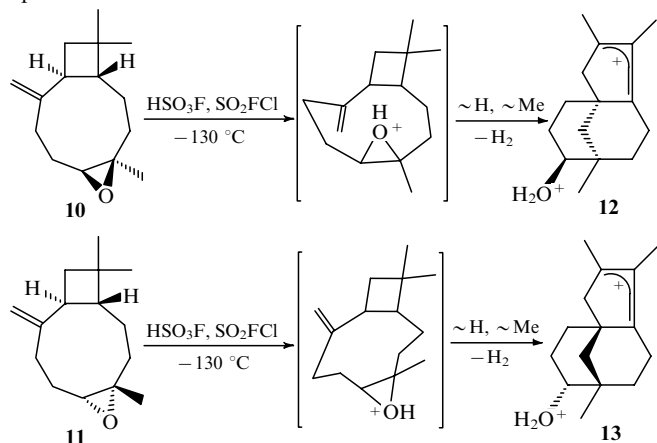
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Heating of the diene **1** in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$ to $-30\text{ }^\circ\text{C}$ and its subsequent neutralisation yield a mixture of enantiomeric dienes **6** and **7** in which the diene **6** with a clovane backbone [judging from optical rotation dispersion (ORD) curves] is predominant. The reaction proceeds *via* the intermediate allylic ions **4** and **5**. The ratio of dienes **6** and **7** corresponds to the ratio of the conformers $\alpha\alpha\text{-1}$ and $\beta\beta\text{-1}$ in SO_2FCl at $-120\text{ }^\circ\text{C}$.

The stable ions derived from conformers $\alpha\alpha$ and $\beta\beta$ can be generated separately from clovene **2** and 1-substituted caryolanones **3** *via* ions **8** and **9**.

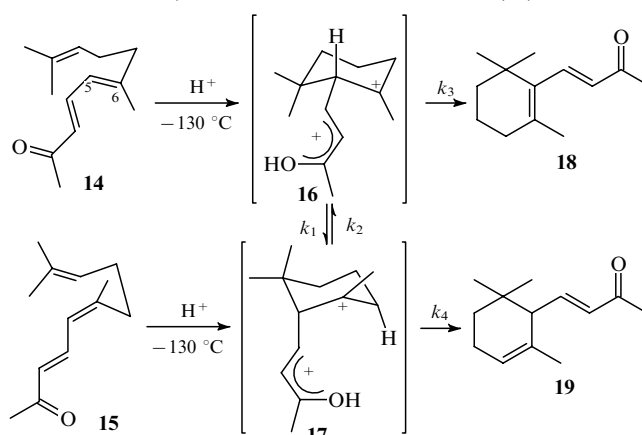
The conformational control can be effected after the carbocation has been formed and be manifested in different ways. The conformationally controlled molecular rearrangements of $4\beta,5\beta$ -(**10**) and $4\alpha,5\alpha$ -epoxides (**11**) of isocaryophyllene in superacids occur enantioselectively and result in the formation of the enantiomeric carbocations **12** and **13** from an epimeric pair of epoxides.³



Presumably, such enantioselective rearrangements take place when the opening of the epimeric monoepoxides generated from an optically active and conformationally flexible cyclic polyene occurs in acidic media with the participation of σ - and π -bonds. The direction of skeletal shifts is determined by the spatial structure of the epoxide. The optically active diene ultimately gives two enantiomeric products without recourse to any optically active reagents, *i.e.*, 'partial asymmetric synthesis' takes place.

The reaction which is controlled by the conformation of the intermediate carbocation may proceed in a structurally selective manner, as is the case with the low-temperature cyclisation of *trans*-5,6- (**14**) and *cis*-5,6- ϕ -ionones (**15**) in a superacidic medium. It was reported previously^{4,5} that the structural direction of cyclisation of isoprenoids containing a conjugated 5,6-double bond does not depend on its configuration. This was explained by decreased nucleophilicity of the double bond as a result of conjugation and, ultimately, a decrease in the cyclisation rate.

More recent studies have shown⁶ that protonation of the ketones **14** and **15** in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$ at $-130\text{ }^\circ\text{C}$ yields conformers **16** and **17** of the same dication. Quenching of an acidic solution of the conformer **16** leads to elimination of the axial proton from the tertiary carbon atom linked with the side chain to give β -ionone (**18**). The conformer **17** eliminates the axial proton from the secondary carbon atom of the ring (in conformity with the ionic elimination rules) and is converted into α -ionone (**19**).



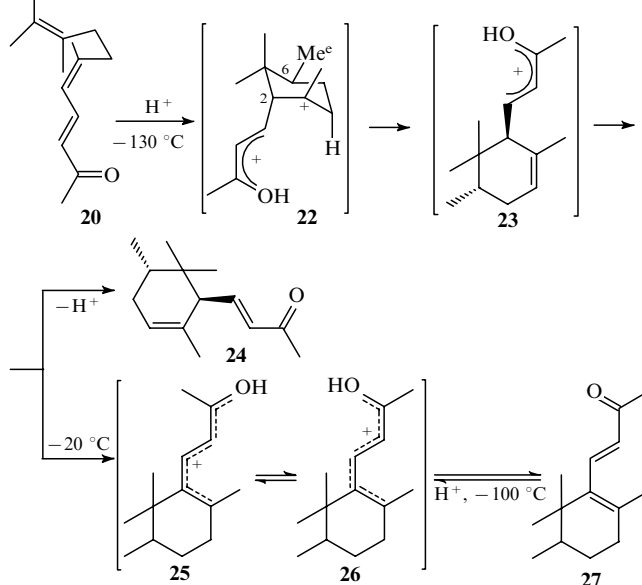
$$k_3, k_4 > k_1, k_2$$

Thus, in this case the conformational stability of intermediate monocyclic carbocations at low temperatures ensures conformational control and, as a result, the structural selectivity of the rearrangement.

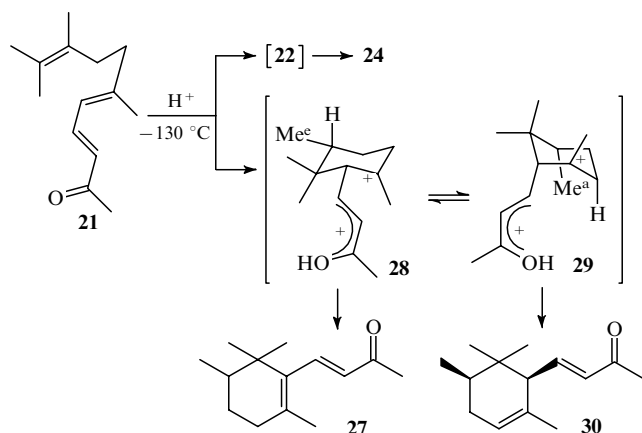
A more complex situation is observed in the protonation of *cis*- (**20**) and *trans*- ϕ -ionones (**21**).⁷

Protonation of the ketone **20** in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$ ($-130\text{ }^\circ\text{C}$) gives the dication **22** in which the methyl group at C(6) is in the *trans*-position relative to the side chain at C(2). The elimination of the axial proton from the secondary carbon atom in the dication **22** is accompanied by its conversion into the 'apparent' ion **23**; 'quenching' of the latter gives *trans*- α -irone (**24**). Heating of an acidic solution of the ion **23** to $-20\text{ }^\circ\text{C}$ results in pentadienyl ions **25** and **26**; their 'quenching' yields β -irone (**27**). Protonation of the latter at $-100\text{ }^\circ\text{C}$ gives a mixture of ions **25** and **26**. It is noteworthy that the ion **23** is not generated in the temperature range from -100 to $-10\text{ }^\circ\text{C}$. Structurally selective and stereo-selective transformation of the ketone **20** in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$ is probably due to the lack of conformational transitions at $-130\text{ }^\circ\text{C}$ (Scheme 1).

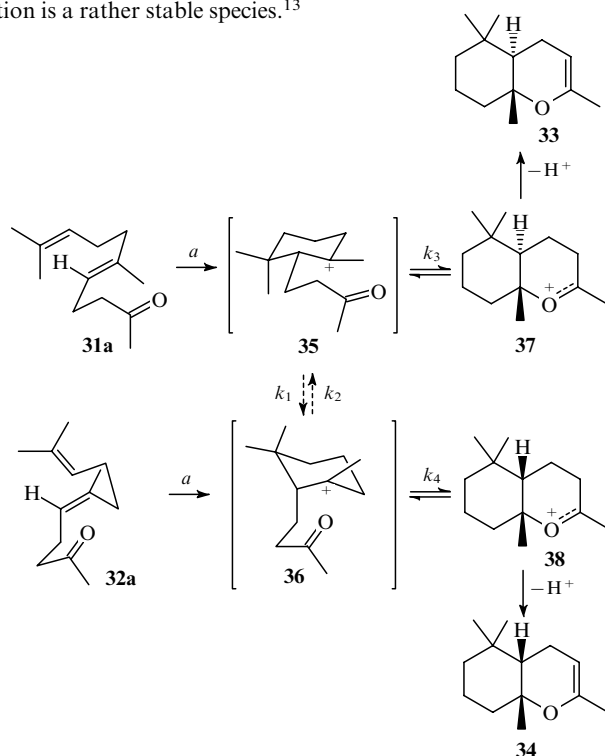
Scheme 1



The transformation of the *trans*-isomer **21** in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$ occurs differently. At -130°C , it gives a mixture of dication **22** and **28**. The latter exists as a mixture with the dication **29** due to conformational transitions of the *chair* $\rightleftharpoons$ *chair* type. 'Quenching' of the reaction mixture gives ketones **24** and **27** and *cis*- α -irone (**30**).



Generation of an ion, which exists in two different conformations that are more rapidly stabilised by intramolecular interactions than by interconversions, from different conformational isomers is yet another typical example of conformational control. However, in contrast with the above examples, this process ensures not only structural selectivity but also stereospecificity of cyclisation reactions. Thus the cyclisation of *trans*- (**31**) and *cis*-geranylacetone (**32**) in 100% sulfuric or fluorosulfonic acids is stereospecific and yields *trans*- (**33**) and *cis*-chromenes (**34**), respectively.^{8,9} It has been suggested¹⁰⁻¹² that the stereospecificity of cyclisation of dienones **31** and **32** is due to the formation of stable conformers **35** and **36**. However, it has been found⁶ that monocyclic ions **35** and **36** were not detected in the NMR spectra after dissolution of dienones **31** and **32** in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$ even at -120°C because of their rapid cyclisation into carboxonium ions **37** and **38**. It should be noted that the methylcyclohexyl cation is a rather stable species.¹³



(a) $\text{HSO}_3\text{F}, \text{SO}_2\text{FCl}, -130^\circ\text{C}$.

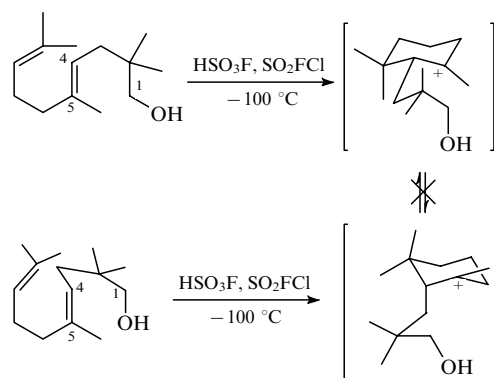
^1H and ^{13}C NMR spectral data point to the formation of carboxonium ions **37** and **38**, which have not been considered previously at all as intermediates in the cyclisation of dienones **31** and **32** into chromenes **33** and **34**.¹⁰⁻¹² Presumably, the stereospecificity of these reactions is determined not by the conformational stability of monocyclic ions **35** and **36** as such, but rather by the ratio of rate constants of their conformational transitions as well as by the ratio of rate constants for the formation of bicyclic ions ($k_3, k_4 \gg k_1, k_2$).⁶ In this case, we are dealing with conformational control, since the ratio of the reaction products is approximately the same as the conformer ratio.¹⁴ The formation of conformationally isomeric monocyclic ions **35** and **36** from dienones **31** and **32** seems to be due to the fact that they react in the most stable conformations **31a** and **32a**.¹⁰ This conclusion is confirmed by the strain energies (*E*) of the conformations of dienones **31** and **32** calculated by the molecular mechanics method using parametrisation described in Ref. 15. It was found⁶ that the majority of geranylacetone atoms in conformations **31a** and **32a** fall into the attraction field of non-valent (van-der-Waals) interactions. Therefore, the energies of these conformations are by 6–8 kcal mol⁻¹ lower than those of non-valent interactions in other conformations, e.g., **31b** and **32b**.

	31b	32a	31b	32b
Conformation	31a	32a	31b	32b
<i>E</i> /kcal mol ⁻¹	218.6	219.5	226.7	225.5

The calculations of the barriers $\Delta H^\ddagger$ to the conformational ion transitions **35** $\rightleftharpoons$ **36** (MMX) and the opening of heterocycles **37** and **38** (PM3)¹⁶ corroborate the conclusion⁶ that $k_3, k_4 \gg k_1, k_2$.

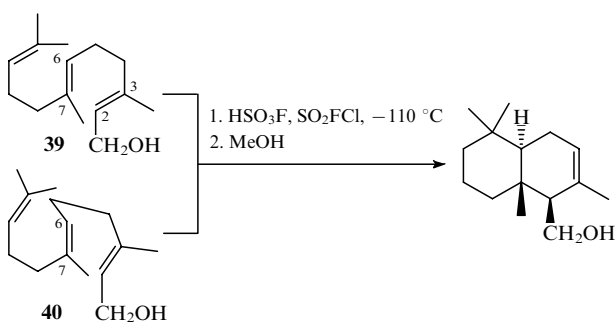
The stepwise mechanism of generation of ions **37** and **38** proposed by Gavrilyuk *et al.*⁶ agrees well with the transition state energies of cyclisation of *cis*- and *trans*-undeca-6,10-dien-2-yl cations into decalin derivatives calculated by the MINDO/3 method. These calculations showed that the activation energies of synchronous processes are by 23–24 kcal mol⁻¹ higher than those of stepwise processes.¹⁷ In addition, experimental data suggest that biogenetic cyclisation of isoprenoids occurs in a stepwise manner.¹⁸

The formation of conformational isomers of cyclic ions as the manifestation of conformational control in the cyclisation of 2,6-dienes stereoisomeric with respect to the 4,5-double bond having a carbonyl or a hydroxy oxygen atom at C(1) is of general character¹⁹ and is observed in the cyclisation of stereoisomeric 2,6,9,9-tetramethyl-2,6-decadien-10-ols.



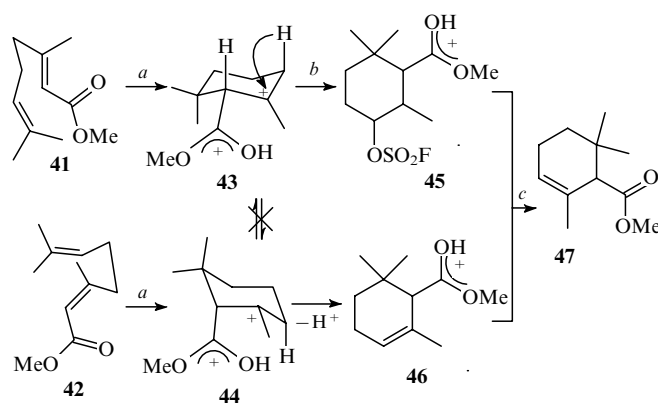
In the above examples, the interaction of the cationic centre in the conformers of monocyclic carbocations containing sufficiently nucleophilic carbonyl or hydroxy groups occurs faster than conformational transitions. In the cyclisation of *trans*, *trans*- (**39**) and *cis*, *trans*-farnesols (**40**), which are isomeric at the 6,7-double bond, the configuration of this double bond does not influence the steric direction of the reaction. Both isomers yield a

product with *trans*-fused rings. Apparently, this is due to decreased nucleophilicity of the 2,3-double bond caused by the $-I$ -effect of the hydroxy group.²⁰



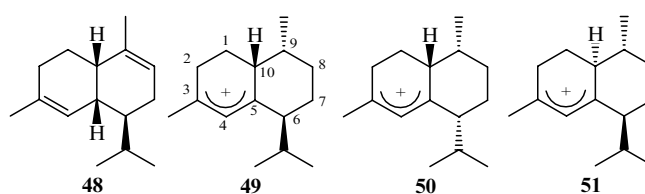
Conformational control is also effected in the stage of formation of intermediate carbocations where the same ion exists in different conformations which give rise to different (but not isomeric) ions.²¹ Thus protonation of methyl 2,3-*trans*- (**41**) and *cis*-geranate (**42**) in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$ at -120°C gives dication **43** and **44**, which are conformers but are not practically inter-converted at temperatures below -70°C . In the dication **43**, the 1,2-hydride shift prevails, so that the cationic centres become more remote. Subsequent addition of the fluorosulfonyloxy group results in the ion **45**. In the dication **44**, the axial proton is eliminated exclusively from the secondary carbon atom to give the ion **46**. It is interesting that 'quenching' of acidic solutions of ions **45** and **46** yields the same compound, *viz.*, methyl α -cyclogeranate (**47**). Thus, the studies of intermediate carbocations generated at low temperatures under 'long-life' conditions allowed Gavriluk *et al.*²¹ to conclude that it is the configuration of the 2,3-double bond that determines the structure of primary cyclisation products (*viz.*, intermediate carbocations) in the cyclisation of acyclic isoprenoids containing an ester group conjugated with the double bond.

It has been shown²² that conformational control can influence the ratio of intra- and intermolecular reaction products in the stage of generation of an intermediate carbocation. Thus stable



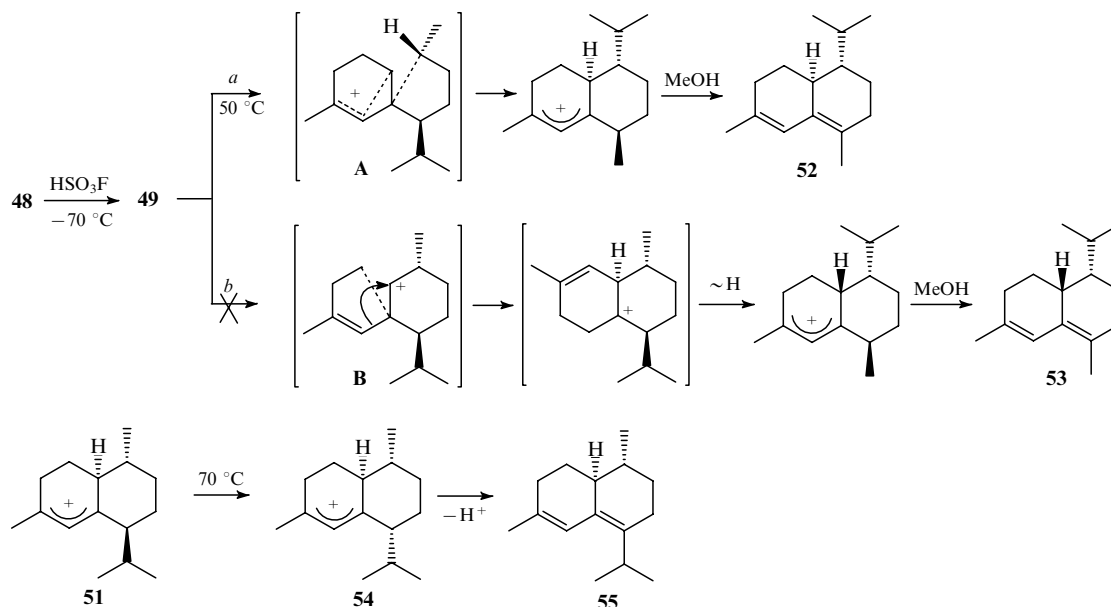
(a) $\text{HSO}_3\text{F}, \text{SO}_2\text{FCl}, -120^\circ\text{C}$; (b) $\text{OSO}_2\text{F}^-, \sim\text{H}$; (c) MeOH .

diastereomeric allylic ions **49–51** generated from (–)- α -murolene (**48**) differ only in the configuration of the asymmetric centre at C(6) or C(10).²³

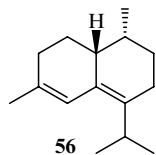


This, in turn, affects the conformation of the corresponding ion and, ultimately, the dihedral angle between the vacant *p*-orbital of the cationic centre and the C(10)–C(9) σ -bond. This angle determines the probability of intramolecular rearrangements in these ions with a 'turnover' of a six-membered ring relative to another. Thus one of the epimers (ion **49**) undergoes intramolecular ring 'turnover' at 50°C to give the diene **52** (Scheme 2), while the other epimer (cation **50**) is converted into the ion **49** at -70°C . In the case of the ion **51**, only intermolecular rearrangement into the ion **54** is realised even upon heating to 70°C ; its 'quenching' gives compound **55** (see Scheme 2).

Scheme 2



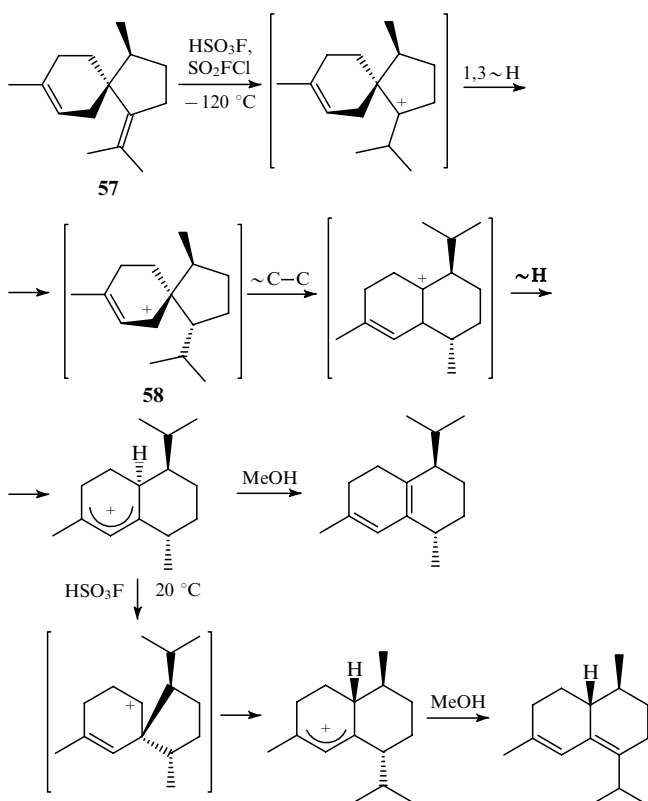
Intramolecular rearrangement of the ion **49** may occur in two pathways, *a* or *b*. Which of them is realised in each concrete case can be established by comparing the ORD curves of dienes **55** and **56** mimicking compounds **52** and **53**, respectively.



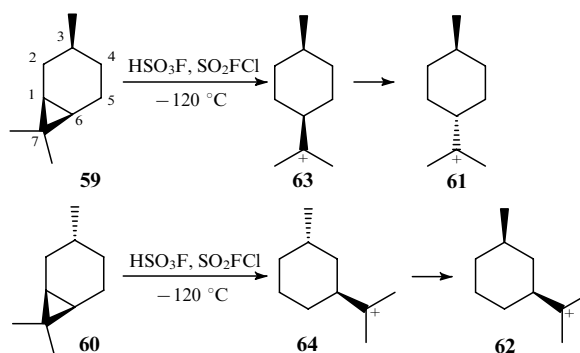
The experimental results²¹ suggest that the rearrangement follows pathway *a*. This is probably due to the fact that of the two secondary spirocations **A** and **B** only the former can be stabilised by homoallylic conjugation. In the case of pathway *b*, such an efficient interaction is impossible due to the perpendicular position of the *p*-orbitals of the cationic centre and the double bond.

It should be noted that superacidic media favour profound molecular rearrangements that cannot be achieved in 'ordinary' media even under most drastic conditions. Since solutions of stable ion salts can be heated up to 100 °C and above, direct observation of 'cation–cation' rearrangements with an activation barrier of ~ 30 kcal mol⁻¹ and higher can be observed. Molecular cationic rearrangements which occur in superacidic media with an activation barrier of ~ 20 kcal mol⁻¹ cannot be reproduced under conditions of an ordinary acid catalysis (*cf.* Ref. 24).

The possibility of intermediate formation of the spirocyclic carbocation **58** in the previously discovered²² rearrangement of allylic cations of the type **49** with the cadalene skeleton has been demonstrated with a sesquiterpenoid hydrocarbon β -alaskene (**57**) having a spiro[4.5]decane backbone as an example.²⁵



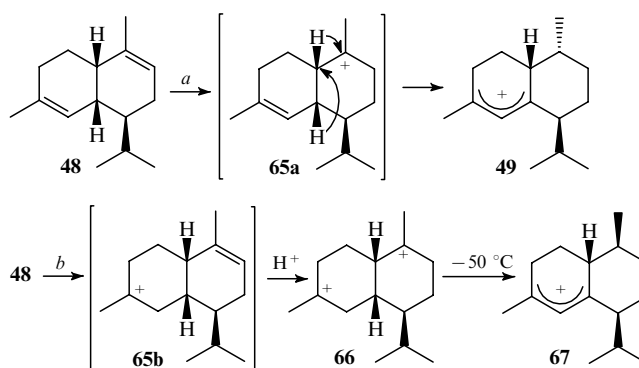
Steric factors have a profound influence on the ratios of intra- and inter-molecular transformations of stable carbocations. They can also affect the regio- and stereoselectivity of these rearrangements as can be exemplified in the isomerisation of *cis*- (**59**) and *trans*-caranes (**60**) in HSO₃F–SO₂FCl (–120 °C) resulting in the formation of apparent ions **61** and **62**, respectively.²⁶



The opening of the cyclopropane rings in epimers **59** and **60** is accompanied by seeming inversion of configuration. This is due to the fact that in the case of long-living cations the conversions of initially formed ions **63** and **64** into thermodynamically more stable cations **61** and **62** occur through hydride shifts as can be judged from the molecular mechanics calculations.²⁷ The calculations of the geometry of the ground states of compounds **59** and **60** made with the use of the parameters described in Ref. 28 suggest certain elongation of the C(1)–C(7) bond relative to the C(6)–C(7) bond in the *cis*-isomer **59** and of the C(6)–C(7) bond relative to the C(1)–C(7) bond in the *trans*-isomer **60**. These data are in good agreement with the results of conversions of compounds **59** and **60** in superacids.

III. The effect of polyfunctionality of the original substrates

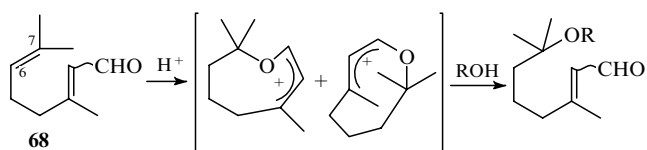
Yet another essential feature of terpenes as starting compounds in the generation of stable ions is their polyfunctionality. Thus terpenes may serve first as potential precursors of both mono- and dications with identical skeletons. The pathways of molecular rearrangements of mono- and dications often differ, which largely increases the diversity of terpene transformations. Thus it has been shown²³ that molecular rearrangements of mono- (**65**) and dications (**66**) generated from the same natural diene **48** give rise to diastereomeric allylic ions **49** and **67**.



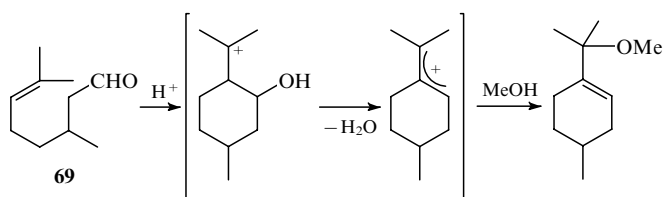
(a) HSO₃F, SO₂FCl, –70 °C; (b) HSO₃F, SO₂FCl, –120 °C.

Second, a polyfunctional terpenoid molecule contains groups that can be both converted into an electrophile and simultaneously act as an internal nucleophile. The direction of a reaction often depends on the structural peculiarities of the original terpenoid. Minor structural changes in such strongly internally interrelated multicentre systems can result in dramatic changes in relative reactivities of different groups, in relative stabilities of intermediate carbocations and, ultimately, in the cyclisation pathway. The results of cyclisation of analogous acyclic terpenoids, *viz.*, citral (**68**), citronellal (**69**) and methyl geranate **41**, were compared under identical conditions (HSO₃F–SO₂FCl, –110 °C).²⁹

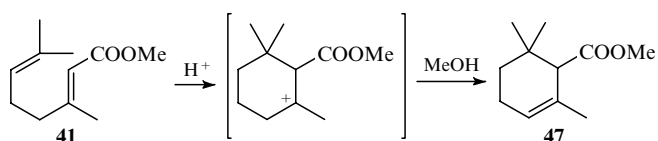
In the citral molecule (**68**), the proton is added to the most nucleophilic 6,7-double bond. The oxygen atom of the carbonyl group, which attacks the cationic centre to give rise to cyclic allylic ions, acts as a nucleophile; quenching of allylic ions with alcohols gives 7-alkoxy-substituted 6,7-dihydrocitral in good yields.



In contrast, in the aldehyde **69** the proton is added to the oxygen atom of the carbonyl group. The carbon atom in the latter attacks the 6,7-double bond to generate an allylic ion. Its 'quenching' gives 7-methoxymenthene.

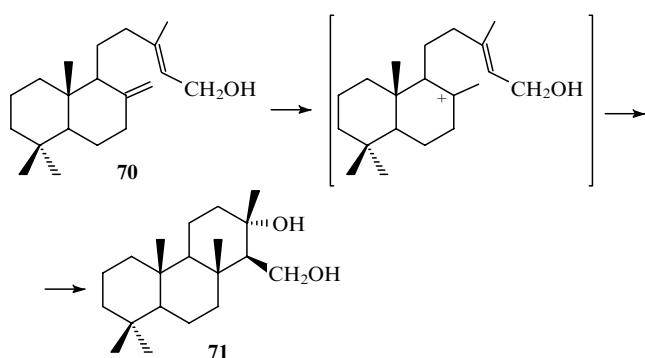


Finally, similarly to the aldehyde **68**, protonation of the ester **41** results in the addition of a proton to the 6,7-double bond. However, in this case the role of a nucleophile is played not by the oxygen atom of the carbonyl group but by the 2,3-double bond, eventually resulting in the ester **47** after 'quenching'.

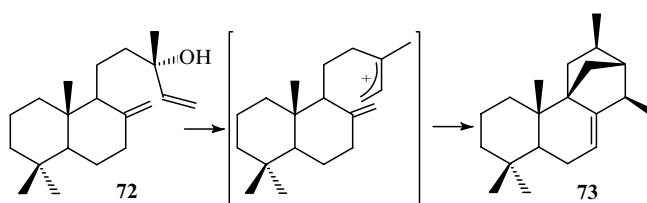


It has been shown³⁰ that isomeric bicyclic labdane diterpenoids **70** and **72**, which differ in the position of the allylic hydroxy group in the side chain undergo radically different conversions under identical conditions ($\text{HSO}_3\text{F} - \text{SO}_2\text{FCl}$, -100°C).

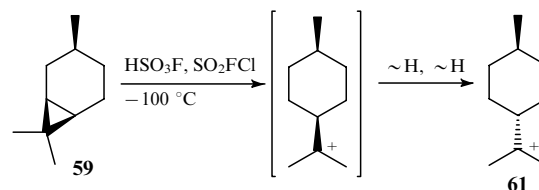
Thus the protonation of the terpene **70** involves the exocyclic double bond to yield a cyclic carbocation; the role of the internal nucleophile is played by the double bond in the side chain. This structurally selective and stereoselective rearrangement gives rise to the bifunctionalised isoagatane **71**.



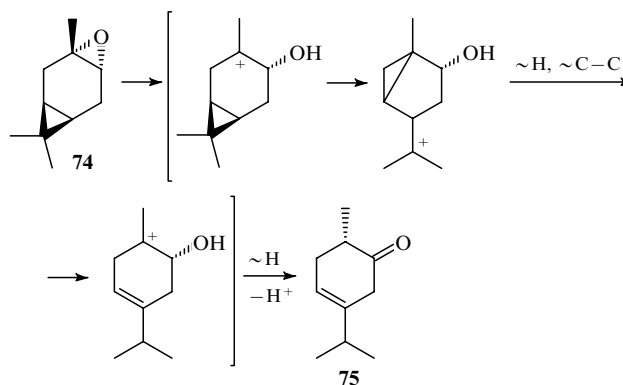
The generation of the cationic centre in the tertiary alcohol **72** is of by the solvolytic type and is accompanied by elimination of the allylic hydroxy group from the side chain. In this case, the exocyclic double bond plays the role of the internal nucleophile, eventually resulting in the tetracyclic hydrocarbon **73**.



If a cationic centre is formed in a terpenoid molecule, it significantly affects the appearance of the second cationic centre in the same molecule (if this does take place) and its further behaviour. Thus the opening of a three-membered ring in carane (**59**) occurs through proton attack at C(1) of the cyclopropane ring.²⁶



In α -trans-3,4-epoxycarane (**74**), the initial opening of the epoxide ring ($\text{HSO}_3\text{F} - \text{SO}_2\text{FCl}$, -100°C) is followed by β -cyclopropylmethyl rearrangement and results ultimately in the formation of the ketone **75**.³¹



IV. Factors affecting the pathway of cationic rearrangements

The behaviour of stable π -conjugated carbocations is largely determined by charge delocalisation and the relative capacity to migration of substituents in 1,2-shifts.³² If ions are generated from terpenes or their analogues, the crucial role will be played by other factors, e.g., the nature of the acidic medium, the mode of generation of the cationic centre (solvolysis or electrophilic addition to the double bond) and the temperatures at which cations are generated and the acidic solutions are defrosted. The 1,2-shifts toward the cationic site are controlled by the competitive (rather than relative) migration capacity of the adjacent groups.

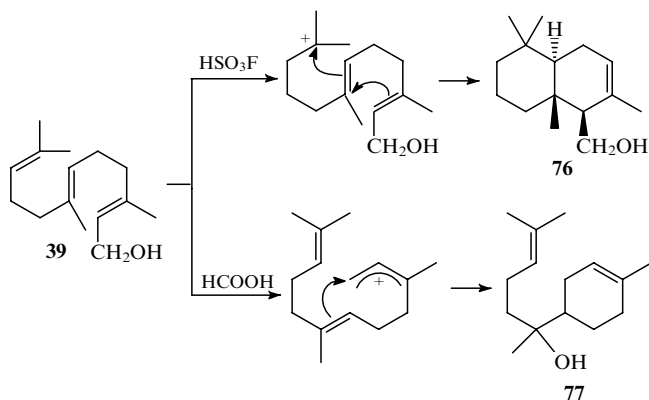
1. The nature of the acidic medium

Elucidation of the relationship between the chemical behaviour of stable carbocations generated in superacidic media and transformations of these original substrates under conditions of acidic catalysis is an important problem. Its solution will allow the use of regularities established in the studies of stable carbocations in prediction of the most probable pathways of multistep carbocationic rearrangements under conditions of conventional acidic catalysis. The solution of this problem is also important for designing organic syntheses in general and syntheses of terpene compounds in particular. However, the publications devoted to this problem are scarce and the conclusions made therein are

rather controversial. Thus Olah, who was a pioneer in the studies of the behaviour of cations generated in superacidic media, considers the chemistry of stable ions as an entirely independent field and conducts even applied investigations under extremely 'hypernon-nucleophilic' conditions.³³ In 1975, Sorensen *et al.*³⁴ generalised the data on carbocationic rearrangements of several monoterpenes in media of different acidities. According to these authors, the increase in the $\Delta G^\ddagger$ barrier to 'ion-to-ion' rearrangements is of the same order both in superacids and under conditions of acidic catalysis, while the stability of alkenes parallels that of the corresponding cations. It was thus concluded that the pathways of carbocationic rearrangements in acidic catalysis can be predicted from the results of direct observation of their rearrangements in superacids. No exceptions were reported.³⁴ In our opinion, this can be due to the limited choice of experimental objects investigated in this study³⁴ (as a rule, compounds with a norbornane skeleton were used). We have found several substantial limitations of Sorensen's statements. Thus in a more recent study, Brown³⁵ has shown that the chemical behaviour of stable ions and the pathway of solvolysis are in rather poor agreement with each other. In 1983, Arnett and Hofelich³⁶ established a correlation between the rate constants of solvolysis of certain chlorides in ethanol and enthalpies of ionisation of these chlorides in superacids and thus confirmed the formation of intermediate short-living carbocations in solvolysis that are analogous to stable ions generated in superacids. However, further multistep conversions of the initially formed ions have not been investigated.³⁶

We believe that the data obtained in the studies of molecular rearrangements in superacids can be used for predicting the most probable pathways of their transformations in ordinary acids with allowance made for possible changes in the nature of the medium, *e.g.*, the site of generation of the cationic centre, the nature of the internal nucleophile, the 'qualitative' changes in the ratio of rates of intra- or inter-molecular rearrangements, the non-correspondence of changes in the relative stabilities of alkenes and the cations derived from them, *etc.* This must be taken into consideration altogether in designing isoprenoid syntheses.

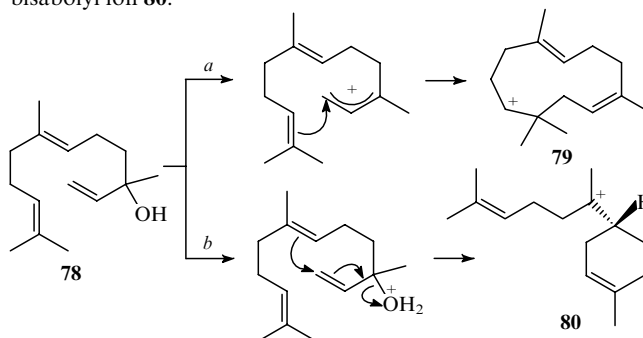
We have studied the effect of the nature of medium on the pathway of terpenoid rearrangements. Thus in the case of *trans*, *trans*-farnesol (**39**), the site of formation of the cationic centre has been shown to depend on the nature of the medium.³⁷



Protonation of the double bond takes place in superacids endowed with high protonating capacity and results in drimenol (**76**). Formic acid, characterised by high ionising capacity, favours solvolysis with the formation of an allylic ion. Its subsequent cyclisation gives bisabolol (**77**).

The medium acidity affects the behaviour of labdanoids **70** and **72** (see above) in different ways. Cyclisation of compound **72** containing a tertiary allylic group in the side chain in both superacids and ordinary acids gives the tetracyclic product **73**. Compound **70** containing a primary allylic group generates the tricyclic diol **71** in superacids and the tetracycle **73** in ordinary acids.³⁰

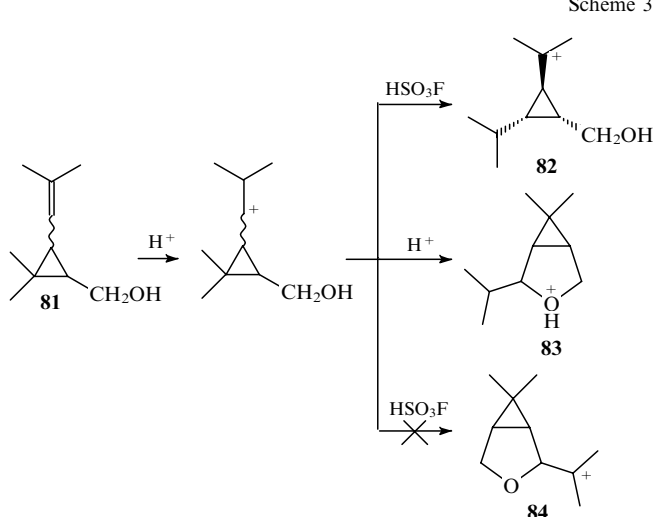
A study of transformations of nerolidol (**78**) in various acidic media has shown³⁷ that carbocyclisation reactions involving different π -bonds can take place even in the presence of a good leaving group (*e.g.*, a tertiary allylic hydroxy group) and in the case where a cationic centre at the same carbon atom is formed in different media. For example, conformational control favours the approaching of the chain termini in superacids at low temperatures to give the secondary ion **79**. In weak acids and at room temperature, this reaction proceeds with the formation of a more stable tertiary bisabolyl ion **80**.



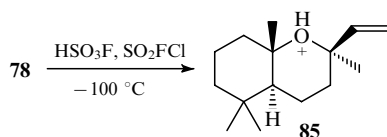
(a) HSO_3F , SO_2FCl , -100°C ; (b) $[\text{H}^+]$, 20°C .

It has been shown³⁸ that cyclisation of chrysanthemyl alcohol (**81**) occurs differently in different media, since the medium determines the mode of reaction of a particular internal nucleophile with the cationic centre. This, in turn, significantly affects the ratio between carbo- and heterocyclisation reactions. Heterocyclisation in ordinary acids and carbocyclisation in superacids give cations **82** and **83**, which have identical stability ($\Delta H_f^\circ = 114.9$ and $114.6 \text{ kcal mol}^{-1}$, respectively, calculated by the MINDO/3 method). In other words, the reaction pathway is not determined by thermodynamic factors but is rather due to a lesser contribution of heterocyclisation because of the protonation of the heteroatom in superacids. In the study by Baig *et al.*,³⁹ the effect of the medium was neglected and the structure **84** was ascribed to the ion generated from the alcohol **81** in a superacid. As a matter of fact, this ion has the structure **82**³⁸ (Scheme 3, see Ref. 40).

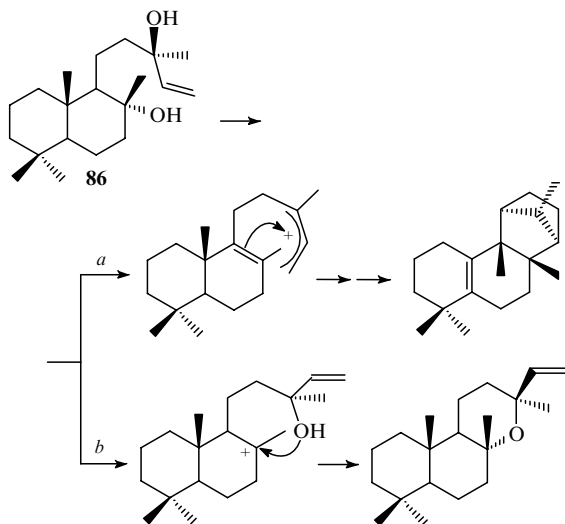
Scheme 3



The direction of a reaction can be affected not only by the nature of the medium but also by changes in the superacid:substrate ratio. Thus cyclisation of the alcohol **78** in the presence of a large (20:1) excess of a superacid results predominantly in carbocyclisation with the formation of the ion **79**, whereas heterocyclisation resulting in the cation **85** occurs at the $\text{HSO}_3\text{F} : \text{78}$ ratio = 5:1.³⁷

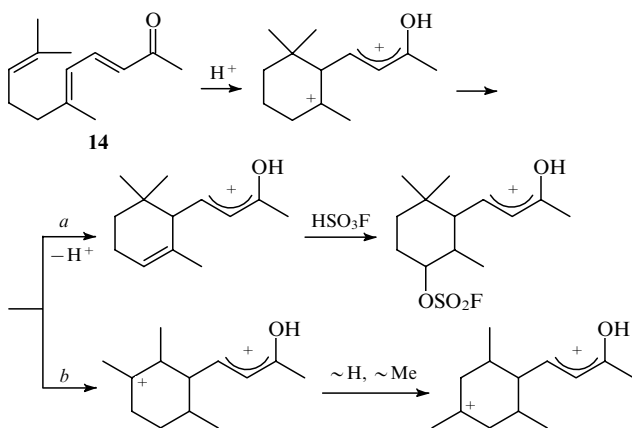


A similar effect of the excess of an acid on the carbo- to heterocyclisation ratio was observed with the diol **86**.⁴¹



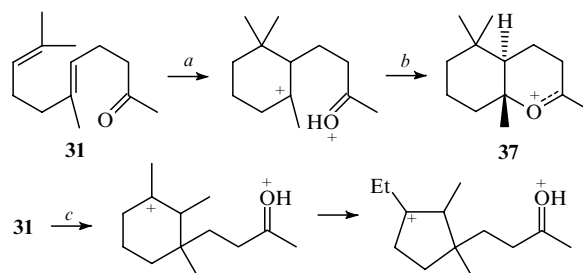
(a) $\text{HSO}_3\text{F} : \mathbf{86} = 2.5 : 1$; (b) $\text{HSO}_3\text{F} : \mathbf{86} = 5 : 1$.

In the above examples, the ratio of carbo- and heterocyclisation reactions changed with variations in the excess of an acid as the result of translocation of the cationic centre and the internal nucleophile. The effect of the medium can also be manifested in a different way. By varying medium acidity and excess of acid with respect to the substrate, one can generate structurally different mono- or dications from the same substrate. Thus by conducting the cyclisation of the ketone **14** in acids of various strengths, one can generate allylic ions (pathway *a*) or dications (pathway *b*) at the same temperature.⁶



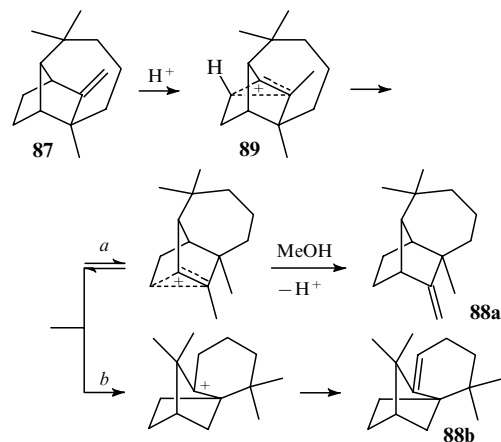
(a) $\text{HSO}_3\text{F}, \text{SO}_2\text{FCl}$; (b) $\text{HSO}_3\text{F} : \text{SbF}_5 = 1 : 1, \text{SO}_2\text{FCl}, \sim \text{H}, \sim \text{Me}$.

A significant effect can be produced by varying only the excess of an acid relative to the substrate without changing medium acidity and reaction temperature. Thus by varying the excess of an acid in the cyclisation of the ketone **31**, one can generate either the bicyclic carboxonium ion **37** or monocyclic dications with six- or five-membered rings.⁶



(a) $\text{HSO}_3\text{F} : \text{SbF}_5 = 1 : 1, \text{SO}_2\text{FCl}$; (b) $\text{HSO}_3\text{F} : \mathbf{31} = 3 : 1$;
(c) $\text{HSO}_3\text{F} : \mathbf{31} = 8 : 1$.

Probably, the first example of a change in the ratio of the rates for intramolecular rearrangements upon transition from a superacid to ordinary acidic catalysis, which may alter both the stereo-isomeric composition and the structure of reaction products, was described in 1981.⁴² Thus the difference in the optical activities of isolongifolene (**88**) specimens ($[\alpha]_{\text{D}}^{20} = 0^\circ$ and -83°) obtained by isomerisation of longifolene (**87**) in HSO_3F and AcOH can be attributed to the change in the ratio of the rates for intramolecular rearrangements upon transition from a superacid to a degenerate (pathway *a*, racemisation) or non-degenerate acetic acid (pathway *b*, retention of optical activity). On going to a more nucleophilic solvent (AcOH), the degree of solvation of ion **89** increases, while the 'requirement' of the cationic centre formed at C(1) for the σ -bond decreases. As a result, the orientation of the vacant *p*-orbital of the cationic site relative to the σ -orbitals of the migrating groups and atoms changes, which affects the rate of their migration (sp^2 -alignment factor).



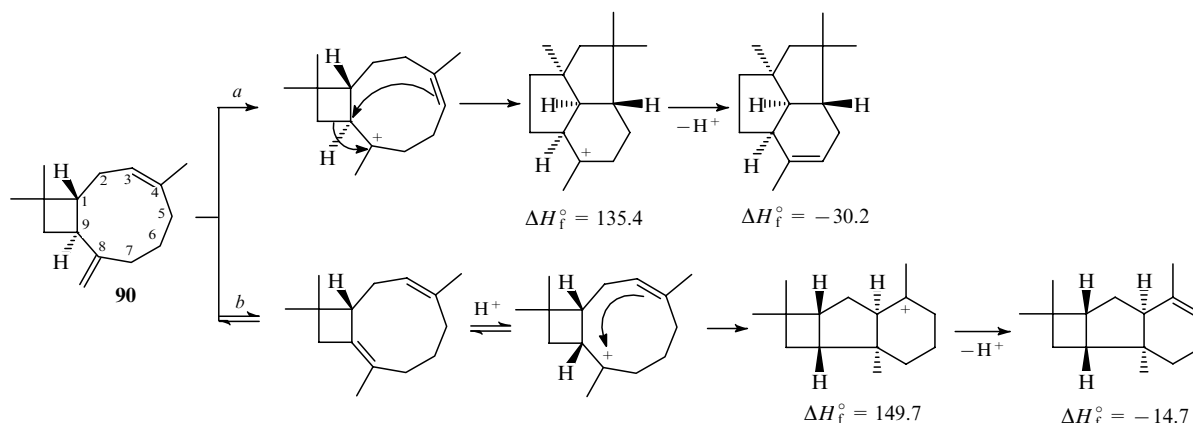
(a) HSO_3F ; (b) AcOH .

In the studies by Sorensen *et al.*,³⁴ it was shown that the rearrangements in mono- and polymethylnorbornyl cations formed as intermediate species independently of the medium gave 2-norbornyl ions; their further transformations occurred only by intramolecular pathways. In other cases, the contribution of intermolecular reactions can influence the comparability of rearrangement processes that occur in different media.

The change in the ratio of rates of intermolecular rearrangements of an isocaryofyllene isomer, *viz.*, the diene (**90**) (Scheme 4), has been established.⁴³ In superacids (pathway *a*), the double bond from position 3,4 migrates to position 4,5 faster than from position 8,12 to position 8,9. An opposite ratio is observed in ordinary acids (pathway *b*). This finding cannot be explained by thermodynamic factors as can be seen from the calculation of enthalpies of formation of the final ions and alkenes (hereinafter ΔH_f° and $\Delta\Delta H_f^\circ$ values are expressed in kcal mol^{-1}).

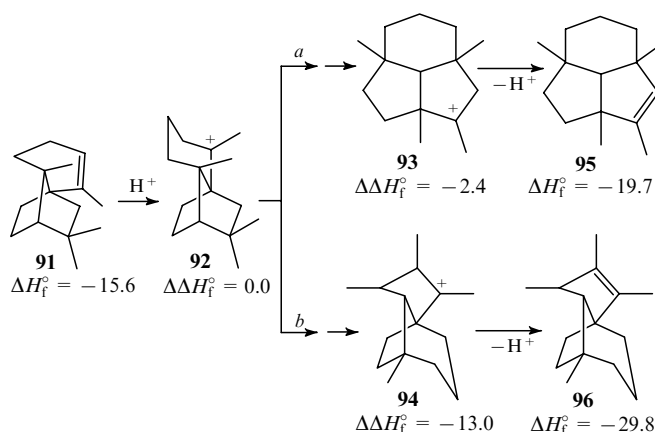
The pathways of neoclovene (**91**) conversions in superacids and ordinary acids differ drastically despite the similar character

Scheme 4



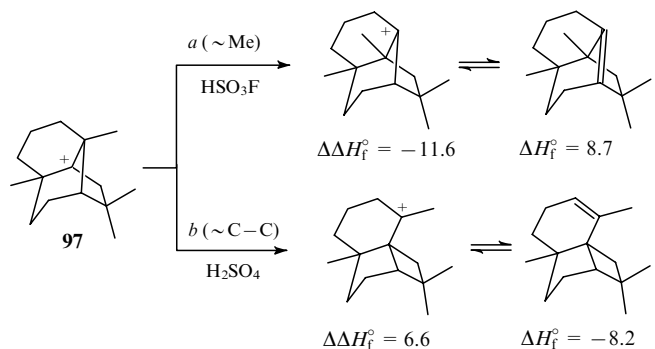
(a) HSO_3F ; (b) $[\text{H}^+]$.

of stabilities of the final ions and alkenes.⁴⁴ Calculations of the enthalpies of formation of ions and alkenes were carried out using the parameters described in Refs 45 and 46. According to NMR spectral data, pathway *b* is predominant in superacids and yields the ion **94**, which is more stable than the ion **93** formed from the ion **92** by pathway *a*. It is still unclear, however, why in sulfuric acid this reaction gives the alkene **95**, which is less stable than the alkene **96** generated by pathway *b*.



(a) H_2SO_4 ; (b) HSO_3F .

In conversions of the intermediate ion **97** in various acidic media, the changes in relative stabilities of carbocations are opposite to those of the corresponding alkenes (NMR data and calculations). In ordinary acids, the direction of these rearrangements is determined by relative stabilities of intermediate alkenes.

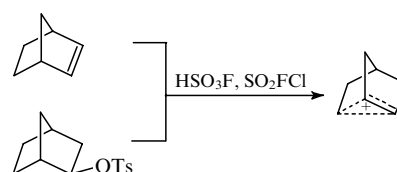


As can be seen from ΔH_f° and $\Delta\Delta H_f^\circ$ values, the Sorensen principle of parallelism of relative stabilities of carbocations and the corresponding alkenes³⁴ is violated in this case. It may be assumed that if several alternative pathways of rearrangements resulting in generation of ions with different skeletons (bridged,

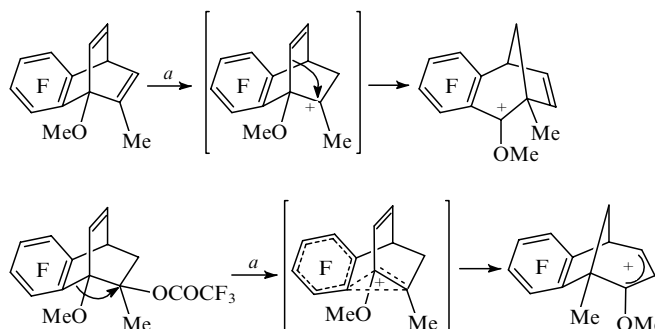
open, monocyclic or fused structures) do exist, the trends of changes in relative stabilities of ions and the corresponding alkenes form opposite series. Thus bridged structures can give rise to stable non-classical ions and the corresponding unstable 'anti-Bredt' alkenes. Stable 'Bredt' alkenes corresponding to unstable classical ions are generated from open, monocyclic and fused compounds.

2. The mode of generation of the cationic centre

A difference in the stereochemical results of solvolysis of an acyloxy derivative and of protonation of the corresponding alkene in identical weakly acidic media has been established.^{47,48} According to Brown,⁴⁷ this effect is due to the fact that more 'loose' carbocations formed upon protonation are trapped by the nucleophile prior to complete establishment of an equilibrium between the ions. An alternative hypothesis⁴⁸ rests on the formation of isomeric non-classical (solvolysis) and classical ions (protonation). However, according to literature data, stable carbocations generated upon protonation of alkenes or upon solvolysis of esters (halides) normally yield identical species irrespective of the reaction type (e.g., see Ref. 49).



In a more recent study,⁵⁰ models were selected for the first time in such a way that isomeric stable ions could be generated upon alkene protonation and ester solvolysis. Their formation was confirmed by NMR spectroscopy.

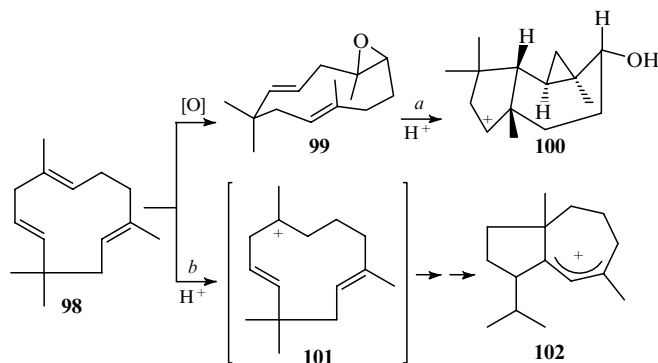


(a) HSO_3F , SO_2FCl , -100°C .

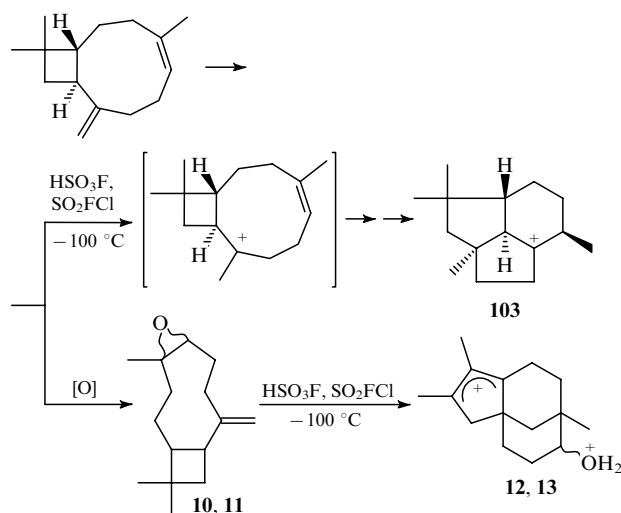
On transition from these model compounds to terpenes, the problem of elucidating the dependence of the main pathway of

cationic rearrangements on the mode of generation of the cationic centre becomes more complicated. First of all, this is due to polyfunctionality and conformational mobility of terpenes. In the following, we will compare the behaviours of an alkene in the protonation and its monoepoxide in the solvolysis. This is of interest for both physical organic chemistry (studies of solvolysis) and terpene chemistry. The opening of epoxides can initiate biomimetic processes.

Two cases should be taken into consideration in comparing the behaviours of an alkene and the corresponding monoepoxide, *viz.*, the coincidence or non-coincidence of the charge localisation sites. However, further rearrangements of the carbocation may occur according to different pathways even in the former case. For example, the conversions of α -humulene (**98**) and its 6,7-epoxide **99**⁵¹ with the identical localisation of the initially formed cationic centre occur by different routes, *viz.*, by concerted, conformationally controlled pathway *a* (epoxide) or by barrier-free conversion of the alkene into the cation **101** (pathway *b*) and then into the ion **102**. The configuration of all the chiral centres in the ion **100** formed by pathway *a* was confirmed by X-ray analysis of the 'quenching' product. The original epoxide **99** seems to have the most stable CT-conformation. Analysis of the ¹³C NMR spectra of compound **99** at -120 to -70 °C revealed the absence of conformational transitions at these low temperatures.

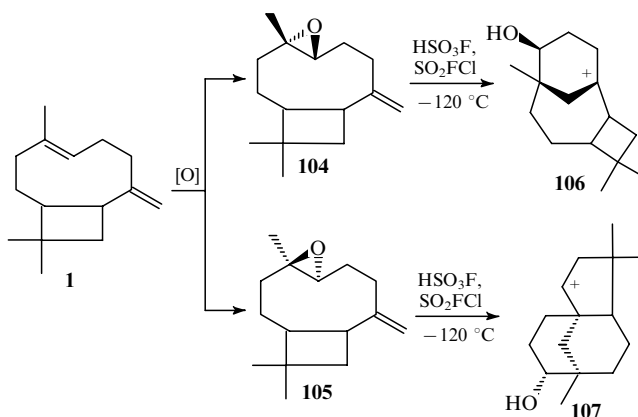


Isocaryophyllene⁴³ and epimeric epoxides **10** and **11**³ derived from it generate different stable ions in superacidic media at all temperatures.

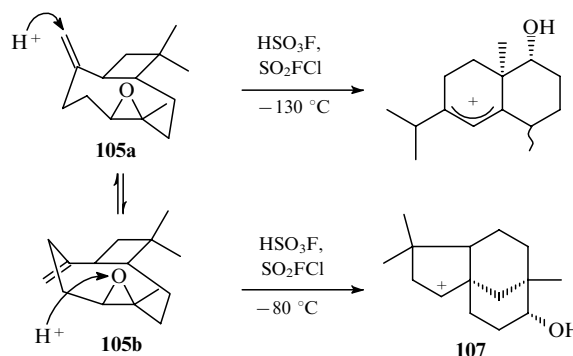


In isocaryophyllene, the energy barriers between individual conformers analogous to those of caryophyllene **1** are rather low, as a result of which it generates only one ion, **103**. The transition to epimeric monoepoxides **10** and **11** is accompanied by stabilisation of individual conformations which further generate enantiomeric ions **12** and **13** (see Section II).

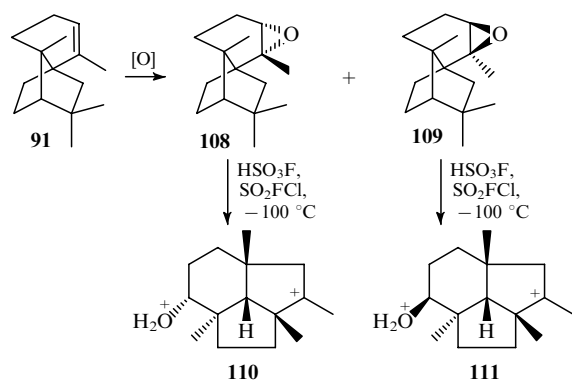
Caryophyllene (**1**)² gives rise to a mixture of carbocations corresponding to the original mixture of conformers (HSO_3F-SO_2FCl , -120 °C). Since diene **1** conformers cannot be isolated in the individual state, the structure of the ion generated from one or another conformation cannot be established experimentally. Epimeric 4,5-monoepoxides **104** and **105**, which may be regarded as 'fixed' conformers, were used to generate one ion each (**106** and **107**) corresponding to those derived from the diene **1**.³



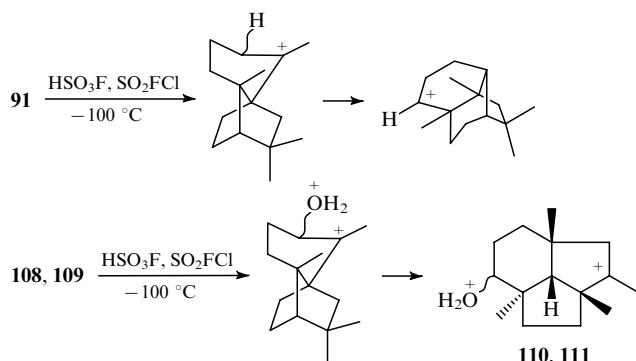
Naturally, the mode of formation of the carbocationic centre is affected by other parameters of cationic rearrangements. Studies with the epoxide **105** have shown³ that a change in temperature alters the position of the cationic centre. This, in turn, changes the composition of the reaction products formed from the monoepoxide **105** at different temperatures and, correspondingly, the pathways of rearrangements in the original diene **1** and its monoepoxide **105** occurring under identical conditions. Obviously, it is the ratio of epoxide **105** conformers that is changed with a change in temperature. As the barriers to the conformational transitions $105a \rightleftharpoons 105b$ and to the reactions of the primary ions are comparable, a change in temperature results in the change in the rearrangement pathways.



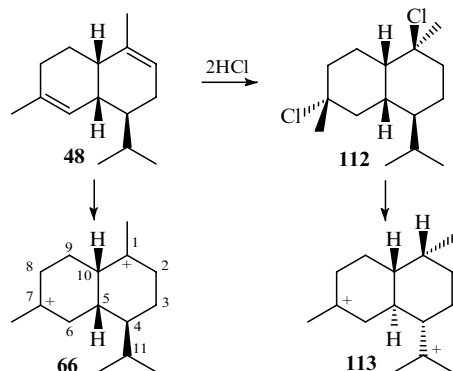
The epoxide transformations described above are concerted processes. However, they can be realised only for such relative arrangement of the epoxide ring that is opened and the part of the molecule where hydride and alkyl shifts toward the cationic site formed occur without difficulty. In other cases, non-concerted epoxide conversions may take place. The latter case has been described⁵² where stable ions **110** and **111**, differing in configuration of the carbon atom containing a hydroxy group, were generated in superacids from neoclovene epoxides **108** and **109**. The stereochemical result of this reaction suggests that conversions of epoxides **108** and **109** into the corresponding alcohols **110** and **111** occur in a non-concerted way.



The non-coincidence of pathways of rearrangements of an alkene and the derived epoxide may reflect the differences in the behaviour of mono- and dications with identical skeletons. For example, different stable ions were obtained from neoclovene (**91**) and epimeric epoxides **108** and **109** with identical backbones and identical sites of formation of the cationic centres under the action of a superacid. The epoxide opening generates a dication with charges on the carbon atom and the oxygen atom of the hydroxy group. Spatial separation of the charges is the driving force for the rearrangement of such a dication. It thus follows that a rearrangement of a cyclic alkene and the derived epoxide will yield the same ion only in the case where the rearrangement of an ion generated from the alkene is accompanied by translocation of the positive charge away from the site of proton addition.

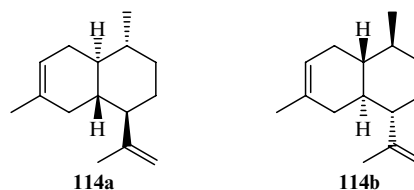


The mode of generation of the cationic centre is also reflected in the structure of carbocations generated from dienes and the corresponding hydrogen chloride addition products. Stable isomeric carbocations **66** and **113** were generated from α -murolene **48** and the dichloride **112** with identical backbones and identical position of the cationic centres formed under identical conditions ($\text{SbF}_5\text{--HSO}_3\text{F--SO}_2\text{FCl}$, -120°C).⁵³



As has been noted earlier, isomeric stable ions were obtained upon changes in the mode of their generation.⁵⁰ The difference in the reaction routes was ascribed⁵⁰ to the formation of non-classical ions upon ester solvolysis and of classical ions upon

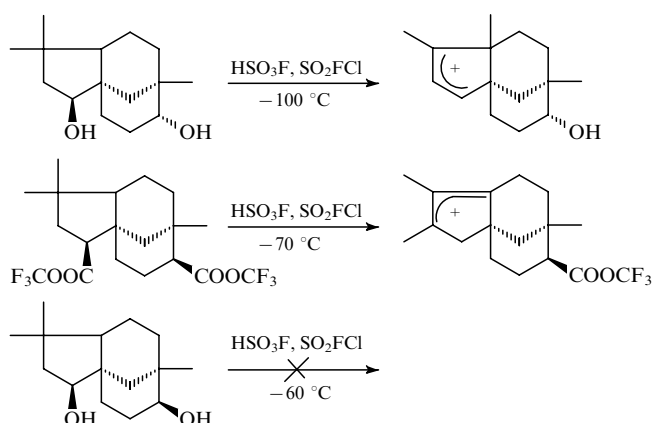
alkene protonation. However, non-classical ions are formed mainly in reactions of bridged polycyclic systems.⁵⁴ If the conversion of the dichloride **112** into the dication **113** occurs through a scheme involving a 1,5-hydride shift from C(11) to C(1), the quenching product should possess the structure **114a**. If this process involves only 1,2-hydride shifts, the diene formed should have the structure **114b**. It has been established⁵³ that ionisation of the dichloride **112** gives the diene **114b** and, correspondingly, translocation of the positive charge from C(1) to C(11) occurs as consecutive 1,2-hydride shifts.



In the dichloride **112**, elimination of the chlorine anion from C(7) is followed by translocation of the positive charge to C(11) through 1,2-hydride shifts and only after this process has been completed, the second chlorine anion is split off from C(1) giving rise to the dication **113**. Protonation of the diene **48** results in immediate generation of the dication **66** in which translocation of the positive charge through 1,2-hydride shifts from C(1) to C(11) does not occur, since the barriers to transition from a classical tertiary carbocation to a classical secondary isomeric carbocation usually exceed 14 kcal mol^{-1} at -120°C (see Ref. 55). Further translocation of the positive charge from C(1) to C(10) is hampered due to the presence of a cationic centre at C(7).

Thus, depending on the mode of cation generation, the difference in reaction routes can be caused by: (i) intermediate formation of classical and non-classical isomeric ions; (ii) concerted epoxide rearrangement and non-concerted rearrangement upon alkene protonation; (iii) change in the site of formation of the cationic centre; (iv) non-coincidence of pathways of rearrangement of mono- and dications having identical backbones and (v) peculiarities of the spatial structure of the original compounds including the ratios between the conformation barriers and barriers to reactions of the primary ions.

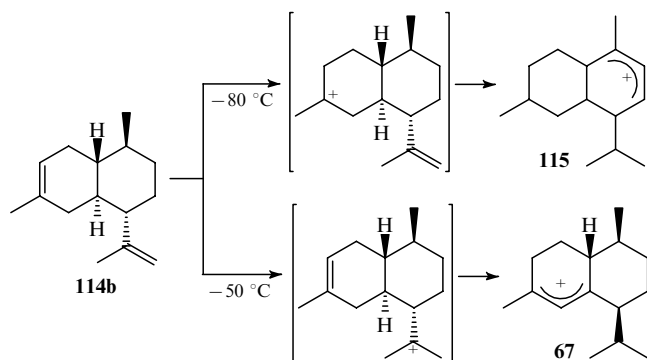
The effect of spatial structure of original compounds, *i.e.*, configuration and the nature of the leaving group, on the direction of a cationic rearrangement can be well illustrated by the following reactions:⁵⁶



3. Cation generation temperature

The temperature at which carbocations are generated is a crucial factor which determines the pathways of multistep cationic rearrangements. It is assumed that ions generated at low temperatures are not converted upon heating into cations that are formed at higher temperatures. In some cases, a change in cation generation temperature influences the position of the cationic

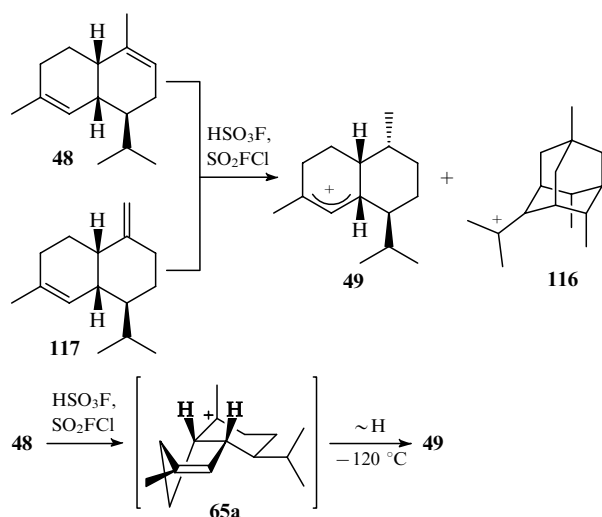
centre. Thus the diene **114b** predominantly generates the ion **115** at $-80\text{ }^{\circ}\text{C}$ and the ion **67** at $-50\text{ }^{\circ}\text{C}$ in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$:⁵³



A change in the conformational composition of the original diene **114b** does not account for the temperature-dependent generation of allylic ions, since the ^{13}C NMR spectra of this diene in CD_2Cl_2 are not changed in the temperature range from -85 to $+10\text{ }^{\circ}\text{C}$. Rather, a change in temperature may affect the direction (the exo- or the endocyclic double bond) of primary protonation.

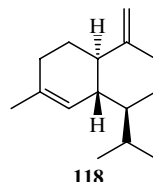
A temperature-dependent change in the ratio of protonation rates of two endocyclic double bonds has been described.²³ Thus ions **66** and **49** are generated upon protonation of the diene **48** at $-120\text{ }^{\circ}\text{C}$ in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$, whereas heating to $-50\text{ }^{\circ}\text{C}$ yields ions **67** and **49** in a $\sim 2.5:1$ ratio. If the ions are generated at $-70\text{ }^{\circ}\text{C}$, the ion **49** is predominantly formed (see Section II). Thus, the ratio of diastereomeric ions can be altered by varying the temperature at which these ions are generated.

The effect of temperature on the ratio of bi- and tricyclic ions formed has been observed.⁵⁷ Thus a mixture of bicyclic (**49**) and tricyclic (**116**) ions is formed from the diene **48** ($\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$, $-30\text{ }^{\circ}\text{C}$) in a $\sim 2:1$ ratio (data from ^1H NMR spectroscopy).

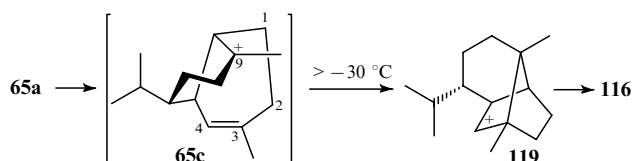


Since the temperature at which ions are generated does not influence the conformational composition of the original diene **48** (the ^{13}C NMR spectra are not changed at temperatures from $-90\text{ }^{\circ}\text{C}$ to $+10\text{ }^{\circ}\text{C}$), it may be supposed that its protonation at -120 to $-70\text{ }^{\circ}\text{C}$ will yield the cation **65a** in the most stable *half-chair-chair* conformation (according to calculations carried out by the MM2 method). 1,2-Hydride shifts in the ion **65a** result in the allylic ion **49**. In the conformation **65c**, the reaction centres are at the shortest distance favourable for transannular cyclisation. The conformation of the ion **65a** is more favourable for transannular cyclisation than that of the ion **65b** as can be judged from

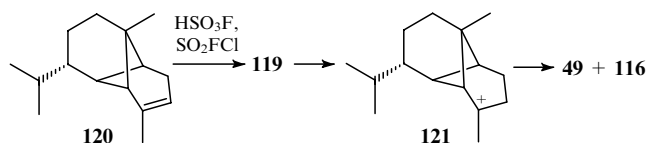
the formation of the ion **116** (in addition to the ion **49**) from γ -murelone (**117**) ($\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$, $-30\text{ }^{\circ}\text{C}$). At $-120\text{ }^{\circ}\text{C}$, the protonation of the diene **117** in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$ gives the ion **49**;²³ at lower temperatures, it is the monocation **65a** that is exclusively formed due to the greater ease of protonation of the exocyclic double bond. γ -Cadinene (**118**), the isomer with a *trans*-fusion of the rings, does not generate either the ion **116** or any other tricyclic cations in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$ at $-30\text{ }^{\circ}\text{C}$.



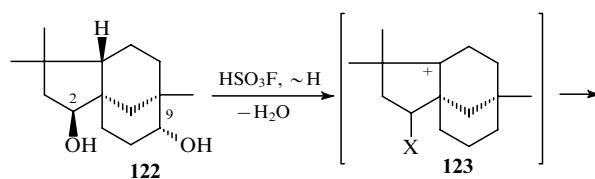
Obviously, the $\Delta H^\ddagger$ value calculated by the MM2 method for the conformational transition **65a** $\rightarrow$ **65c** ($10.9\text{ kcal mol}^{-1}$) significantly exceeds the barriers to 1,2-hydride shifts in the ion **65a** in the conversion of one tertiary ion into another ($< 4\text{ kcal mol}^{-1}$).⁵⁸ This explains the effect of the conformational composition of the ion **65** on the ratio of ions **49** and **116** at -120 to $-70\text{ }^{\circ}\text{C}$. The rise in ion generation temperature (but not in defrosting temperature) favours the conformational transitions **65a** $\rightarrow$ **65c** and increases the contribution of transannular interaction of the carbocationic centre with the double bond, resulting in the initial generation of ions **119** and **120**. Taking into account the difference in ΔH_f° values for these ions ($22.9\text{ kcal mol}^{-1}$) and the short C(3)–C(9) and C(4)–C(9) distances in the conformation **65c**, it may be supposed that the cyclisation of the ion **65c** gives a more stable ion **119**. The latter is further rearranged into the ion **116** according to the schemes⁵⁷ suggested on the basis of estimation of free energies of activation.⁵⁹

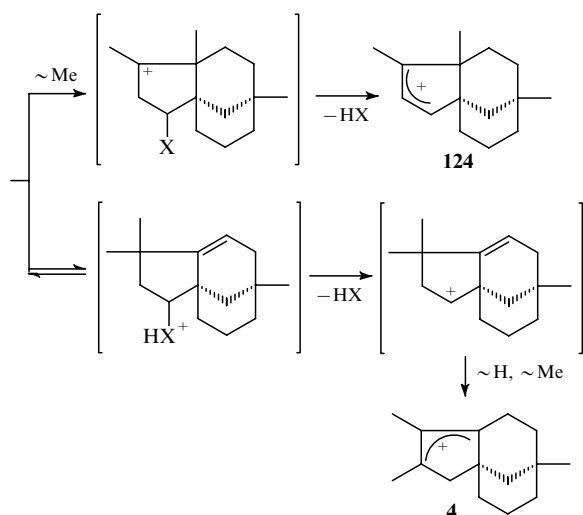


According to ^1H NMR spectral data, dissolution of α -copaene (**120**) in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$ at $-115\text{ }^{\circ}\text{C}$ and subsequent heating to $-30\text{ }^{\circ}\text{C}$ yield a mixture of ions **49** and **116** ($\sim 3:1$). Hydrocarbon **120** is a direct precursor of the ion **119**; which rearranges further into the ion **121**. The observed rearrangement corroborates the pathway proposed for generation of the ion **116**.



An interesting example of the effect of ion generation temperature on the pathway of a cationic rearrangement has been described.⁵⁶





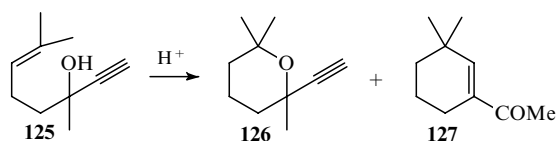
X is fluorosulfonate residue.

The hydroxy group at the C(9) atom in the diol **122** is the first to be eliminated under the action of HSO_3F . Subsequent 1,2- and 1,3-hydride shifts in the cation formed give the ion **123**. The latter is subject either to a 1,2-shift of the methyl group with subsequent elimination of an HX species (its nature is unknown) to give the ion **124** or to elimination of a proton and the HX species⁴ to give ultimately the ion **4**. The ratio of the pathways of ion **123** conversions is determined by the temperature of its generation from the diol **122**. Thus, the ion **124** is predominantly formed at -100°C , while the ion **4** is generated at 20°C .

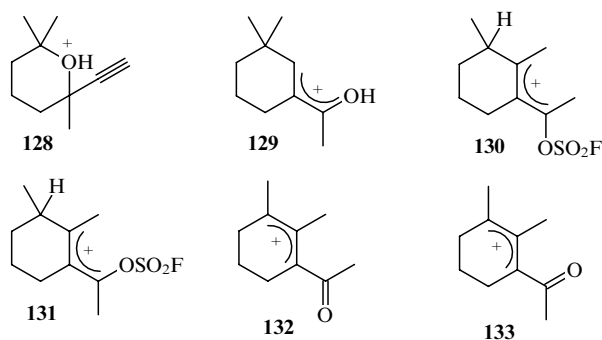
4. Defrosting temperature

Yet another factor which controls cationic rearrangements is the temperature at which an acidic solution is defrosted.

First, the reaction mixture obtained following treatment with superacids (HSO_3F , $\text{HSO}_3\text{F}-\text{SbF}_5-\text{SO}_2\text{FCl}$ in a solvent or without it) can be heated from -130°C to $+100^\circ\text{C}$. This temperature range allows one to overcome the barriers to ion-to-ion transitions of up to 30 kcal mol^{-1} . Second, these 'hypernon-nucleophilic' media favour profound molecular rearrangements which have no analogues in acid-catalysed reactions. Thus cyclisation of dehydrolinalool (**125**) in 'ordinary' acidic media gives a mixture of compounds **126** and **127**.⁶⁰

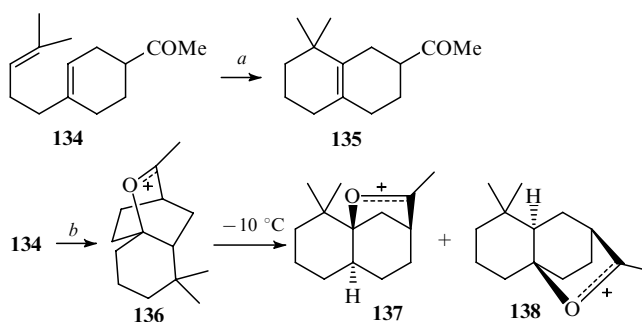


In superacids, the rearrangements resulting in the formation of stable ions **128**–**133** are much more diverse.⁶¹



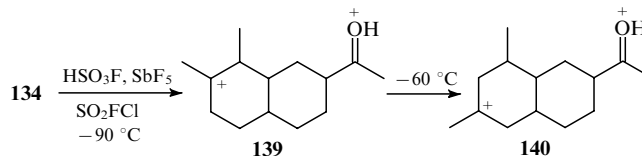
According to literature data,⁶² acid-catalysed cyclisation of isolone (**134**) gives exclusively florione (**135**). Ketone **134** generates the ion **136** in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$ at -110°C . Heating of the

resulting acidic solution to -10°C yields a mixture of carboxonium ions **137** and **138**.⁶³

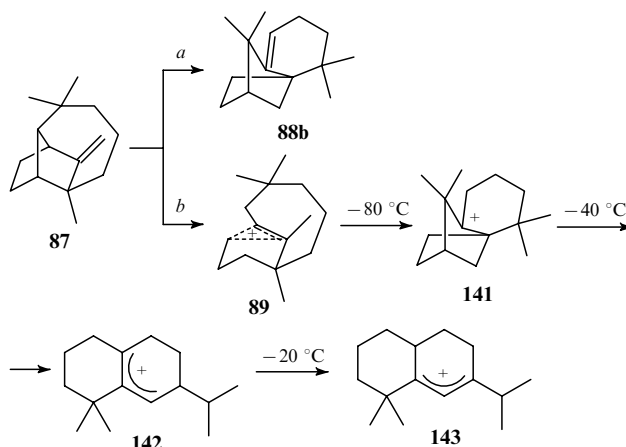


(a) $[\text{H}^+]$; (b) HSO_3F , SO_2FCl , -110°C .

The ketone **134** generates the dication **139** ($\text{HSO}_3\text{F}-\text{SbF}_5-\text{SO}_2\text{FCl}$, -90°C); heating to -60°C results in the dication **140**.

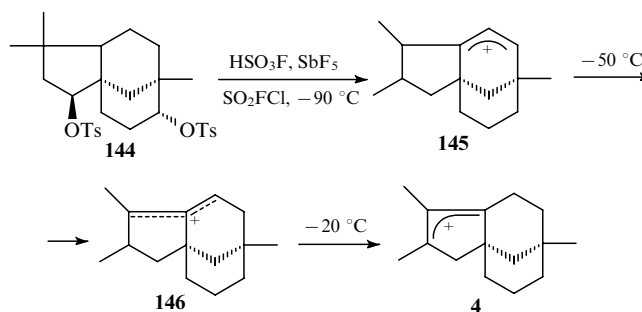


Longifolene **87** is predominantly converted into isolongifolene **88b** in acidic media.⁶⁴ Four carbocations (**89** and **141**–**143**) were generated in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$ by varying the defrosting temperature;⁴² these carbocations were successively interconverted with the rise in temperature.



(a) $[\text{H}^+]$; (b) HSO_3F , SO_2FCl , -120°C .

The effect of defrosting temperature on the structure of carbocations formed has been observed.⁵⁶ It has been shown that ditosylate **144** generates the ion **145** in $\text{HSO}_3\text{F}-\text{SbF}_5-\text{SO}_2\text{FCl}$ at -90°C . Heating of the mixture to -50°C leads to its rearrangement into the ion **146**, which is further isomerised into the ion **4** with the rise in temperature to -20°C .



V. Selection rules

Irrespective of the complex structure of the original substrates, high selectivity of rearrangements of stable ions generated from terpenes is a very important factor which determines their behaviour in superacidic media. This selectivity is provided by a combination of regio- and stereocontrol.

Thus studies of diene **48** conversions in $\text{HSO}_3\text{F}-\text{SbF}_5--\text{SO}_2\text{FCl}$ have shown²³ that at temperatures from -120 to -50 °C all ionic isomerisations occur exclusively as 1,2-hydride shifts and deprotonation-protonation, but not as C–C shifts. Although the theoretically possible protonation–deprotonation reactions and 1,2-hydride shifts in the diene **48** can lead to an extremely complex mixture, this gives rise to a limited number of stable ions that are generated by several relatively short pathways. The selection rules realised in this case can be formulated as follows:

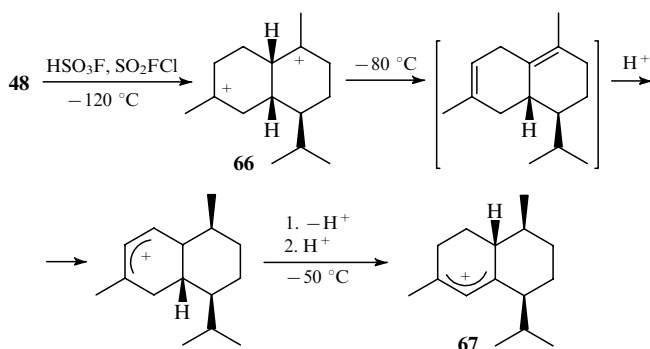
1. Protonation of double bonds and further rearrangements occur predominantly through the formation of both intermediate and final tertiary carbocations; secondary ions are not normally formed.

2. In superacidic media, 1,2-hydride shifts occur more easily than deprotonation reactions, if tertiary and allylic ions are formed.

3. Allylic ions in which all three carbon atoms are incorporated in a single ring and which do not involve two carbon atoms of the bond common to both rings are the most stable.

4. Protonation and deprotonation occur regio- and stereo-selectively. This may be due to both inherent steric hindrances for approaching a protonating reagent or a base (the conformational transitions are strongly hampered at -120 to -50 °C) and stereoelectronic factors in the deprotonation. These peculiarities distinguish the compounds under study from more simple, monocyclic or aliphatic models, *e.g.*, those in which protonation is non-selective as a rule.

The conversions of the dication **66** into the allylic ion **67** described above may occur through stereoselective addition of protons to the double bonds of intermediate dienes. An alternative scheme implies that under kinetically controlled conditions the protonation occurs non-selectively, whereas under thermodynamically controlled conditions the equilibrium between diastereomeric ions is practically completely shifted toward the ion **67**. This suggestion seems unlikely, since diastereomeric ions **49–51** generated separately are stable and are not interconverted under these conditions.²³

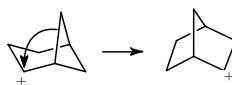


VI. Computational methods for predicting the most probable pathways of multistep cationic rearrangements

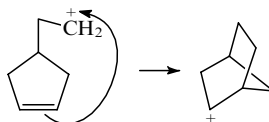
The 'selection rules' are valid in small groups of related compounds²³ and allow one to predict qualitatively the most probable pathways of multistep carbocationic rearrangements. Several approaches to quantitative estimations have been proposed.¹⁶ An original computer programme 'ICARUS' was used to investigate plausible mechanisms of multistep carbocationic rearrange-

ments.⁶⁵ This programme entails generation of the whole variety of multistep rearrangements of a definite chemical structure and control over realisation of the generated routes. All the cationic rearrangements can be divided into six main groups:

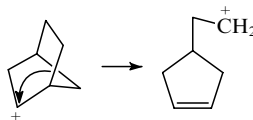
- (1) 1,2-shift of the σ -bond



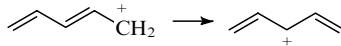
- (2) addition at the multiple bond



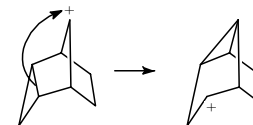
- (3) β -fragmentation



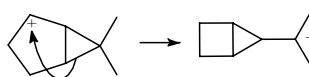
- (4) allylic rearrangement



- (5) β -cyclopropyl–carbinyl rearrangement



- (6) α -cyclopropyl–carbinyl rearrangement



Validation of the pathways proposed by the programme is carried out using an empiric data base on the peculiarities of carbocationic rearrangements. In particular, the ICARUS data base involves the following selection rules:

1. Only the rearrangements occurring as 1,2-shifts of the C–C and C–H bonds fall under investigation; more distant 1,3-, 1,4-shifts, *etc.*, are not analysed.

2. Only intramolecular rearrangements (*i.e.*, those not resulting in degradation of the original structure into two independent species, *e.g.*, proton elimination followed by generation of an alkene) are subject to analysis.

3. Reactions resulting in generation of unstable intermediates (primary cations, structures containing strained small rings, *etc.*) are excluded from consideration. Also excluded are β -fragmentation reactions, since they produce high-energy intermediates: the formation of a double bond significantly increases the enthalpy of the reaction.

4. 1,2-Shifts of the σ -bonds in allylic ions are excluded from consideration.

However, estimation of the probability of such rearrangements on the basis of qualitative speculations alone does not always permit one to rule out improbable mechanisms. Quantitative estimations require calculation of thermodynamic characteristics of the intermediates by molecular mechanical or quantum mechanical methods. The enthalpy of a reaction can be calculated using a set of special force field parameters of the MM2 programme and bond increments for carbocations.⁶⁶ Estimation of the energy barriers demands simultaneous account of thermo-

dynamic and orbital factors, since their separate consideration often gives contradictory predictions. The enthalpies of formation of primary and final ions can be used as a thermodynamic factor. The orbital factor is associated with the value of the dihedral angle between the vacant p -orbital and the neighbouring migrating bond. It was assumed⁵⁹ that in the first approximation the internal barrier to the 1,2-shift (A) of a degenerate rearrangement is connected with the interorbital angle (φ) by equation (1):

$$A = A_0/\cos \varphi, \quad (1)$$

where A_0 is the internal barrier at $\varphi = 0^\circ$.

For a non-degenerate process, the thermodynamic factor was calculated by the Marcus equation (2) (in isoentropic approximation):

$$\Delta G^\ddagger = \left(1 + \frac{\Delta\Delta H}{4}\right)^2 \quad (2)$$

or in its linear Polanyi–Semenov approximation (3):

$$\Delta G^\ddagger = A + b\Delta\Delta H, \quad (3)$$

where $\Delta\Delta H$ is the difference between the ΔH_f° values of the generated and rearranged ions; $b = 0.25$ (for $-4A < \Delta\Delta H < 0$), 0.75 (for $0 < \Delta\Delta H < 4A$), $\Delta G^\ddagger = 0$ (for $\Delta\Delta H < -4A$), $\Delta\Delta H$ (for $\Delta\Delta H > 4A$).

The internal barriers, A_0 , for the orbitally optimum situation of a 1,2-shift were estimated according to Sorensen²⁴ from the values of barriers to 1,2-shifts of the C–C bond and the hydrogen atom in polymethylnorbornyl ions.

Degenerate 1,2-shifts can be estimated from equation (4):

$$A_0 = \Delta G_S^\ddagger \cos \varphi_S, \quad (4)$$

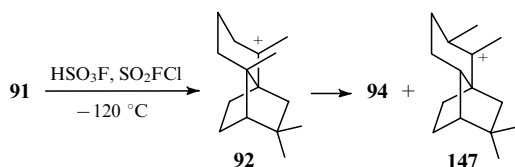
where $\Delta G_S^\ddagger$ is the barrier to the shift according to Sorensen and φ_S is the orbital factor in a norbornyl cation.

Since according to Sorensen's data the difference in the enthalpies of formation of secondary and tertiary isomeric norbornyl cations (in $\Delta\Delta H$) is equal to $5.5 \text{ kcal mol}^{-1}$, non-degenerate processes can be estimated from equation (5):

$$A_0 = (\Delta G_S^\ddagger + 5.5b) \cos \varphi_S. \quad (5)$$

The above equations allow one to predict the most probable pathways for the rearrangements of 1-chlorocaryolane,⁵⁹ clovene (2),² α -copaene (120)⁵⁷ and neoclovene (91)⁴⁴ in superacidic media.

Thus calculations have shown⁴⁴ that the ion 92 generated initially from neoclovene (91) is further converted into a mixture of two carbocations 94 and 147 with an energy gain, $\Delta\Delta H_f^\circ$, -13.0 and $-10.7 \text{ kcal mol}^{-1}$, respectively. This result was confirmed in experiments on protonation of the alkene 91 in $\text{HSO}_3\text{F} - \text{SO}_2\text{FCl}$ at -120°C .⁴⁴



Thus, the relatively simple technique for estimating the barriers to 1,2-shifts for the migrating ion⁵⁹ can efficiently be used for predicting rearrangements in alicyclic carbocations. However, this approach has some drawbacks. For example, the angle φ is not an unambiguous characteristic of the transition state strain. The internal barriers, A_0 , were estimated⁵⁹ on the basis of kinetic data for rearrangements of σ -delocalised 2-norbornyl ions. The choice of such specific models has led to overestimated barriers for open and monocyclic ions.

The correlation ratios (6) and (7) for estimating $\Delta G^\ddagger$ for 1,2-shifts of the hydrogen atom and the methyl group in aliphatic and alicyclic carbocations which actually determine the barrier to a degenerate rearrangement have been proposed.⁶⁷

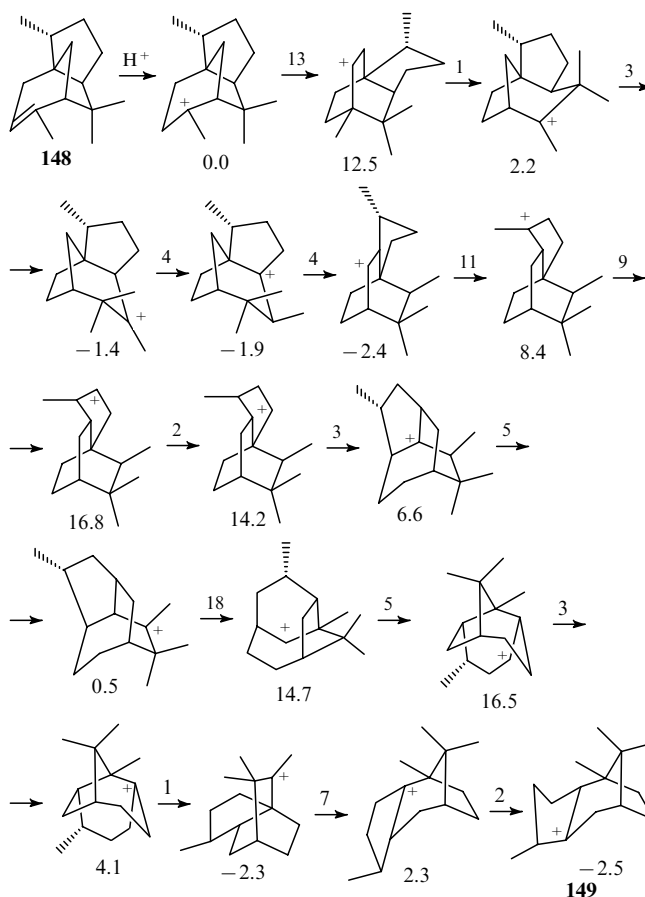
$$\Delta G_H^\ddagger = 15.33 - 10.79q_{\pi_x} + 0.232 \log K_i, \quad r = 0.986, s = 0.9, n = 8, \quad (6)$$

$$\Delta G_{\text{CH}_3}^\ddagger = 25.74 - 21.48q_{\pi_x} + 0.303 \log K_i, \quad r = 0.995, s = 0.8, n = 7, \quad (7)$$

where q_{π_x} is the value of the Hückel charge on the atom toward which the migrating group is displaced and K_i is the basicity constant of the i th position formed upon migrant detachment.

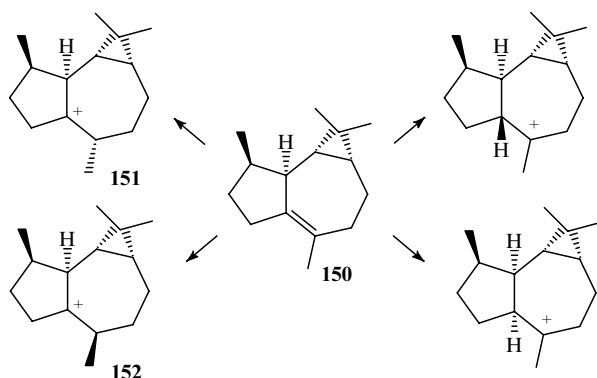
In this approach, the alkene formed upon elimination of the migrating group from the original cation serves as a model of the transition state of a 1,2-shift. The non-degeneracy of this process can be estimated by the Marcus equation (2). An advantage of this approach is the possibility of indirect estimation of the orbital factor and 'olefin strain',⁶⁸ since both these factors are included in the proton affinity value. However, the correlation ratios (6) and (7) are inapplicable to the Wagner–Meerwein rearrangement; in this case, $\Delta G^\ddagger$ can be determined only as described in Ref. 59.

The use of the above approaches^{59,67} for estimating ΔH_f° and $\Delta G^\ddagger$ has made it possible to propose the most probable pathway for α -cedrene (148) rearrangement in superacids resulting in the ion 149.⁶⁹ The latter could be obtained experimentally (the figures under the structures refer to the $\Delta\Delta H_f^\circ$ values; the figures above the arrows indicate the values of the barrier to 1,2-shift in kcal mol^{-1}).

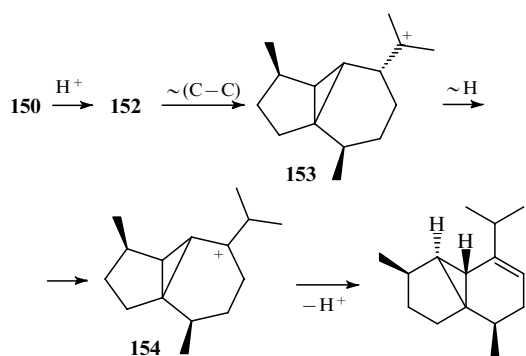


The primary site at which the cationic centre is formed in the alkene 148 having a trisubstituted double bond leaves no doubt. The primary proton attack in ledene (150) may involve both the double bond and the cyclopropane ring. Estimation of the proton affinity of the double bond and the three-carbon ring by the molecular mechanics method (MMX programme) revealed that the protonation of the double bond is much more preferable (by $3.5 \text{ kcal mol}^{-1}$).⁶⁹ As for the regio- and stereoselectivity of proton addition to the double bond, it has been found⁶⁹ that the protonation of the double bond at the carbon atom containing a

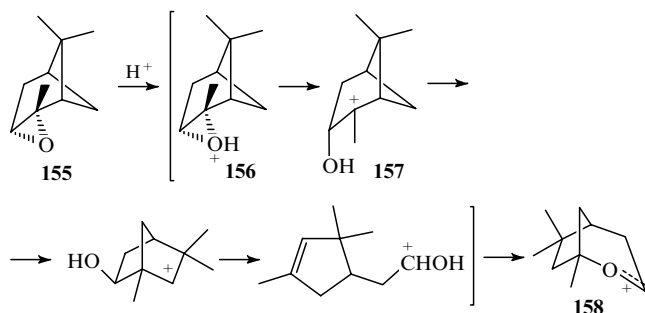
methyl group is more preferable for both α - and β -attack (by 9.2 and 8.3 kcal mol⁻¹, respectively) (MMX).



The isomeric ions **151** and **152** formed ($\Delta H_f^\circ = 157.4$ kcal mol⁻¹) have identical stability. Therefore, the stereodirection of their protonation was established with the use of additional data, viz., analysis of the Dreiding models of the alkene **150**, estimation of stability of epimeric epoxides prepared therefrom and estimation of steric accessibility of the double bond of the alkene **152** by the method described in Ref. 70. These data altogether suggest that the proton attack will occur largely from the α -side to yield the ion **152**.⁶⁹ The use of these approaches permits one to predict the rearrangement into the ion **153** and then into the ion **154** as the most probable pathway for alkene **150** transformations in 'long-living' ions; this conclusion was confirmed by the results of the reaction carried out in HSO₃F–SO₂Cl at –110 °C. The calculations predicted a gain in energy for the conversion of the ion **152** into the ion **154** (10.7 kcal mol⁻¹) (MMX).

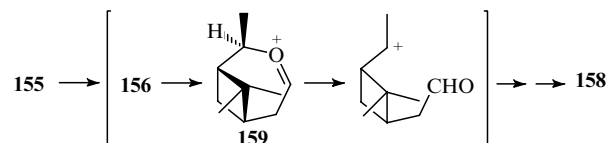


It should be noted that neglect of calculation methods in predicting the most probable pathways of multistep carbocation rearrangements may lead to serious misinterpretations of experimental data. Thus analysis of ¹³C NMR data has led to a conclusion that dissolution of the epoxide **155** in HSO₃F–SO₂ at –70 °C yields the ion **158** according to the following scheme:⁷¹

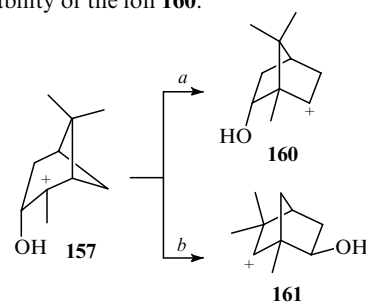


The CH₂ group in the ion **157** undergoes a shift, although it is migration of the Me₂C group that should occur in this type of ions. To overcome this controversy, an alternative scheme has been proposed where the ion **156** is not converted into the ion **157** but

undergoes an unusual for epoxides cleavage of the C–C bond in a three-membered ring.⁷¹ This is followed by a hydride shift to the tertiary carbon atom with generation of the ion **159** and then into the ion **158**.

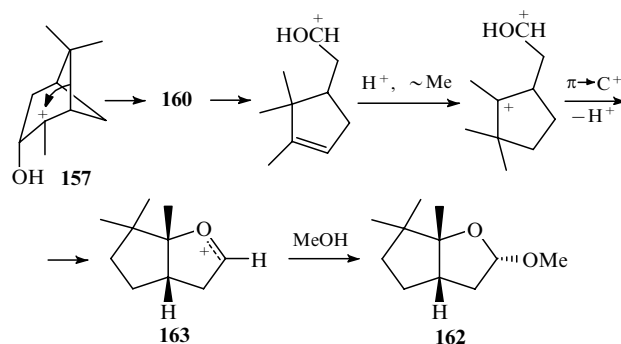


Later it was shown⁷² that this scheme of epoxide ring cleavage contradicts both the experimental and calculated data. According to the calculations performed by the AM1 method, the ion **156** is converted into the ion **157** (but not into the ion **159**) without a barrier. Further rearrangements of the ion **157** occur predominantly by pathway *a* resulting in the ion **160** ($\Delta H_f^\circ = 145.1$ kcal mol⁻¹) but not by pathway *b* (the ion **161**, $\Delta H_f^\circ = 150.3$ kcal mol⁻¹), which is attributed to the greater stability of the ion **160**.

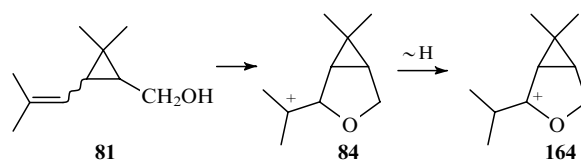


(a) $\Delta G^\ddagger = 5.9$ kcal mol⁻¹; (b) $\Delta G^\ddagger = 6.5$ kcal mol⁻¹.

In addition, it has been shown⁷² that dissolution of the epoxide **155** in HSO₃F–SO₂Cl at –110 °C and subsequent 'quenching' with methanol yield acetal **162** as the main reaction product. The carboxonium ion **163** generated from the ion **158** by a standard route with a 1,2-shift of the Me₂C group is its immediate precursor.



We can cite another example of an error resulting from disregard of calculation methods. As has been noted above, the structure **84** was ascribed to the ion generated from the alcohol **81**.³⁹ However, quantum-chemical calculations by the MINDO/3 method (AMPAC programme) revealed that the cation **84** was converted into the ion **164** without a barrier. This suggests that the ion **84** could not be regarded as a stable species.

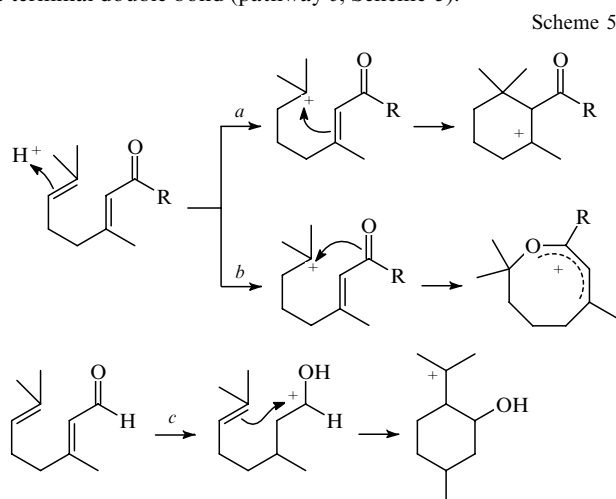


VII. A system of 'blocks' for aliphatic models

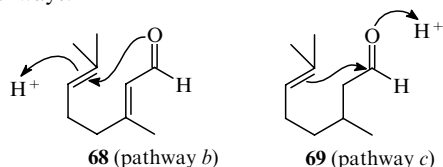
The synthesis of complex organic compounds from renewable plant material, particularly from widely accessible aliphatic monoterpenes by cationoid cyclisation acquires increasing importance (see Section VIII). Therefore, prediction of the most probable pathways of these processes becomes especially urgent. Unfortunately, pathways of structure-dependent cyclisation of acyclic compounds cannot be predicted either by quantum chemistry or molecular mechanics methods. By virtue of its 'non-rigid' geometry, the original compound can exist in different, relatively stable and energetically close conformations. Therefore, its cyclisation may occur by several different pathways; their choice is hampered by imperfection of the methods used.

An alternative approach to the experimental proof of the cyclisation schemes consists in fixation of intermediate cations in the rearrangement of aliphatic monoterpenes and establishment of a correlation between their generation and the presence of definite structural 'blocks' in the molecule of the original compound.⁷³

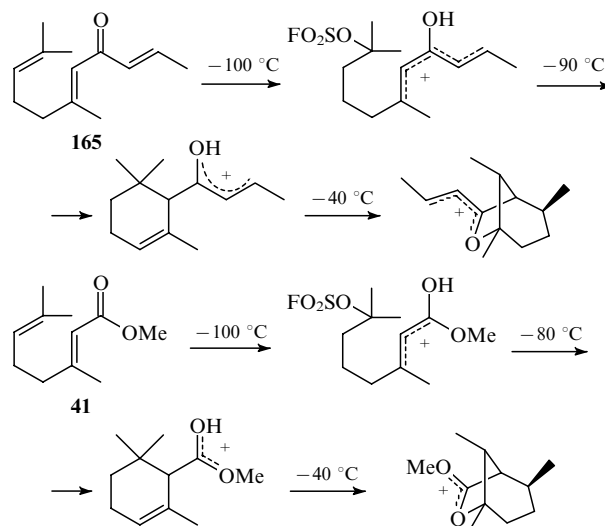
Systematic studies of the behaviour of terpenoids with identical carbon skeletons [e.g., citral (**68**), ionone (**14**) and methyl geranate (**41**)] in superacidic media have made it possible to propose three main pathways of primary cyclisation,^{73,74} viz., proton attack at the terminal double bond resulting in generation of a tertiary carbocation and its subsequent addition to the carbon (pathway *a*) or oxygen atom (pathway *b*); addition of a proton to the oxygen atom and subsequent attack of the cationic centre at the terminal double bond (pathway *c*, Scheme 5).



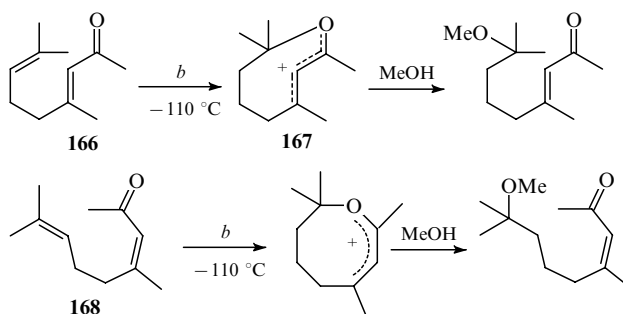
However, the cyclisation of citral (**68**) and citronellal (**69**), i.e., two aldehydes with identical skeletons, occurs by totally different pathways.²⁹



In some cases, compounds under study contain a common structural block which determines the pathway of cyclisation. This structural block is not necessarily identical with the carbon skeleton commonly used for classification of terpene compounds. For example, cyclisation in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$ of ϕ -damascone (**165**) and methyl geranate (**41**) having different skeletons and belonging to different classes of organic compounds occurs by a similar route (pathway *a*, Scheme 5).²¹

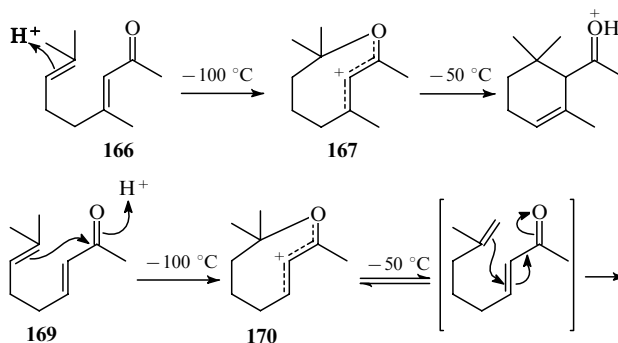


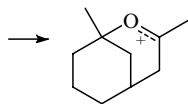
Studies with *trans*-(**166**) and *cis*-4,8-dimethylnona-3,7-dien-2-ones (**168**) have shown that reactions of isomeric acyclic isoprenoids with a conjugated 3,4-double bond can occur in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$ in a stereospecific way (pathway *b*, Scheme 5) both in the stage of generation of intermediate ions and the formation of 'quenching' products from acid solutions. Hence, the structural direction and stereochemical result of cyclisation of α,β -unsaturated carbonyl compounds of the terpene series depend on the configuration of the 3,4-double bond.



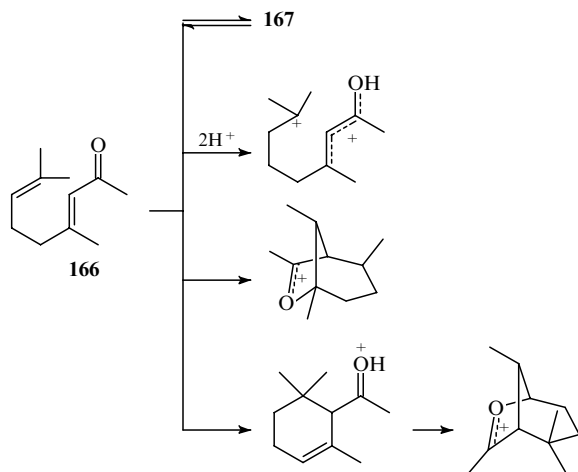
At first glance, ketones **166** and **168** share a common structural block with compounds **41** and **165** but the pathways of their primary cyclisation are totally different. Comparison of these models allows one to conclude that carbocyclisation requires that the structural fragment, $\text{Me}_2\text{C}=\text{CH}(\text{CH}_2)_2\text{C}(\text{Me})=\text{CHCO}$, was linked with a substituent X able to stabilise the positive charge by a mesomeric effect (OMe, $\text{CH}=\text{CHMe}$); otherwise heterocyclisation will take place.

Substitution of the hydrogen atom for the methyl group at C(4) in the ketone **166** ($\rightarrow$ **169**) changes substantially the pathways of cyclisation of compound **166** (Scheme 5, pathway *b*) and compound **169** (Scheme 5, pathway *c*) due to secondary conversions of the homologous carbocations **167** and **170**.

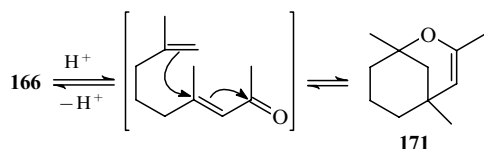




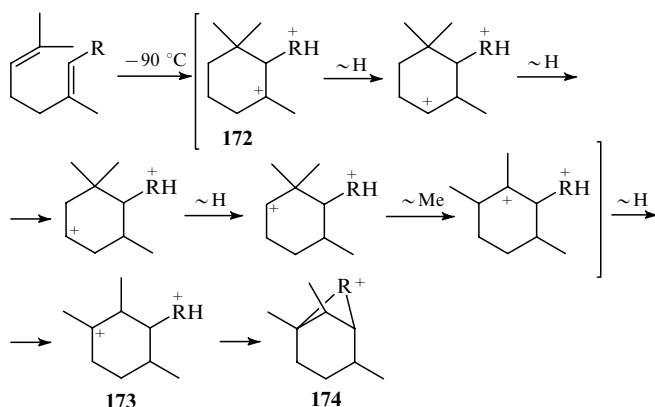
Varying the conditions of ion generation, particularly the acidity of the medium and temperature, makes it possible to carry out directed multistep rearrangements, *e.g.*, carbo- or heterocyclisation of ketones **166** and **168**.⁷³ In this case, heterocyclisation strongly depends on the configuration of the conjugated 3,4-double bond. Cyclisations of the 'ionone' type are independent of the spatial structure of the original substrate.



It is of note that compound **171** is the main product formed from the ketone **166** in dilute sulfuric acid.⁷³ In this case, the main pathways of cyclisation in superacids and 'ordinary' acids are different, since in the latter case intramolecular rearrangements prevail, which is not the case with superacids.



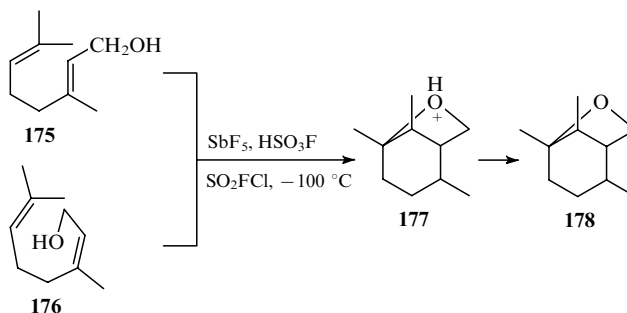
It was shown^{21,73,74} that many acyclic terpenoids (compounds **14**, **15**, **41**, **165**, **166**, **168**) undergo similar conversions in $\text{SbF}_5 - \text{HSO}_3\text{F} - \text{SO}_2\text{FCl}$ according to the following scheme:



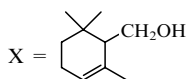
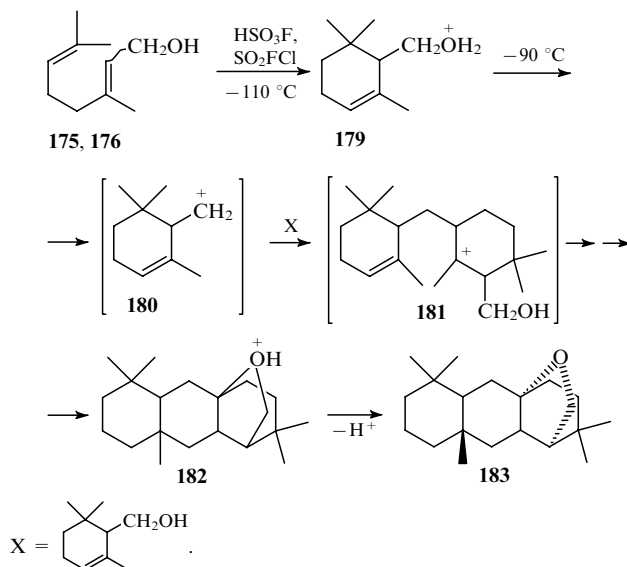
$\text{R} = \text{COCH}=\text{CHMe}, \text{COMe}, \text{CH}=\text{CHCOMe}, \text{COOMe}.$

Electrostatic repulsion of positive charges in the primary dication **172** is the reason for its rearrangement into the dication **173** (from ketones **14** and **15**) or a bridged ion of the type **174** (from the ester **41** and ketones **166** and **168**). Erroneous structures were ascribed to the conversion products of geraniol (**175**) and nerol (**176**) in superacids.^{75,76} We assumed⁷⁷ that rearrangements of

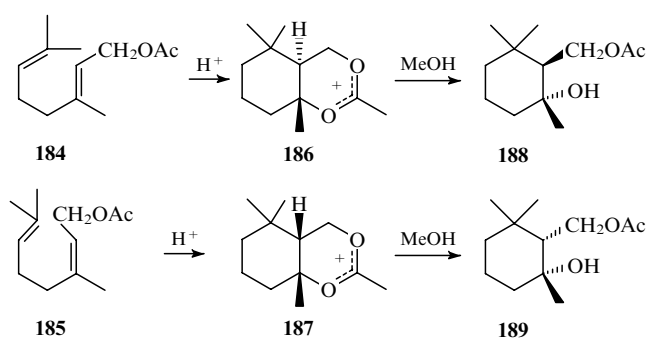
aliphatic alcohols **175** and **176** proceeded in accordance with the above scheme and gave the ion **177** and the ester **178**, since they have a common structural block with compounds **165**, **166** and **168**. This hypothesis was confirmed experimentally.



The type of rearrangements of alcohols **175** and **176** depends on reaction conditions. Thus the cyclic oxonium ion **179** was obtained in $\text{HSO}_3\text{F} - \text{SO}_2\text{FCl}$ at -110°C , while the tetracyclic ion **182** was formed from intermediates **180** and **181** upon heating of the reaction mixture to -90°C . Deprotonation of the ion **182** gives the ether **183**. Such a conversion of a monoterpene into a diterpene has no analogues either among cyclisation reactions of acyclic isoprenoids occurring in superacids or among monoterpene reactions realised in ordinary acidic media.⁷⁸



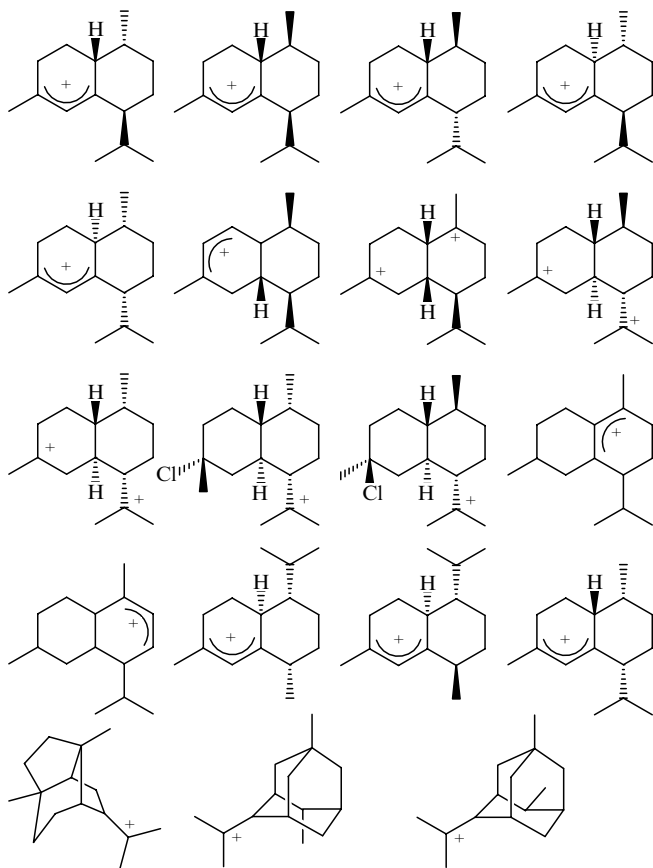
The outcome of rearrangements of stereoisomeric alcohols **175** and **176** is independent of the configuration of the 2,3-double bond,⁷⁷ while reactions of geranyl (**184**) and neryl acetates (**185**) gave different products. In $\text{HSO}_3\text{F} - \text{SO}_2\text{FCl}$ (-120°C), these compounds are predominantly converted into acyloxonium ions **186** and **187**, respectively. 'Quenching' of acidic solutions of ions **186** and **187** results in diastereomeric hydroxy acetates **188** and **189**.



VIII. Synthetic aspects of terpene reactions in superacidic media

One of the goals of studies of behaviour of terpenoids in superacids is to extend the range of new synthetic substances that can be prepared from accessible natural compounds and their analogues. Structural features of these compounds and the use of superlow temperatures and hypernon-nucleophilic media in the reactions ensure great diversity of molecular rearrangements. In contrast with acid-catalysed processes, the use of superacids allows for: (a) multistep conversions due to hypernon-nucleophilicity of the medium; (b) the possibility to obtain dications, which has no analogues in acid-catalysed reactions; (c) rapid conversion of original substrates into carbocations, which prevents cationic polymerisation due to high acidity; (d) high structural and stereochemical selectivity owing to the use of superlow temperature.

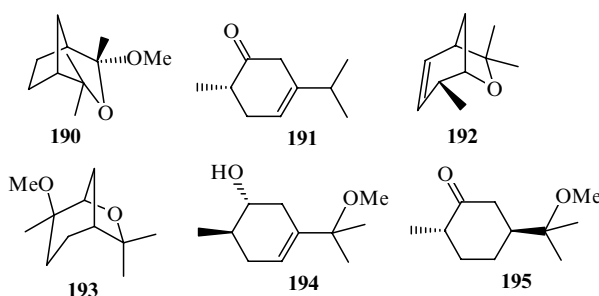
The preparation of 19 stable carbocations (which represent optical isomers) from an optically active diene, *viz.*, (–)- α -murelone (**48**), serves as an illustrative example of synthesis of different compounds from terpenes in superacids.⁵³ The direction of reaction was changed by varying the mode of ion generation (protonation of the diene or solvolysis of the corresponding dichloride), the acidity of the reaction system and the temperature at which ions were generated or ‘defrosted’. Reactions of these ions with nucleophiles gave rise to different dienes, *viz.*, natural terpenes or previously unknown isomers.



The conversions of compounds **14**, **15**, **31**, **32** and **125** considered in this review demonstrate the possibility of synthesis of various compounds through intermediate generation of di- and monocations having identical skeletons.

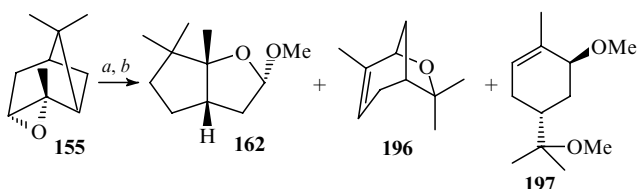
Conducting reactions in superacidic media provides greater possibilities for varying the structure of reaction products in comparison with ordinary acidic media.^{72, 79} Thus treatment of the epoxide **74** with proton acids usually gives products with retention of a carane skeleton and few compounds with a bicyclo[3.1.0]hexane skeleton.⁸⁰ In $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$ at

-110°C , this epoxide generates a mixture of compounds **190–195**.



Compounds **190–195** have not been previously obtained upon acid-catalysed cleavage of the epoxide **74**. Their formation can be ascribed to the initial opening of the epoxide ring, subsequent rearrangements with cleavage of the cyclopropane ring and stabilisation of cations by virtue of reactions with internal or external nucleophiles or elimination of a proton.

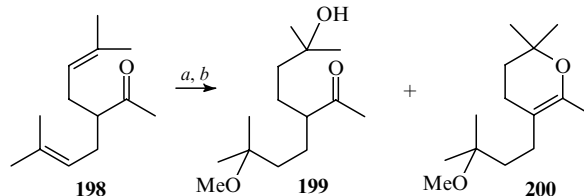
The behaviour of the epoxide **155** in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$ (-110°C) has been studied.⁷² The three main reaction products were acetal **162** and esters **196** and **197**.



(a) HSO_3F , SO_2FCl , -100°C ; (b) MeOH .

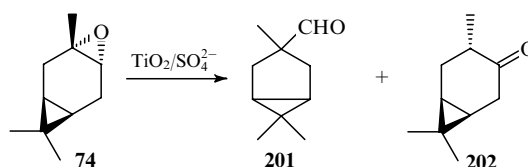
These compounds have also not been isolated earlier upon acid-catalysed cleavage of the epoxide **155**.

6-Methyl-3-(3-methylbut-2-enyl)hept-5-en-2-one **198** does not yield monomeric products under acid-catalysed conditions but is resinified. However, it gives a mixture of compounds **199** and **200** (yield 80%) upon treatment with $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$ (-110°C) with subsequent ‘quenching’.²⁹

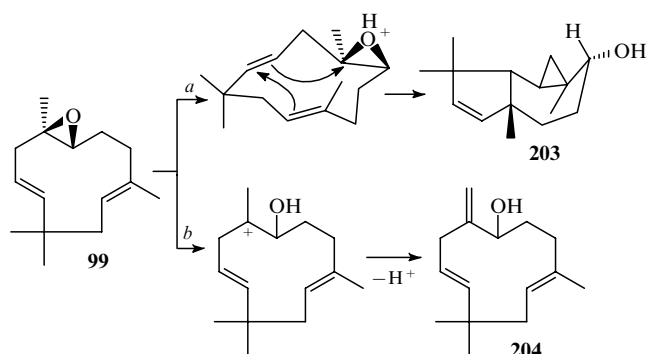


(a) HSO_3F , SO_2FCl , -110°C ; (b) MeOH .

As has been noted above, the use of liquid superacidic media allows one to obtain a more complete set of substrate transformation products. If the problem is to prepare a specific compound, it is necessary to choose an appropriate solid catalyst, *e.g.*, a solid superacid. The role of such catalysts may be played by sulfates of transition metal oxides, which, according to literature data, have not been used previously as acid catalysts in terpene reactions. It has been shown⁷⁹ that the use of $\text{TiO}_2/\text{SO}_4^{2-}$ as an acid catalyst in isomerisation of the epoxide **74** allows one to obtain a mixture of reaction products in which the aldehyde **201** and the ketone **202** predominate, which is different from the results obtained with liquid superacids. Earlier, compounds **201** and **202** were considered to be intermediate products in the preparation of the acetal **190** and the ketone **195** in liquid superacids.



The pathways of conversions of conformationally flexible substrates in both liquid and solid superacids can be different. Thus the isomerisation of the epoxide **99** in a liquid superacid ($\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$) differs from that on a solid catalyst ($\text{Al}_2\text{O}_3/\text{SO}_4^{2-}$) and alcohols **203** and **204** are formed, respectively.⁸¹

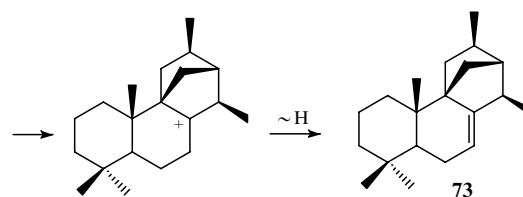
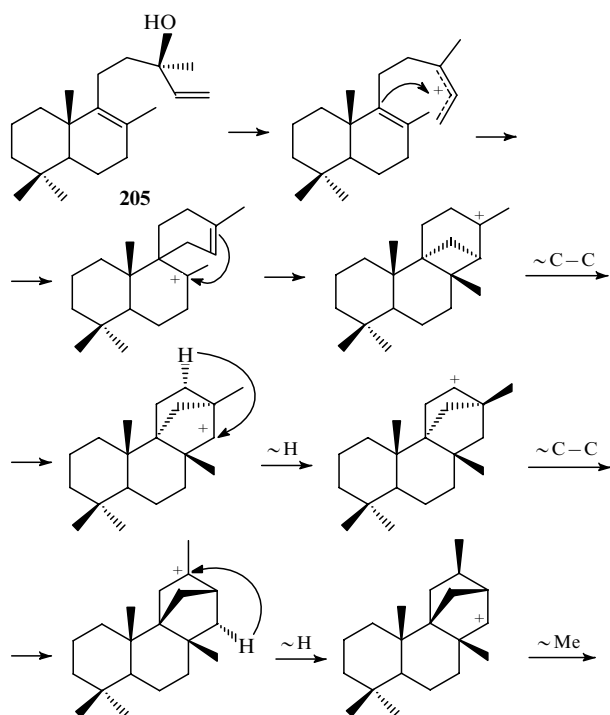


(a) HSO_3F , $-80\text{ }^\circ\text{C}$; (b) $\text{Al}_2\text{O}_3/\text{SO}_4^{2-}$, $20\text{ }^\circ\text{C}$.

This phenomenon can be explained by the difference in conformational control due to low temperature and epoxide binding on the catalyst surface.

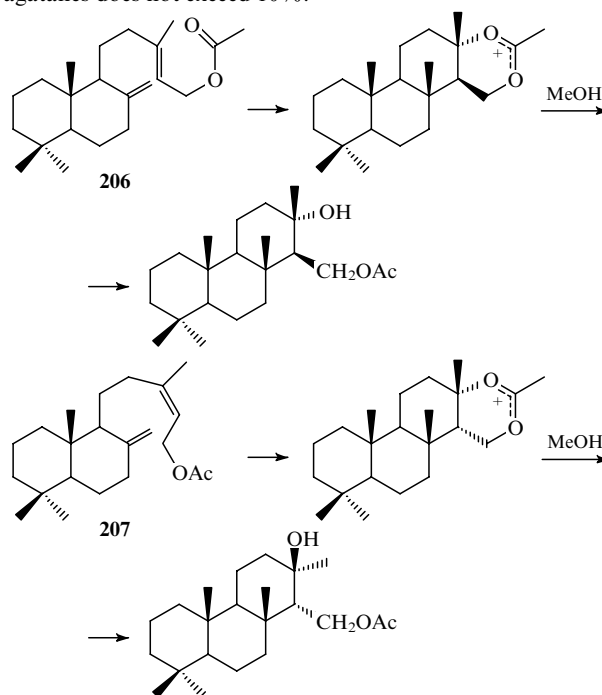
IX. Biogenetic aspects of terpene reactions in superacidic media

The biogenetic aspect is the last to be considered in this review. A question then arises about the relationship between the processes occurring under natural conditions and in superacidic media. According to Nishizawa *et al.*,¹⁸ biomimetic cyclisation of terpene alkenes is a 'stepwise' process which involves intermediate formation of cationic species. Their properties are best studied by modelling the behaviour of carbocationic salts under 'long-life' conditions. Low temperatures favour regio- and chemoselectivity of the reactions and conformational control, whereas hypernon-nucleophilic media are beneficial for more profound conversions. An example of such a conversion is cyclisation of isomanool (**205**) in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$ ($-110\text{ }^\circ\text{C}$) into tetracyclic compound **73**, which occurs in nine steps.³⁰

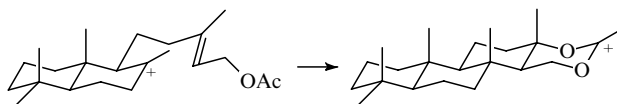


The conditions of acid catalysis are much more distant from those of biogenetic reactions because they occur in accordance with the Curtin–Hammett hypothesis, *i.e.*, in the absence of conformational control, and the reactions do not involve profound rearrangements and are often stopped due to interactions with nucleophiles. Thus, superacidic media favour biomimetic reactions 'mimicking' natural processes and provide chemical evidence for practicability of various biogenetic schemes.

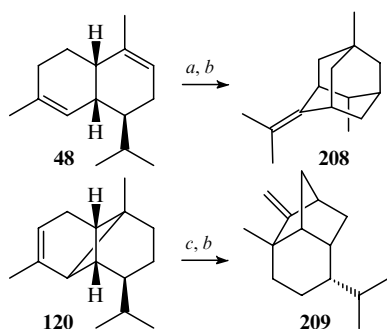
Thus it has been shown³⁰ that cyclisation in superacids ($\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$, $-100\text{ }^\circ\text{C}$) of labdane diterpenes **206** and **207** with primary allylic oxygen-containing groups in the side chain can be used for stereoselective syntheses of bifunctional compounds of the isoagatane series of specific structures. The ease of their cyclisation at low temperatures suggests that bicyclic labdanes might be biogenetic precursors of isoagatane compounds. Cyclisation of these compounds in ordinary acids yields a very complex mixture of reaction products in which the content of isoagatanes does not exceed 10%.



A similar mechanism has earlier been proposed for biogenetic cyclisation by Nishizawa *et al.*¹⁸

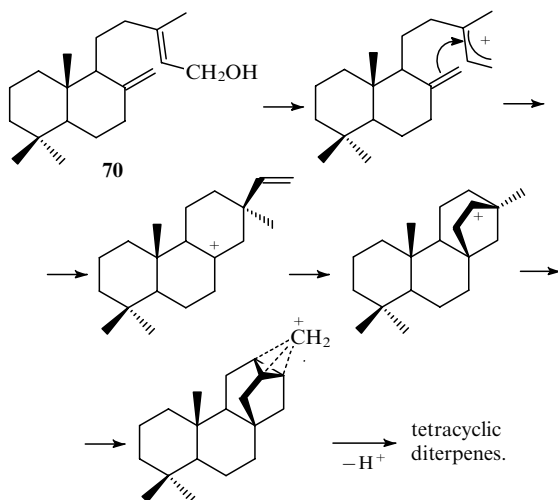


A key role in biogenetic schemes of sesquiterpenes has been ascribed to the diene **48**, which is considered as a precursor of tricyclic compounds with cubebane, copabornane and copaane skeletons. However, attempts to synthesise tricyclic products from the diene **48** and the alkene **120** by acid-catalysed reactions have failed. In contrast, tricyclic compounds **208** and **209** were obtained in $\text{HSO}_3\text{F}-\text{SO}_2\text{FCl}$.⁵⁷

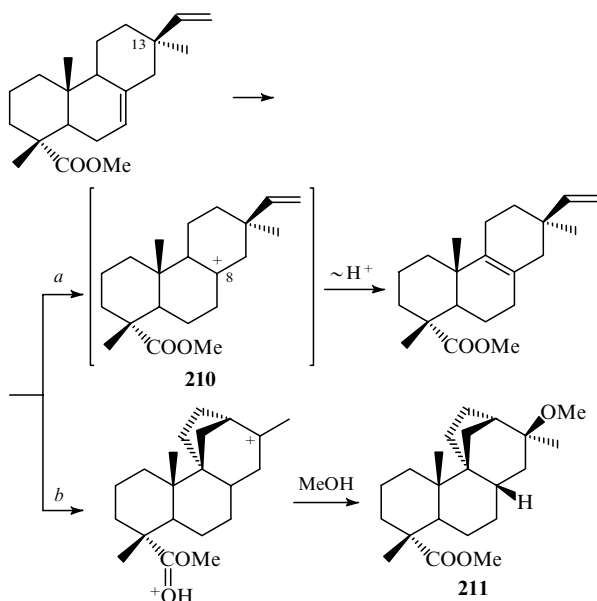


(a) HSO_3F , SO_2FCl , -30°C ; (b) MeOH ; (c) HSO_3F , SO_2FCl , -110°C .

Wenkert⁸² has hypothesised that tetracyclic diterpenoids with different skeletons are formed from bicyclic diterpenoids according to the following scheme:



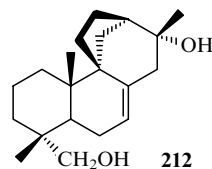
However, the attempts at *in vitro* synthesis of tetracyclic diterpenes from tricyclic ones have not met with success.⁸³ Thus treatment of pimaradienes with ordinary acids resulted merely in their isomerisation. It was therefore concluded that in contrast with the Wenkert scheme, pimaradienes are not biogenetic precursors of tetracyclic compounds. However, the use of superacidic media allowed, for the first time, cyclisation of pimaradienes into the tetracyclic compound **211**.⁸⁴ The failure to effect



(a) $[\text{H}^+]$; (b) HSO_3F , SO_2FCl , -100°C .

this cyclisation under conditions of acid catalysis was due to the higher rate of cation deprotonation at C(8) (compound **210**) resulting in the formation of a sterically hindered tetra-substituted double bond in comparison with the rate of cyclisation involving the vinyl group.

The skeleton of compound **211** is similar to that of stemarine **212** isolated recently from a natural source.⁸⁵



It is assumed that the latter is biosynthesised from pimaradienes. The preparation of the same stemarane-type stereoisomers from compounds of the pimaric and isopimaric series that are diastereomeric at the C(13) atom⁸⁴ provides evidence for the practicability of the Wenkert scheme postulating intermediate generation of a non-classical ion.

X. Conclusion

Thus, the main factors that control multistep multiroute cationic molecular rearrangements in superacidic media at superlow temperatures are the following: the nature of the acidic medium, the mode of generation of the cationic centre (solvolysis or proton addition to the alkene double bond), the temperature at which the cationic centre is generated and the temperature at which the acidic solution is 'defrosted'. The most probable pathways of multistep cationic rearrangements can thus be predicted with due regard to the orbital and thermodynamic factors. In practical syntheses of products of multistep cationic rearrangements, preference should be given to solid acidic (particularly superacidic) catalysts rather than to liquid superacids.

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Synthesis, reactions and structures of complexes of metal carbonyls and cyclopentadienyl carbonyls with organotellurium ligands[†]

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Abstract. Published data on the synthesis, reactivity and structure of complexes formed in the reactions of organic derivatives of tellurium with metal carbonyls and cyclopentadienyl carbonyls are described systematically and generalised. The bibliography includes 142 references.

I. Introduction

The substantial progress achieved in synthetic organotellurium chemistry has stimulated studies dealing with metal complexes with organotellurium ligands.^{1–11} In recent years, considerable attention has been paid to metal complexes, in particular, complexes of metal carbonyls and cyclopentadienyl carbonyls with organochalcogens, including organotellurium, ligands. Study of these complexes has allowed researchers to elucidate the influence of the nature of donor atoms (sulfur, selenium and tellurium) on the reactivity and structural and spectral features of compounds of the same type containing these atoms. Compounds prepared by the reactions of metal carbonyls with phosphine tellurides^{12–14} and diphenyl ditelluride¹⁵ and of tetracarbonylmanganese complexes with tellurium-containing ligands^{16,17} are convenient precursors of metal tellurides, the synthesis of which can be performed at relatively low temperatures.

This review is concerned with the synthesis, structures and reactivity of complexes formed by metal carbonyls and cyclopentadienyl carbonyls with organotellurium ligands. Various tellurium-containing clusters which contain either telluride (–Te–) or ditelluride (–Te–Te–) bridges have been considered in earlier reviews;^{2–4,18} therefore, we do not dwell on them here.

II. Complexes with organic derivatives of monocoordinated tellurium

This Section contains data on the reactions of metal carbonyls and cyclopentadienyl carbonyls with organic derivatives of monocoordinated tellurium. This type of derivative includes phosphine tellurides $R_3P=Te$ and compounds with $C=Te$ bonds. Since organytellurolate anions RTe^- can also be formally classified as

derivatives of monocoordinated tellurium, this Section also presents data concerning complexes with bridging and terminal RTe groups.

1. Phosphine tellurides

Methods for the synthesis and some reactions of complexes of phosphine tellurides with metal carbonyls and cyclopentadienyl carbonyls have been considered fairly comprehensively in a review.¹⁹ Therefore, here we present only recent data concerning the structure, synthesis and transformations of some of these compounds (Table 1). Spectral characteristics of complexes **1a–c** are listed in Table 2.

Table 1. Some complexes of phosphine tellurides with metal carbonyls and cyclopentadienyl carbonyls.

Initial compounds		Reaction products	Ref.
R ₃ P=Te	Metal complexes		
Bu ₃ P ^t =Te	M(CO) ₆ (M = Cr, Mo, W)	(CO) ₅ M–Te=PBu ₃ ^t (1a–c) ^a (M = Cr (a), Mo (b), W (c))	20
Et ₃ P=Te	Co ₂ (CO) ₈	[(Et ₃ P) ₂ (CO) ₂ CoTe] ₂ (2) (Et ₃ P) ₄ (CO) ₆ Co ₄ Te ₂ (3) (Et ₃ P) ₆ Co ₆ Te ₈ (4) ^b	13, 14
	Mn ₂ (CO) ₁₀	[(Et ₃ P) ₂ (CO) ₃ MnTe] ₂ (5)	12
Me ₃ P=Te	BnMn(CO) ₅	BnTeMn(CO) ₃ (PMe ₃) ₂ (6a)	16, 17
Et ₃ P=Te	BnMn(CO) ₅	BnTeMn(CO) ₃ (PEt ₃) ₂ (6b)	16, 17
	MeMn(CO) ₅	MeTeMn(CO) ₃ (PEt ₃) ₂ (6c) ^{c, d} MeMn(CO) ₃ (PEt ₃) ₂ (7)	16, 17
R ₃ P=Te	[CpFe(CO) ₂ THF] ⁺ ·BF ₄ [−] (9)	[CpFe(CO) ₂ TePR ₃] ⁺ BF ₄ [−] (10) ^e	23, 24

^a As opposed to thiophosphorane complexes of a similar structure, phosphine telluride in the complexes **1a–c** cannot be replaced by Ph_3P or CO even at 80 °C.²¹ ^b A complex with a similar structure, $(Ph_2PrP)_6Co_6Te_8$, was prepared by the reaction of Ph_2PrP with $PhTe-SiMe_3$ and $CoCl_2$.²² ^c A mixture of **6c** and **7** is formed. ^d The complex **6c** can also be prepared by the reaction of $BrMn(CO)_3(PEt_3)_2$ (**8**) with $MeTeLi$.¹⁷ ^e Decomposition of the complex **10** affords the complex $[CpFe(CO)_2PR_3]^+ BF_4^-$ (**11**), while the reaction of **10** with I_2 gives $[CpFe(CO)_2I]_2$ (**12**).²³

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[†] Dedicated to the blessed memory of Doctor of Chemical Sciences Gusein Kurban-Ismaïlovich Magomedov.

Table 2. Spectral characteristics of the complexes **1a–c**.²⁰

Com- pound	$\delta_{31\text{P}}$	$\delta_{125\text{Te}}^a$	$\delta_{\text{C=O}}$		$J_{31\text{P}-125\text{Te}}$ /Hz	$\nu_{\text{C=O}}$ / cm ⁻¹
			<i>cis</i>	<i>trans</i>		
1a	53.5 (744) ^b	−635 (−839) ^b	218.5	224.9	1502 (1600) ^b	2052, 1927, 1986, 1913, 1937
1b	54.7	−749	206.8	213.1	1602	2055, 1937, 1988, 1912, 1941
1c	49.9	−770	199.4	200.4	1600	2063, 1927, 1982, 1909, 1932

^a With respect to Me₂Te. ^b The chemical shifts for the free ligand are given in parentheses.

According to X-ray diffraction analysis,²⁰ complex **1c** has an octahedral structure, the P–Te bond length being equal to 2.439 Å. Comparison of this value with the lengths of the P = Te bonds in phosphine tellurides, which range from 2.305 to 2.371 Å,^{25–31} shows that the P–Te bond in the complex **1c** is mainly a single bond. This finding was explained²⁰ by assuming that the bipolar ionic structure Bu₃P–Te = M²⁺(CO)₅ makes the predominant contribution to the ground electronic state of the complex **1**.

The structures of clusters **2–5** have been studied by X-ray diffraction analysis. Here we shall briefly describe only the structures of the compounds **2**¹⁴ and **5**¹² closest to compounds that constitute the subject of this review. The molecules of the clusters **2** and **5** contain ditelluride bridges, Te–Te, the tellurium atoms of these bridges being bound to the Co and Mn atoms, respectively. The Te–Te bonds (2.765 Å in the cluster **2** and 2.763 Å in the compound **5**) are somewhat longer than those in diaryl ditellurides [2.697 Å in di(4-methylphenyl) ditelluride,³² 2.702 Å in di(4-chlorophenyl) ditelluride,³³ 2.710 Å in di(4-methoxyphenyl) ditelluride³⁴ and 2.712 Å in diphenyl ditelluride³⁵]. The Co–Te–Te and Mn–Te–Te bond angles (101.7° and 105.5°, respectively) are also somewhat greater than the C–Te–Te angle in diaryl ditellurides [for example, in di(4-methoxyphenyl) ditelluride, this angle is 99.8°]. The coordination polyhe-

dron about the Co atom is a distorted trigonal bipyramid in which the apical positions are occupied by the Et₃P groups; the environment of the Mn atoms is a distorted octahedron with *trans*-arranged phosphine ligands.

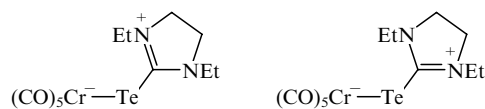
According to X-ray diffraction data,^{16,17} the crystal unit cell in the complex BnTeMn(CO)₃(PEt₃)₂ **6a** contains two crystallographically independent molecules, which differ in the conformation of the ethyl groups at the phosphorus atoms. The bond geometry about the manganese atom is a slightly distorted octahedron with *trans*-arrangement of the Et₃P groups. The Mn–Te bond length (2.702 Å) is close to the bond length in the cluster **5** (2.763 Å),¹² and the C–Te bond length is within the range normal for this type of bond.³⁶

2. Tellurocarbonyl compounds

Synthesis and reactions of complexes of metal carbonyls with tellurocarbonyl compounds have been described in detail in a review.¹⁹ Here we present only some examples of these complexes for which X-ray diffraction data have been obtained or chemical reactions have been studied (Tables 3, 4).

The bond lengths in the complex **17**, determined by X-ray diffraction analysis,⁴² point to the presence of a weak coordination bond W–Te, the length of which (2.808 Å) is close to the upper limit of the lengths of single W–Te bonds (2.88 Å).⁴⁶ The C=Te bond length amounts to 1.987 Å, which is close to the length of this bond in S=C=Te (1.904 Å⁴⁷). This indicates that the carbon–tellurium bond in the complex **17** is close to a double bond. The fact that upon heating of the complex **17** in a MeCN solution, the solvent displaces the telluroketone **16c** to give the complex (CO)₅W·MeCN confirms the conclusion that the coordination in this complex is weak.⁴²

The molecular and crystal structures of the complex **19a** were studied by X-ray diffraction analysis.⁴³ The geometry of bonds about the chromium atom corresponds to a distorted octahedron. The C–Te bond length (2.12 Å) falls into the range of lengths typical of single C–Te bonds,³⁶ while the Cr–Te–C bond angle is 96.1°. The Cr–Te bond length (2.765 Å) differs only slightly from

**Table 3.** Complexes of transition metal carbonyls with monocoordinated tellurium.

Initial compounds		Reaction products	Ref.
metal carbonyls	tellurium derivatives		
(CO) ₅ W = CPhR (13a,b) [R = Ph (a), H (b)]	(Ph ₃ P = N = PPh ₃) ⁺ (TeCN) [−]	(CO) ₅ W–Te = CPhR (14a,b) (CO) ₅ WTe = CPhH (15) W(CO) ₅	37, 38
(CO) ₅ W·THF	 [R = (CH ₂) ₂ (a), CH = CH (b), <i>o</i> -C ₆ H ₄ (c) ^a]	 [R = <i>o</i> -C ₆ H ₄)	40–42
M(CO) ₅ ·MeCN [M = Cr (a), Mo (b), W (c)]	 Et	 Et	43

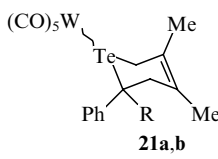
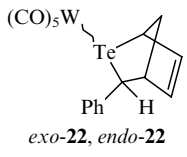
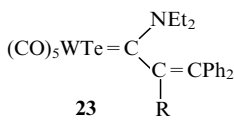
^a Spectral characteristics of the compound **16c**: $\delta_{13\text{C}} = 301$ (C=Te), $\delta_{125\text{Te}} = 2858$, $\lambda_{\text{max}} = 825$ nm.⁴⁰

^b Diferrocenyl telluroketone does not form complexes with metal carbonyls.³⁹

^c Spectral characteristics of the compound **17**: $\delta_{13\text{C}} = 285$ (C=Te), $\delta_{125\text{Te}} = 1783$, $\lambda_{\text{max}} = 525$ nm.⁴²

^d The complex **19a** (M = Cr) decomposes on exposure to light to give complex EtN(CH₂)₂N(Et)Cr(CO)₅ (**20**).

Table 4. Products of the addition of the complexes **14a,b** to unsaturated compounds.

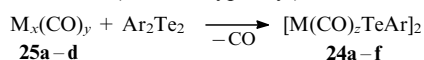
Complex	Unsaturated compound	Product	Ref.
(CO) ₅ WTe = CPhR (14a,b) (R = Ph (a), H (b))		 21a,b	39, 44
(CO) ₅ WTe = CHPh (14b)		 <i>exo</i> - 22 , <i>endo</i> - 22	34, 44
(CO) ₅ WTe = CPh ₂ (14a)	RC≡CNEt ₂	 23	45

those in other complexes containing chromium and tellurium. The C–Te bond in the complex **19a** is much longer than the carbon–tellurium bond in the compound **17** (1.987 Å), which is due to the predominant contribution of polar resonance structures to the ground state of the molecule.⁴³

3. Organyltelluroate complexes

An important method for the synthesis of the complexes **24**, containing metal carbonyl fragments and organyltelluroate (mainly, aryltelluroate) bridging groups is based on reactions of various metal carbonyls **25** with diaryl ditellurides.^{48–54}

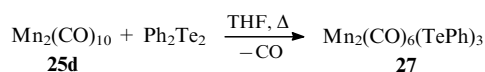
Dodecacarbonyltriiron,^{48–51} dodecacarbonyltriruthenium,⁴⁹ dodecacarbonyldimanganese^{53,54} and hexacarbonylmolybdenum⁵² enter into this reaction. The number of diaryl ditellurides that have been involved in this reaction is quite limited. The use of diphenyl ditelluride,^{49,52–54} bis(pentafluorophenyl) ditelluride^{50,51} and di(4-methoxyphenyl) ditelluride⁴⁸ has been reported.



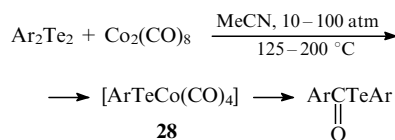
M _x (CO) _y	[M(CO) _z TeAr] ₂	Ref.
Fe ₃ (CO) ₁₂ (25a)	[Fe(CO) ₅ TeC ₆ F ₅] ₂ (24a)	50, 51
	[Fe(CO) ₅ TePh] ₂ (24b)	49
	[Fe(CO) ₅ TeC ₆ H ₄ OMe-4] ₂ (24c)	48
Ru ₃ (CO) ₁₂ (25b)	[Ru(CO) ₃ TePh] ₂ (24d)	49
Mo(CO) ₆ (25c)	[Mo(CO) ₄ TePh] ₂ (24e)	52
Mn ₂ (CO) ₁₀ (25d)	[Mn(CO) ₄ TePh] ₂ (24f)	53, 54

These reactions occur under relatively mild conditions. Whereas in the case of Fe₃(CO)₁₂ **25a**, the complexes **24a–c** are the only reaction products, the reaction of ruthenium carbonyl **25b** with diphenyl ditelluride yields, depending on the ratio of the reactants, either a mixture of **24d** and [Ru(CO)₂(TePh)₂]_n (*n* = 6, 7, 12) **26** or only the latter compound.⁴⁹ When a molar excess of diphenyl ditelluride is used, only the complex **26** is formed, whereas with a **25b**:Ph₂Te₂ ratio of 3:2, a mixture containing the compound **26** (~90%) and the complex **24d** (~10%) is produced.⁴⁹

Variation of the reaction temperature has a substantial influence on the composition of manganese complexes. Indeed, UV irradiation of a tetrahydrofuran solution of Mn₂(CO)₁₀ **25d** and diphenyl ditelluride at room temperature affords the bis-bridged complex **24f**,⁵³ whereas refluxing of the initial solution yields paramagnetic compound **27**, containing three bridging PhTe groups.⁵³



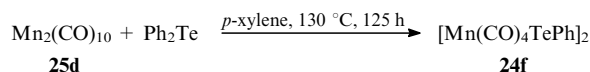
Unlike other carbonyls, Co₂(CO)₈ reacts with diaryl ditellurides in an atmosphere of CO (pressure 10–100 atm) to give telluroesters.^{55,56} It was assumed⁵⁶ that these reactions yield complexes **28** as intermediates.



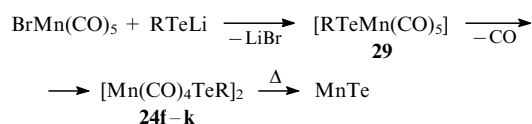
Ar = Ph, 4-MeOC₆H₄.

In the case of dialkyl ditellurides, no telluroesters are formed, the corresponding dialkyl tellurides being the only reaction products.⁵⁶

Diaryl tellurides can be used instead of diaryl ditellurides as the sources of bridging ArTe ligands in the preparation of complexes of the type **24**. Thus the complex **24f** is formed when a mixture of manganese carbonyl **25d** and diphenyl telluride is heated under rigorous conditions.⁴⁸



Yet another approach to the synthesis of binuclear manganese complexes of type **24**, containing various bridging ligands TeR [R = Ph, Alk, (Me₃Si)₃Si] is based on the nucleophilic replacement of the bromine atom in bromo(pentacarbonyl)manganese by lithium organyltelluroates.^{17,53} The reaction products **29** formed initially are quite unstable; they eliminate a CO molecule being thus converted into the binuclear complexes **24** in 10%–52% yields.¹⁷ The attempts to stabilise the mononuclear complexes **29** by introducing the bulky tris(trimethylsilyl)silyl group failed.¹⁶

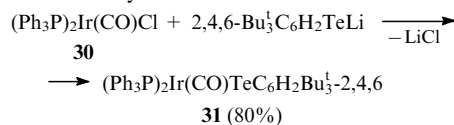


R = Ph (f), Me (g), Et (h), Prⁱ (i), CH₂SiMe₃ (j), (Me₃Si)₃Si (k).

The reductive thermolysis of the complexes **24g, h** carried out by heating them under a hydrogen atmosphere at 300 and 200 °C, respectively, affords films containing manganese telluride in addition to manganese and tellurium.¹⁷

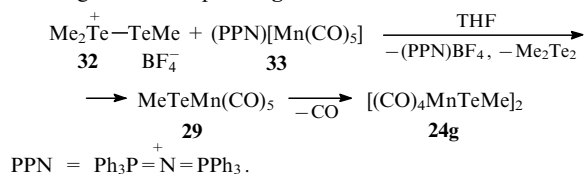
The attempts to convert the complexes **24** into the complexes **6** (*cf.* Section II.1) by substituting triorganylphosphines for the CO groups were unsuccessful.¹⁷ At room temperature, the reaction proceeded very slowly, while at an elevated temperature, it gave a complex mixture of non-identified products.

Nucleophilic substitution of chlorine in iridium complex **30** occurring on treatment of this complex with relatively stable lithium 2,4,6-tris(*tert*-butylphenyl)telluroate has been used to prepare complex **31** the structure of which was studied by X-ray diffraction analysis.⁵⁷



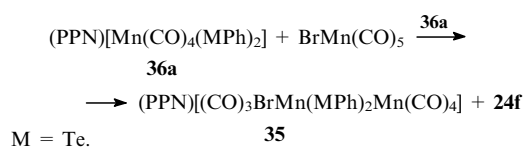
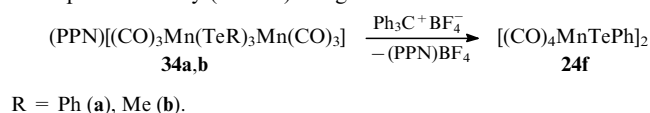
Recently the complex **24g** was synthesised⁵⁸ by virtue of a new tellurium-containing reagent, dimethyl(methyltelluro)tellurium tetrafluoroborate **32** (which was prepared by alkylation of dimethyl ditelluride by trimethyloxonium tetrafluoroborate in acetonitrile). Treatment of a THF solution of the compound **32** with salt **33** gives initially, like the reaction of bromo(pentacarbonyl)manganese with lithium methyltelluroate described

above,¹⁷ the mononuclear complex **29** (R = Me), the existence of which in solution at 0 °C was proved by spectroscopy (IR, ¹H NMR). This product rapidly dimerises with abstraction of CO to give the complex **24g**.

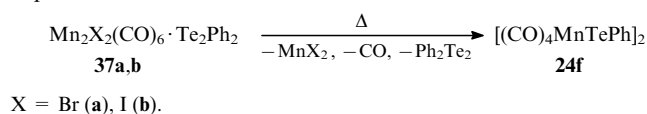


Since the natures of both components can be varied, this reaction can become a convenient method for the synthesis of binuclear complexes of type **24**. The prospects for using the salt **32** and its analogues in preparative organic chemistry are not less important. Sulfonium salts with similar structures containing alkyl and aryl radicals at the disulfide bridge^{59–61} and also dimethyl(phenylseleno)sulfonium tetrafluoroborate⁶² are used in the synthesis of episulfonium salts, S-arylation (alkylation) of alkenes, phenylselenation of aromatic compounds and in other reactions.

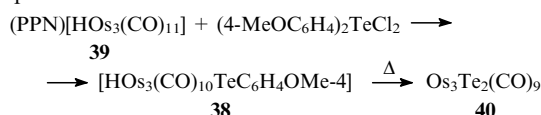
Manganese complexes of the type **24** have also been obtained using tellurium-containing anionic compounds **34a,b** (their synthesis is described below).⁶³ Treatment of the salt **34a** with triphenylmethyl tetrafluoroborate gave the complex **24f** in 34% yield. The same complex was isolated in 30% yield together with anionic complex **35** when salt **36a** (M = Te) was made to react with 'pentacarbonyl(bromo)manganese'.⁵⁸



Now we shall briefly describe two other reactions resulting in the formation of complexes with bridging aryltelluroate groups. Thus the compound **24f** has been synthesised by refluxing complexes **37**, prepared by the reaction of octacarbonyldihalomanganes (for details, see Section III.2) with diphenyl ditelluride, in heptane⁶⁴ or benzene.⁵³



Osmium complex **38** (yield 7%) has been obtained, together with non-identified compounds, on treatment of complex **39** with di(4-methoxyphenyl)tellurium dichloride at room temperature.⁶⁵ Thermolysis of the complex **38** (refluxing in octane for 2 h) affords cluster **40** (yields 6%). The mechanism of transformation of the compound **39** into **38** has not been discussed.



The molecular and crystal structures of the complexes **24e**,⁵² **24f**,^{53, 63} and **24g**⁵⁸ have been studied by X-ray diffraction analysis (Fig. 1). The structure of the molecules **24e–g** is a planar rhombus M_2Te_2 , in which the methyl groups occupy *syn*-positions;⁵⁸ the phenyl groups in the complex **24f** occupy *trans*-positions. The most important bond lengths and bond angles in the complexes **24e–g** are presented in Table 5.

The ¹H, ¹³C and ¹²⁵Te NMR spectra of the complex **24g** indicate the presence of two different TeMe groups, which is

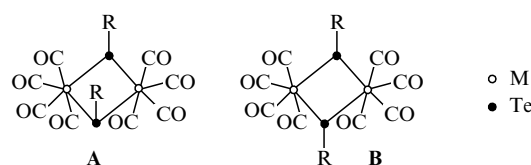


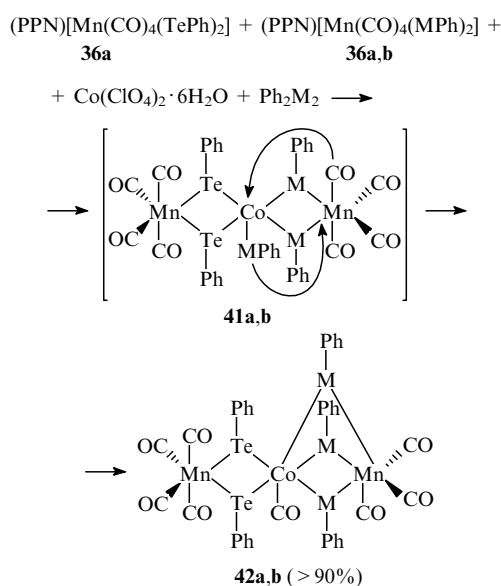
Figure 1. Molecular geometry of **24e–g**; **A** is the *syn*-isomer, **B** is the *anti*-isomer.

Table 5. Bond lengths and bond angles in the complexes **24e–g**.⁵⁸

Complex	Bond lengths/ Å		Bond angles/ deg.	
	M–Te	C–Te	M–Te–M	Te–M–Te
[Mo(CO) ₄ TePh] ₂ 24e	2.756	2.133	68.8	111.2
[Mn(CO) ₄ TePh] ₂ 24f	2.661	2.129	95.96	84.04
[Mn(CO) ₄ TeMe] ₂ 24g	2.661	2.183	95.71	83.66

consistent with the finding that two conformers (**A** and **B**, see Fig. 1) exist in solution in a ratio of 4 : 5.¹⁷ The signals of the two TeMe groups in this complex coalesce at 361 K, and those for **24j** coalesce at 343 K, although the ¹²⁵Te NMR spectrum of the latter compound exhibits only one ¹²⁵Te signal. The data of multinuclear NMR spectroscopy for solutions of the complexes **24h,i** also point to the presence of two isomers. Judging by the fact that ¹²⁵Te NMR spectra of the complexes **24f,k** exhibit singlet ¹²⁵Te signals, these complexes exist as a single, more stable, isomer due to fast interconversion of the isomers.¹⁷

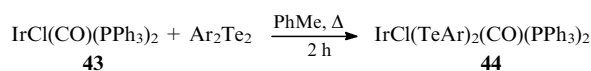
The binuclear manganese complex **27**,⁵³ which contains three bridging PhTe groups, has been described above. Recently,^{63, 66} trinuclear complexes containing either five PhTe bridges (**42a**, M = Te) or two PhTe bridges and three PhSe bridges (**42b**, M = Se) have been prepared. The complex **42a** was synthesised by the reaction of cobalt perchlorate hexahydrate with diphenyl ditelluride in the presence of the anionic complex **36a**; the reaction is accompanied by oxidation of Co²⁺ to Co³⁺.⁶³ The mixed selenium-and-tellurium complex was prepared from cobalt perchlorate hexahydrate, diphenyl diselenide and the anionic complexes **36a** and **36b**.⁶⁶ Evidently, the compounds **42a,b** result from rearrangement of the complexes **41a,b** formed intermediately.



M = Te (a), Se (b).

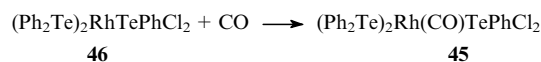
According to X-ray diffraction data,^{63,66} the complexes **42a,b** contain linear chains of atoms Mn–Co–Mn. The Co(III) ion is bound either to five PhTe bridging ligands and a terminal CO group (**42a**) or to two PhTe bridging groups, three PhSe bridging groups and a carbonyl group (**42b**). Thus, the coordination environment of the Co(III) atom in both complexes is a distorted octahedron. One Mn atom in **42a,b** is coordinated to two PhTe bridging ligands and four terminal carbonyl groups; the other manganese atom is linked to three carbonyls and three PhTe (**42a**) or PhSe (**42b**) bridges. Thus, the coordination polyhedron formed about each manganese is also a distorted octahedron. The Te–metal bond lengths in **42a** are the following: Co–Te (Mn–Te) 2.657 Å;⁶² in **42b**, they are 2.576 and 2.654 Å, respectively; the Co–Se bond length is 2.450 Å.⁶⁶

Unlike octacarbonyldihalo-manganese⁶⁴ and -rhenium,⁶⁷ which react with diphenyl ditelluride with retention of the Te–Te bond (for details, see Section III.2), oxidative addition of diaryl ditellurides to the carbonyl chloro iridium complex **43** occurs with rupture of the Te–Te bond and gives complexes **44** containing terminal ArTe ligands. Spectral characteristics of the complexes (shift of the singlet signal in the ³¹P NMR spectrum by ~100 ppm in relation to that in the spectrum of the initial complex **43** and the ¹²⁵Te chemical shifts) are consistent with the structure **44**; however, the exact geometry of these complexes is unknown. During the reaction, a broad EPR signal typical of tellurium-centred radicals was observed; based on this fact, a reaction mechanism was proposed which includes the initial addition of the ditelluride to the Ir(I) complex **43** followed by homolytic cleavage of the Te–Te bond to give the Ir(III) complexes **44**.⁶⁸

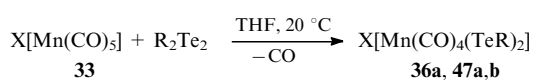


Ar = 4-EtOC₆H₄, 4-MeC₆H₄, Ph, 4-ClC₆H₄.

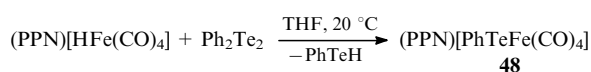
Among other halo carbonyl complexes containing ArTe ligands, rhodium complex **45** should be noted. It was synthesised in a yield of more than 50% by passing CO through a benzene solution of complex **46**.⁶⁹



In addition to the neutral carbonyl and halo carbonyl complexes described above, anionic carbonyl complexes with terminal RTe ligands have been reported. The synthesis of these compounds is based on a reaction typical of diorganyl ditellurides, namely, cleavage of the Te–Te bond by various nucleophiles: organolithium and organomagnesium compounds, alkalis, cyanide anion, *etc.*⁷⁰ When anionic metal carbonyls such as [Mn(CO)₅][–] (see Refs 58, 63) and [HFe(CO)₄][–] (see Refs 71–74) are used as nucleophiles, the reactions with diorganyl ditellurides result in the synthesis of the anionic tellurium-containing complexes **36a**, **47a,b**,^{58,63} and **48**,^{71–74} the yields of the complexes being higher than 90%. The reactions occur under mild conditions (THF, room temperature) at a reactant molar ratio of 1:1. Dimethyl ditelluride reacts with [Mn(CO)₅][–] similarly to diphenyl ditelluride but the reaction occurs more slowly. The formation of an intermediate complex of the type **36b** was judged only by the IR spectra of the reaction mixture; the reaction with dimethyl ditelluride yields the complex **34b** as the final product.⁶³



X = PPN: R = Ph (**36a**), Me (**47a**); X = Na-18-C-6, R = Ph (**47b**).



The complexes **36a**, **47a,b**, and **48** are crystalline compounds, stable in the absence of air and readily soluble in polar solvents.

The molecular and crystal structures of the complexes **47b**⁶³ and **48**⁷² were studied by X-ray diffraction analysis. The crystal lattice of the former compound contains separate [Na⁺ 18-C-6 · 2 THF] cations and *cis*-[Mn(CO)₄(TePh)₂][–] anions. As was to be expected, the manganese ion has an octahedral configuration of bonds; the average Mn–Te bond length is 2.673 Å.

The complex **48**⁷² has a trigonal-bipyramidal configuration of bonds about the Fe atom; the TePh group occupies the axial position. The Fe–Te bond length is 2.630 Å. The Fe–CO_{ax} bond (1.83 Å) is substantially longer than the Fe–CO_{eq} bond (1.73 Å).

The transformation of the compounds **36a** and **47a** on refluxing in a THF solution and the transformation of the complex **47b** at room temperature afford the complexes **34a,b** and **49** in high yields.⁶³

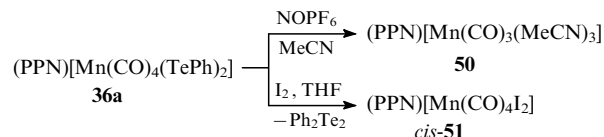


X = PPN: R = Ph (**34a**), Me (**34b**); X = Na-18-C-6, R = Ph (**49**).

According to X-ray diffraction data,⁶³ the crystals of **34a,b** consist of discrete cations and anions with slightly distorted octahedral configurations of bonds about each manganese atom (three bridging RTe ligands and three terminal carbonyl groups). The Mn–Te bond lengths are 2.674 Å in **34a** and 2.688 Å in **34b**.⁶³

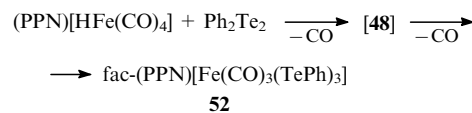
It is noteworthy that the Mn–Te bond in the neutral binuclear triply bridged compound **27** (2.638 Å)⁵³ is on the average somewhat shorter than the corresponding bonds in the anionic complexes **34a,b**. The Mn–Te–Mn bond angles (average values) are also appreciably different; in the neutral derivative **27**, this angle (70.9°)⁵³ is much smaller than those in the anionic complexes **34a** and **34b** (82.8° and 81.0°, respectively).⁶³

The complex **36a** is detellurated upon the reaction with iodine⁵⁸ or NOPF₆ in acetonitrile⁶³ to give complexes **50** and *cis*-**51**.



The reaction of the complex **34a** with Ph₃C⁺ BF₄[–] giving rise to the complex **24f**⁶³ and the reaction of the complex **36a** with pentacarbonyl(bromo)manganese giving a mixture of **24f** and **35**⁵⁸ have been described previously.

The anionic iron complex **52**, containing three terminal PhTe groups, is formed in the reaction of the anionic iron carbonyl derivative with two moles of Ph₂Te₂ in THF at room temperature.⁷¹ The reaction rate markedly increases when the amount of Ph₂Te₂ in the reaction mixture increases. The complex **48** is formed as the intermediate compound.

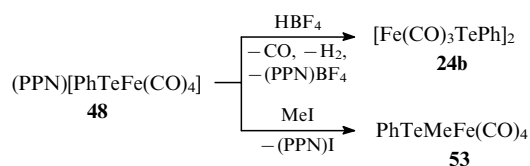


It should be noted that the complex **52** is formed in the reaction of (PPN)[HFe(CO)₃PPh₃] with diphenyl ditelluride instead of the expected complex (PPN)[Fe(CO)₂PPh₃(TePh)₃], *i.e.* in this case, the triphenylphosphine ligand rather than CO is replaced.⁷¹

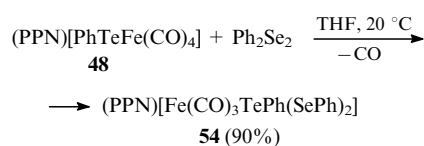
The crystal structure of the solvate **52** · 0.5THF is formed from separate cations and anions.⁷¹ The coordination polyhedron around the iron atom is a distorted octahedron with a Fe–Te bond length of 2.630 Å.

The complex **48** is a convenient starting compound for the synthesis of both new and known neutral^{72,73} and anionic

tellurium-containing metal carbonyl complexes.⁷⁴ Thus its alkylation with methyl iodide gives rise to an oily telluride complex **53**,^{72,73} while the reaction with HBF₄ affords the binuclear compound **24b**, described above.⁷²

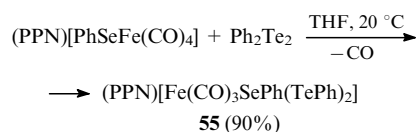


It follows from published data^{71,74} that the complex **48** undergoes oxidative addition to diphenyl ditelluride to give the complex **52**. The reaction of the complex **48** with Ph₂Se₂ follows a similar pattern and gives rise to complex **54**.⁷⁴ Diphenyl disulfide does not react with **48**.



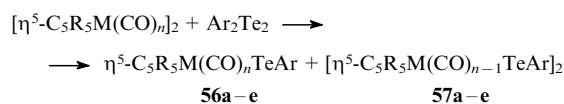
Thus, the ability of diphenyl chalcogenides to enter into oxidative addition reactions with the complex **48** decreases in the sequence Ph₂Te₂ > Ph₂Se₂ > Ph₂S₂ due to the decrease in the nucleophilicity of the chalcogens.

Complex **55**, in which the ratio of PhTe to PhSe groups is the opposite to that in the complex **54**, was prepared by the reaction of the selenium analogue of the complex **48** with diphenyl ditelluride.⁷⁴



The molecular and crystal structures of the complexes **54** and **55** were studied by X-ray diffraction analysis.⁷⁴

The reactions of diaryl ditellurides with metal cyclopentadienyl carbonyls are mostly accompanied by rupture of the Te–Te bonds and give complexes containing terminal or bridging ArTe ligands. Depending on the conditions (temperature, solvent, the presence or absence of UV radiation), the reactions of diaryl ditellurides with molybdenum,^{75–77} chromium⁷⁸ and iron^{79,80} cyclopentadienyl carbonyls give rise to complexes of four types. Under relatively mild conditions (room temperature or short-term refluxing in benzene), mononuclear complexes **56** with terminal ArTe ligands are formed.



Compound 56	<i>n</i>	R	M	Ar	Ref.
a	3	H	Mo	Ph	75
b	3	H	Cr	Ph	78
c	3	Me	Mo	Ph	76
d	2	H	Fe	Ph	79
e	2	H	Fe	4-EtOC ₆ H ₄	80

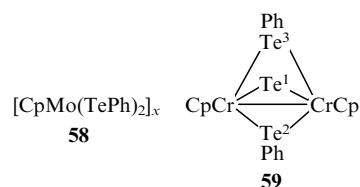
An X-ray diffraction study showed that the Te–C and Te–Cr bond lengths in the complex **56b** are 2.117 and 2.763 Å, respectively; the C–Te–Cr bond angle is 105.4°.⁷⁸

In some cases, in addition to the complexes **56**, binuclear complexes **57** with bridging ArTe groups were also isolated. They become the major products when the reaction is carried out under more drastic conditions (many-hour heating in toluene at 60 °C or under reflux for chromium and molybdenum complexes or

refluxing in benzene for iron compounds). The complexes **57** can also be obtained on heating or exposure to UV radiation of solutions of the compounds **56**.

The complex **57a** is formed in 50% yield when [CpMo(CO)₂]₂ is made to react with diphenyl ditelluride in toluene at room temperature.⁷⁷

Refluxing of bis(tricarbonylcyclopentadienyl)molybdenum with diphenyl ditelluride in xylene results in the formation of completely decarbonylated complex **58**.⁷⁵ When bis(tricarbonylcyclopentadienyl)chromium reacts with diphenyl ditelluride in toluene at 80 °C, complex [CpCr(TePh)₂]₂Te **59**, containing three telluride bridges, is produced.⁷⁸



It should be noted that the reaction of tricarbonyl(cyclopentadienyl)molybdenum with diphenyl diselenide occurs under milder conditions than that with diphenyl ditelluride.⁷⁵ In this case, the complexes CpMo(CO)₃SePh and [CpMo(SePh)₂]_x were isolated, although judging by the IR spectra, the solution contained the selenium analogue of the complex **57**. The reaction with diphenyl disulfide gave the completely decarbonylated complex of the type **58** as the only product.⁷⁵ Thus, the capability of ArE groups (E = S, Te, Se) of stabilising mono- and binuclear complexes decreases in the series Te > Se > S.⁷⁵ The same series of the stability of complexes as a function of the chalcogen nature holds for iron mononuclear complexes **56**.⁷⁹

Several geometric isomers are possible for the complexes **57a,c**. However, the ¹H NMR spectrum of the complex **57a** contains only one set of signals of cyclopentadienyl protons, indicating that only one isomer is present in the solution.⁷⁵ The binuclear complexes of iron **57d,e** can exist as five geometric isomers (A–E, Fig. 2).

Judging by the ¹H NMR spectra, the complex **57d** exists in solution as a mixture of two isomers; the attempts to separate the mixture into components failed.⁷⁹

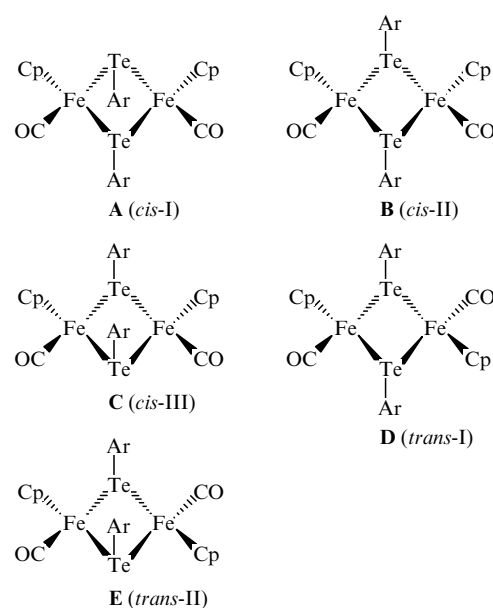


Figure 2. Geometric isomers of the complexes **57d,e**. The given nomenclature is proposed in Ref. 80.

In the case of **57e**, crystals of two isomers (**A** and **D**, see Fig. 2) have been isolated in < 5% yields.⁸⁰ The molecular structures of these isomers were studied by X-ray diffraction analysis.⁸⁰ Both isomers contain Fe₂Te₂ rings, which are slightly bent along the axis connecting the iron atoms. The Te–Fe bond lengths (average) are 2.541 Å for isomer **A** and 2.547 Å for isomer **D**; the Fe–Te–Fe angles are 82.88° and 94.16°, respectively. The environments of the iron and tellurium atoms in both isomers are approximately the same. Each iron atom is situated at the centre of a distorted tetrahedron and the tellurium atoms are at a vertex of a trigonal pyramid. The difference between the isomers is that identical substituents (cyclopentadienyl, *p*-ethoxyphenyl, and carbonyl groups) in isomer **A** (Ar = *p*-EtOC₆H₄) occupy *cis*-positions with respect to each other, whereas in isomer **D** (Ar = *p*-EtOC₆H₄), they are *trans*-arranged. According to a proposed nomenclature,⁸⁰ the former compound is defined as the *cis*-I isomer and the latter one is referred to as *trans*-I.

The molecular structures of binuclear molybdenum (**57a**)⁸¹ and chromium (**57b**)⁷⁸ complexes have also been studied by X-ray diffraction analysis.

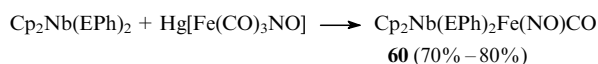
The structure of the complexes **57a,b** is close to the structure of the corresponding sulfur derivatives. Both compounds incorporate non-planar four-membered M₂Te₂ rings with Mo–Te distances of 2.822 Å and Cr–Te distances of 2.721 Å. The Te–Mo–Te and Mo–Te–Mo bond angles are 70.18° and 97.05°, respectively, and Te–Cr–Te and Cr–Te–Cr, are 70.39° and 98.12°. The Te–Te distance in the complex **57a** is 3.24 Å, while that in **57b** is 3.14 Å. Taking into account the fact that the sum of the van der Waals radii of tellurium atoms is 4.4 Å,⁸² it can be considered that there exist weak bonds between the tellurium atoms in these complexes. In the molybdenum complex **57a**, the phenyl groups, the cyclopentadienyl rings, and the carbonyl groups occupy *trans*-positions with respect to each other.⁸¹

The bond lengths and bond angles in compound **59** (X-ray diffraction data⁷⁸) are listed in Table 6.

Table 6. Average bond lengths and angles in the complex **59**.⁷⁸

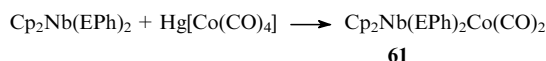
Bond	Length/ Å	Bond angle	Size/ deg
Te ² –C	2.15	Cr–Te ¹ –Cr	68.47
Te ³ –C	2.13	Cr–Te ² –Cr	67.06
Te ¹ –Cr	2.609	Cr–Te ³ –Cr	67.34
Te ² –Cr	2.65		
Te ³ –Cr	2.647		

The heteronuclear cyclopentadienyl carbonyl complexes **60** and **61** with bridging PhE ligands (E = S, Se, Te) have been synthesised by the reaction of bis(phenylchalcogeno)niobocenes with nitrosyl carbonyl mercury complexes.⁸³



E = S, Se, Te.

Niobium-and-cobalt-containing complexes **61** were prepared according to the following scheme:



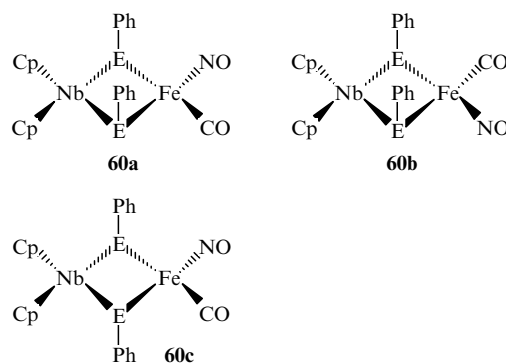
E = S, Se, Te.

The rate of formation of the complexes **60** and **61** increases in the sequence S < Se < Te, which was attributed⁸³ to the increase in the nucleophilicity of chalcogens in the same series.

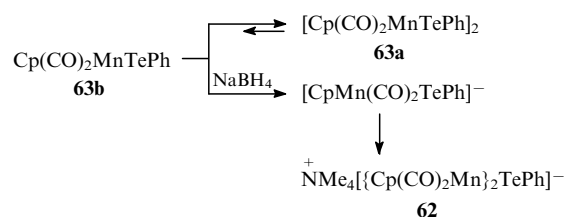
The complexes **60** and **61** are more stable than the initial cyclopentadienyl derivatives of niobium. They are stable in DMSO solutions under an inert atmosphere but rapidly decompose in air.⁸³

The IR spectra of the complexes **60** exhibit bands at 1610 (NO) and 1840 cm^{–1} (C=O). The complexes **61** are characterised by

two bands, 1850 and 1910 cm^{–1}. The ¹H NMR spectra of the compounds **61** (E = Se, Te)[‡] contain three singlets for the cyclopentadienyl protons, which was explained by *cis*–*trans* isomerism. The ¹H NMR spectra of the complexes **60** exhibit six singlets due to the cyclopentadienyl protons, which correspond to two *cis*- (**60a,b**) and one *trans*-isomer (**60c**).⁸³

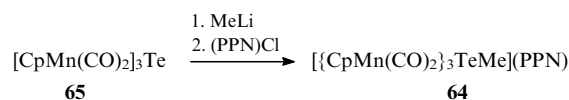


Apart from the neutral complexes described above, which contain bridging and terminal RTe groups, several anionic and cationic cyclopentadienyl carbonyl complexes with organyl telluride ligands have been synthesised. Thus anionic complex **62** is formed when paramagnetic monomeric complex **63b**, which occurs in solution in equilibrium with diamagnetic dimer **63a**, is reduced by sodium borohydride.⁸⁴

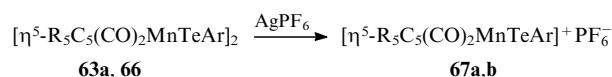


The coordination polyhedron around the tellurium atom in the complex **62** is a pseudo-tetrahedron, the Mn–Te bond length being 2.556 Å.⁸⁴

Anionic complex **64**, containing a bridging MeTe ligand, is formed in 85% yield when complex **65**⁸⁵ is made to react with methyllithium.^{86, 87}



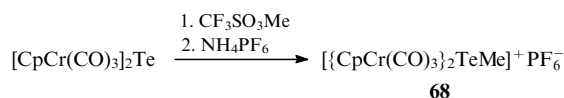
Oxidation of neutral cyclopentadienyl carbonyl complexes **63a** and **66** by silver hexafluorophosphate has given rise to cationic complexes **67a**⁸⁴ and **67b** (yield 56%).⁸⁸ In the cation **67a**, the tellurium atom forms a pyramidal configuration of bonds; the Mn–Te bond length is 2.513 Å.⁸⁴



R = H, Ar = Ph (**63a**, **67a**); R = Me, Ar = Mes (**66**, **67b**).

Cationic chromium complex **68** has been prepared in a nearly quantitative yield by methylation of the corresponding neutral complex with methyl trifluoromethanesulfonate followed by treatment of the reaction mixture with NH₄PF₆.⁸⁶

[‡] The spectrum of the sulfur analogue could not be recorded due to its low solubility.



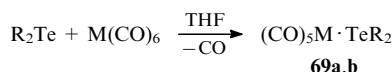
III. Complexes with organic derivatives of dicoordinated tellurium

This Section surveys data on the synthesis, structure and reactions of carbonyl and cyclopentadienyl carbonyl complexes of transition metals containing as ligands organic derivatives of dicoordinated tellurium such as diorganyl tellurides R^1TeR^2 , tellurium-containing heterocycles, diorganyl ditellurides $\text{RTe}-\text{TeR}$ and organoelement compounds with $\text{C}-\text{Te}-\text{E}$ and $\text{E}-\text{Te}-\text{E}$ fragments (E is a Group IV or V element). For tellurols RTeH , tellurenyl halides RTeHal and tellurocyanates RTeCN , complexes of this type are unknown.

1. Complexes of diorganyl tellurides

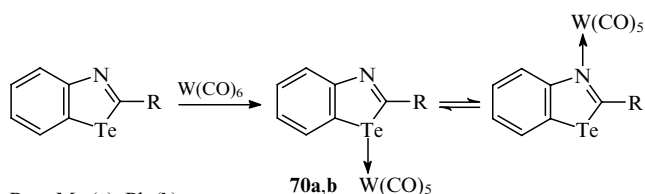
Several types of complexes of metal carbonyls and cyclopentadienyl carbonyls with acyclic (tellurium-containing heterocycles) diorganyl tellurides have been obtained.

Thus heating or UV irradiation of solutions of diorganyl tellurides and hexacarbonyls of Group VI metals [or complexes $(\text{CO})_5\text{M} \cdot \text{THF}$, which can be readily prepared from them] results in the formation of pentacarbonyl complexes **69a**,⁸⁹ **70a,b**⁹⁰ and **69b**.⁹¹



M = Cr, R = 2-Me₂NCH₂C₆H₄ (**a**);

M = W, R = 2,4,4-tris(trimethylsilyl)cyclopenta-2,5-dien-1-yl (**b**).

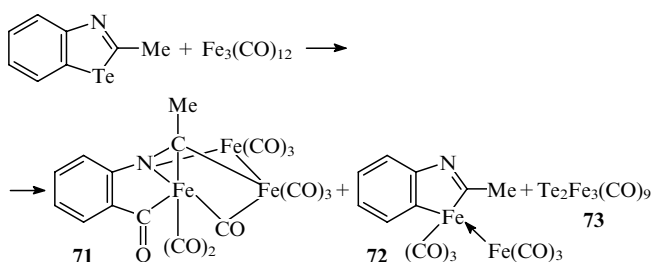


R = Me (**a**), Ph (**b**).

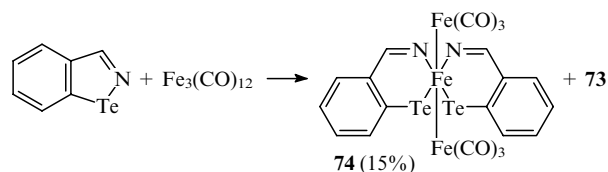
The structure of the complexes **69a,b** was proved by X-ray diffraction analysis.^{90,91} However, in another study,⁹² the product of reaction between chromium hexacarbonyl and dimethyl telluride was identified as $[\text{Cr}(\text{CO})_5]_2\text{TeMe}_2$ (IR spectroscopy and elemental analysis data).

The results obtained by ¹H NMR spectroscopy indicate that in solutions of the compounds **70a,b** [in C₆D₆ or (CD₃)₂CO], an equilibrium between Te- and N-centered complexes exists, as in the case of metal carbonyl complexes of benzothiazoles and benzoselenazoles.⁹³

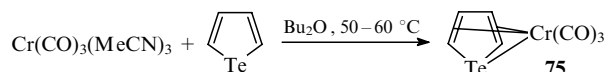
When examining the formation of benzotellurazole complexes of the type **70**, one can follow the influence of the nature of the metal carbonyl on the structure of the final product, which has been repeatedly noted for other ligands. Thus the reaction of 2-methylbenzotellurazole with Fe₃(CO)₁₂ in boiling toluene gives rise to a mixture, formed in a low yield (6%–13%), of detellurated complexes **71** and **72** and tellurium-containing cluster **73**.⁹⁴



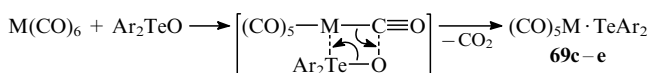
The reaction of benzoisotellurazole with Fe₃(CO)₁₂ is also accompanied by the destruction of the heterocycle and gives complex **74** and the cluster **73**.⁹⁴



Whereas in **69a,b** and **70a,b** the metal is coordinated only by the tellurium atom, the reaction of tellurophene, possessing heteroaromatic properties, with the chromium acetonitrile complex affords a different type of product, namely, π -complex **75** (yield 80%).⁹⁵ Similar complexes are formed with thiophene and selenophene.⁹⁵

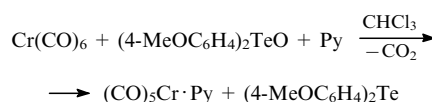


Recently,^{96,97} a new approach to the synthesis of the complexes **69c–e** has been proposed, which is based on the reaction of metal hexacarbonyls with diaryl telluroxides in THF. Presumably,⁹⁷ the reaction occurs *via* a four-membered transition state.



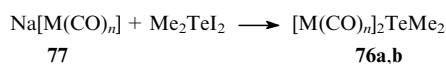
Compound 69	Ar	M	Yield (%)	Ref.
c	4-MeOC ₆ H ₄	Cr	50	96
d	4-MeOC ₆ H ₄	Mo	42	97
e	4-MeOC ₆ H ₄	W	29	97

It should be noted that in the presence of pyridine, chromium hexacarbonyl reacts with di(4-methoxyphenyl) telluroxide to give the corresponding telluride and a complex of pyridine with chromium pentacarbonyl.⁹⁶



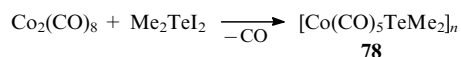
The reaction of hexacarbonyls of Group VI metals and iron pentacarbonyl with organoelement oxides R_nEO ($n = 2, 3$; E = Se, Te, As, Sb) is a fairly general process. It has been reported⁹⁶ that the reactions of chromium hexacarbonyl with the oxides obey second-order kinetics and that their relative rates decrease in the sequence $\text{TeO} > \text{SeO} > \text{SbO} > \text{AsO}$. Meanwhile, the least basic compounds among Group V and VI element oxides — triphenylphosphine oxide and diphenyl sulfoxide — do not react with hexacarbonyls of chromium group metals at all. It has been shown⁹⁷ that the rates of reactions of di(4-methoxyphenyl) telluroxide with metal hexacarbonyls $\text{M}(\text{CO})_6$ decrease in the series $\text{W} > \text{Mo} > \text{Cr}$ (the relative rates are 9.4, 4.4 and 1.0, respectively).

It follows from the above data that in order to prepare complexes of the type **69**, metal carbonyls should be made to react with diorganyl tellurides. Diorganyl tellurides can arise as intermediates in the reactions of metal hexacarbonyls with other organotellurium compounds and then react with excess metal hexacarbonyls, present in the reaction mixture, to give complexes of the type **69**. This idea has been confirmed by the synthesis of complexes **76a,b**, containing a dimethyl telluride ligand, from an organic compound containing tetracoordinated tellurium (dimethyltellurium diiodide) and salts **77**.⁹⁸ However, these complexes exist only in solution and rapidly decompose when the solvent is removed *in vacuo*.⁹⁸

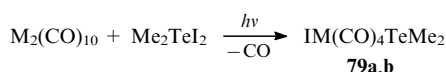


M = Co, $n = 4$ (**a**); M = Mn, $n = 5$ (**b**).

The vigorous reaction of octacarbonyldicobalt with dimethyltellurium diiodide affords polymeric complex **78**.⁹⁸ However, the mechanism of this reaction is unknown.

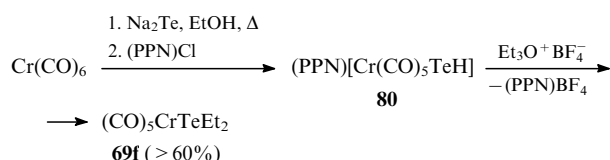


It is of interest that the photoinduced reaction of Me_2TeI_2 with decacarbonyl-dimanganese and -dirhenium affords iodo carbonyls **79** in 60%–80% yields.⁹⁸

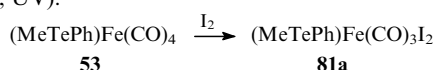


M = Mn (**a**), Re (**b**).

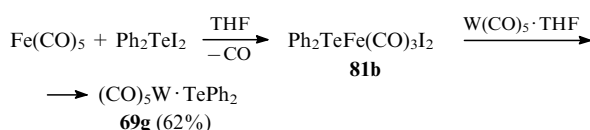
The chromium complex **69f** has been synthesised using a specific method for the synthesis of diethyl telluride derivatives, namely, alkylation of anionic complex **80** with triethyloxonium tetrafluoroborate.⁹⁹



Another example in which alkylation has been used to prepare telluride complexes — the synthesis of the complex **53**^{72, 73} — is described in Section II.3. On treatment with iodine, the complex **53** is oxidised to give halo carbonyl complex **81a** (yield 94%), which was characterised by spectroscopy (¹H NMR, ¹³C NMR, IR, UV).⁷³



The diphenyl analogue of the compound **81a** — complex **81b** — has been synthesised from diphenyltellurium diiodide. This complex reacts with $(\text{CO})_5\text{W} \cdot \text{THF}$ to give the diphenyl telluride derivative **69g**.⁷³ The mechanism of formation of this product and the structures of other reaction products have not yet been elucidated.

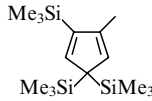
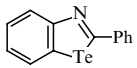


The molecular and crystal structures of the complexes **69a–c,g** and **70b** were studied by X-ray diffraction analysis. The most important bond lengths and bond angles are listed in Table 7.

The coordination polyhedron about the metal atom in all the studied complexes is a distorted octahedron; the tellurium atom normally has a pyramidal environment. The secondary intramolecular coordination N → Te, occurring in the free ligand, is retained in the structure **69a**.⁸⁹ The N–Te distance (3.096 Å) in **69a** coincides almost completely with the average N–Te distance in the ligand.

In the complex **70b**, formed by a bidentate tellurium-containing heterocycle, 2-phenylbenzotellurazole, with tungsten hexacarbonyl, of the two possible sites of coordination, namely, the ‘hard’ nitrogen atom and the ‘soft’ tellurium atom, it is the latter that is involved in coordination with tungsten, in conformity with the principle of hard and soft acid and bases (see Table 7).¹⁰⁰ In all probability, the complex **70b** is the first structurally characterised

Table 7. Bond lengths and bond angles in the complexes $(\text{CO})_5\text{M} \cdot \text{TeR}_2$.

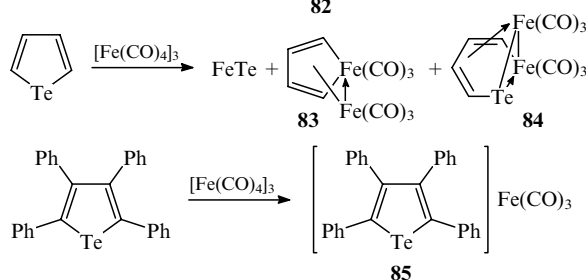
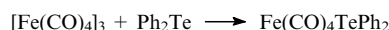
Com- po- und	M	R	Bond lengths / Å		C–Te–C bond angle / deg	Ref.
			M–Te	C–Te ^a		
69a	Cr	2-Me ₂ NCH ₂ C ₆ H ₄	2.667	2.133	97.2	89
69b	W		2.839	2.139	98.5	91
69c	Cr	4-MeOC ₆ H ₄	2.684	2.131	95.5	97
69g	W	Ph	2.809	2.125	94.8	73
70b	W		2.809	2.17	78.0	90

^a The average bond lengths and angles are given.

complex of a benzochalcogenazole with chalcogen–metal coordination.

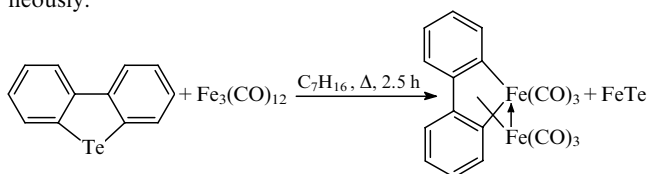
The reactions of binuclear and trinuclear metal carbonyls with diorganyl tellurides give different products, depending on the nature of the substrate. The reaction of $\text{Mn}_2(\text{CO})_{10}$ with diphenyl telluride, accompanied by rupture of the C–Te bond and yielding the complex **24f** with bridging PhTe ligands,⁴⁸ has been described above (see Section II.3). The reaction of the trinuclear complex $\text{Fe}_3(\text{CO})_{12}$ with the same telluride gives complex **82** in a moderate yield (25%).⁴⁸

When dodecacarbonyltriiron is made to react with tellurophene in benzene, a mixture of FeTe, ferrole **83** and complex **84** is formed.¹⁰¹ Based on the mass spectra [molecular ion peak with $m/z = 459$ and peaks due to ions with $m/z = 459 - 28n$ ($n = 0 - 6$)] and the IR spectra (absorption bands for three terminal carbonyl groups in the range 1995–2064 cm^{-1}), a metallocene structure was ascribed to **84**.¹⁰¹ Tetraphenyltellurophene reacts with $\text{Fe}_3(\text{CO})_{12}$ to give complex **85** in a low yield.¹⁰²



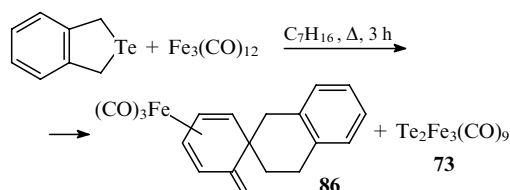
According to the data of McWhinnie *et al.*,¹⁰¹ when conditions of the reaction of tellurophene with $\text{Fe}_3(\text{CO})_{12}$ are changed (refluxing in heptane, 2.5 h), this reaction yields ferrole **83** (45%) and FeTe, which appears to arise upon elimination of CO and $\text{Fe}(\text{CO})_5$ molecules from ferrole **83**.

Under the same conditions, dibenzotellurophene is converted into dibenzoferrole in 28% yield, FeTe being formed simultaneously.¹⁰¹

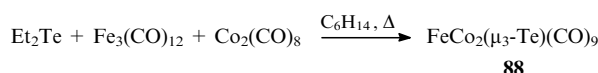
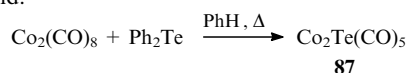


The reaction of telluroindan follows a different route. Refluxing a mixture of telluroindan with $\text{Fe}_3(\text{CO})_{12}$ gives rise to new

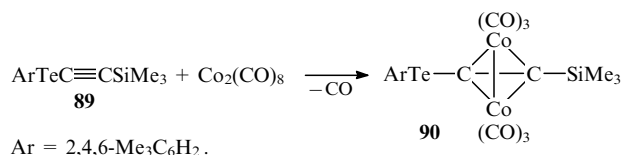
complex **86** (yield 15%) and the cluster **73**. The structure of the compound **86** was confirmed by X-ray diffraction analysis.¹⁰¹



The reaction of $\text{Co}_2(\text{CO})_8$ with diphenyl telluride is accompanied by rupture of both C–Te bonds, binuclear complex **87** being the final reaction product.⁴⁸ Heating of a mixture of diethyl telluride, $\text{Co}_2(\text{CO})_8$ and $\text{Fe}_3(\text{CO})_{12}$ affords cluster **88** in 30% yield.¹⁰³



Aryl ethynyl telluride **89** reacts with octacarbonyldicobalt in a different way.¹⁰⁴ The reaction carried out in a 1:1 pentane–toluene mixture at 25 °C gives complex **90** in 45% yield. According to X-ray diffraction data,¹⁰⁴ in this complex, as in other alkynyl complexes, the cobalt atom is coordinated to the multiple-bond carbon atoms rather than to tellurium.

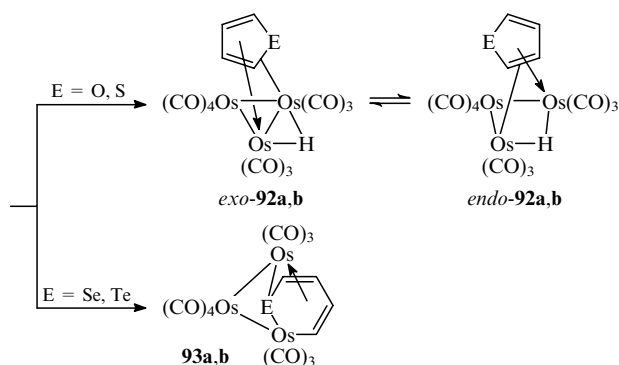
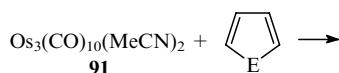


The lengths of the Co–Co, C–C, Ar–Te and C–Te bonds in the complex **90** are 2.465, 1.31, 2.311 and 2.066 Å, respectively.¹⁰⁴

The reaction of nickel carbonyl with diphenyl telluride, unlike the reactions of manganese and cobalt carbonyls, is accompanied by complete dearylation and decarbonylation, tellurium and nickel being the only reaction products.⁴⁸ It is noteworthy that nickel carbonyl reacts with derivatives of tetracoordinated tellurium, ArTeCl_3 and Ar_2TeCl_2 , to give (after hydrolysis of the reaction mixture) carboxylic acids.¹⁰⁵

The structure of complexes resulting from the reaction of the osmium carbonyl cluster **91** with five-membered aromatic heterocycles is determined by the nature of the heteroatom.^{106, 107} Thus when the complex **91** reacts with furan¹⁰⁷ or thiophene,¹⁰⁶ the corresponding hydrido furyl (**92a**) or hydrido thienyl (**92b**) complex is obtained. The complexes **92a, b** have similar spectral characteristics. According to the X-ray diffraction data obtained for **92a**,¹⁰⁷ the heterocyclic fragments in these compounds act as μ, η^1, η^2 -vinylid ligands. The ¹H NMR spectra imply that the thiophene complex **92b** exists in solution at –55 °C as a mixture of *exo*- and *endo*-isomers (ratio 4:1), which undergo fast interconversion at room temperature.¹⁰⁶

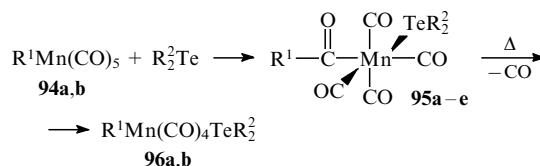
The reactions of the complex **91** with selenophene and tellurophene in cyclohexane give rise to complexes **93a, b**.¹⁰⁶ The spectral characteristics of these compounds are close to each other but sharply differ from those of the complexes **92**. The X-ray diffraction data obtained for the selenophene complex **93a** indicate that it has resulted from insertion of the Os atom into the Se–C rather than C–H bond.¹⁰⁶



E = O (**92a**, 46%), S (**92b**, 57%), Se (**93a**, 20%), Te (**93b**, 35%).

Carbonyl-containing complexes of various types are also formed in the reactions of diorganyl tellurides with alkyl and acyl manganese carbonyls and manganese, rhenium, ruthenium, rhodium and iridium halo carbonyls.

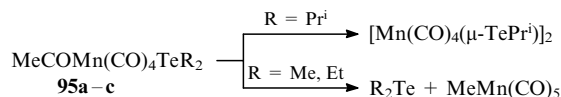
The reactions of pentacarbonyl(methyl)manganese **94a** with dialkyl tellurides in THF at room temperature occur in the same way as reactions with other Lewis bases, giving rise to (acetyl)tetra-carbonyl(dialkyl telluride)manganes **95a–c** in yields of more than 80%.¹⁰⁸ The reaction with diisopropyl telluride occurs very slowly; the complex **95c** has not been isolated in an analytically pure state. When dialkyl tellurides are made to react with benzyl(pentacarbonyl)manganese **94b**, the complexes **95d, e** are formed together with substantial amounts of decarbonylated products **96**. Thus the reaction of **94b** with dimethyl telluride affords an unseparable mixture consisting of the initial carbonyl (10%), the complex **95d** (80%) and the corresponding decarbonylated product **96a** (10%). The reaction of **94b** with diethyl telluride in boiling pentane yields the decarbonylated complex **96b** as the only product.¹⁰⁸



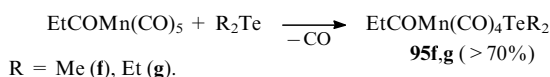
Compound	94a	94b	95a	95b	95c	95d	95e	96a	96b
R ¹	Me	Bn	Me	Me	Me	Bn	Bn	Bn	Bn
R ²			Me	Et	Pr ⁱ	Me	Et	Me	Et

¹H and ¹²⁵Te NMR spectra (singlets in the region of 153.0 to 688.6 ppm) and IR spectra indicate that the complexes **95a–e** exist in solutions as single isomers with *cis*-arrangement of the acetyl and dialkyl telluride ligands.¹⁰⁸

The complexes **95a–e** decompose when distilled *in vacuo* (0.5 mm Hg, 40–70 °C), the reaction pathway depending on the nature of the substituent at the tellurium atom.¹⁰⁸

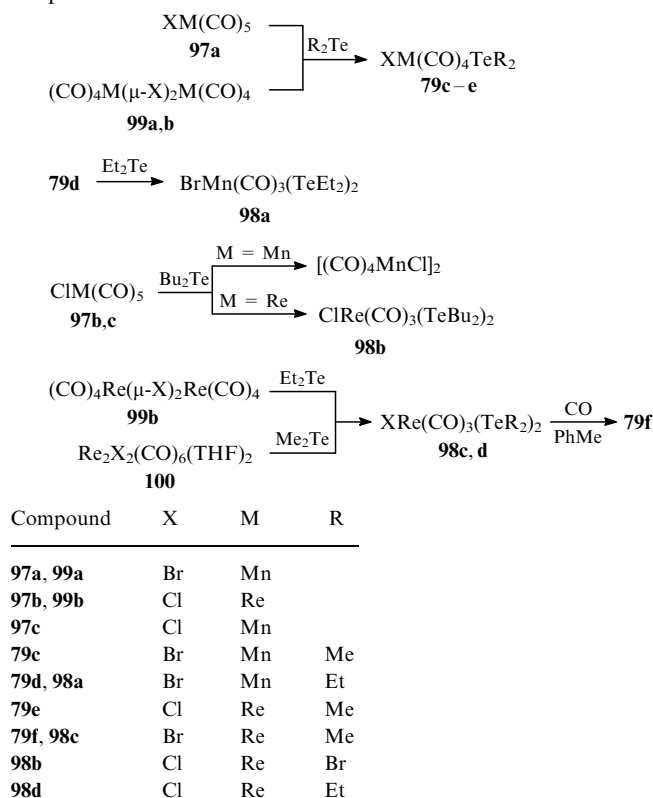


The complexes **95f, g** have been synthesised by the reaction of pentacarbonyl(propionyl)manganese with dialkyl tellurides.¹⁰⁸



The reductive thermolysis of the complexes **95b, c, g** under a hydrogen atmosphere at 200 °C yields films containing manganese and tellurium.¹⁰⁸

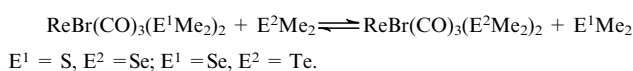
The reactions of manganese^{48, 108–111} and rhenium^{111–113} halo carbonyls with dialkyl and diaryl tellurides have been studied. Dimethyl and diethyl tellurides react with bromo(pentacarbonyl)manganese **97a** giving rise to dialkyl telluride complexes **79c,d**, their yields exceeding 80%.¹⁰⁸ The reaction of pentacarbonylchloromanganese **97b** with dibutyl telluride affords the binuclear complex $[(\text{CO})_4\text{MnCl}]_2$.⁴⁸ When the complex **79d** is treated with a second mole of diethyl telluride, it is converted into bis(diethyl telluride) complex **98a**.¹⁰⁸ Compounds of this type are formed as the only products in reactions of diphenyl telluride^{48, 109, 110} and phenoxatellurine⁴⁸ with manganese⁴⁸ and rhenium¹¹¹ halo carbonyls. The complex **98b** also arises in the reaction of pentacarbonylchlororhenium **97c** with dibutyl telluride,¹¹² i.e. the rhenium and manganese compounds react in different ways. Evidently, this implies that the rhenium complexes **98** are more stable than the corresponding manganese analogues. Rhenium bis(dialkyl telluride) complexes **98c,d** were prepared by the reaction of di- μ -chlorobis[tetracarbonyl-rhenium(I)] **99b** with diethyl telluride under drastic conditions¹¹³ and by the reaction of complex **100** with dimethyl telluride at room temperature.¹¹¹



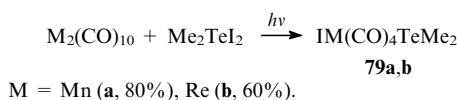
The reaction of the binuclear rhenium complex **99b** with dimethyl telluride¹¹³ gives the complexes **79e**, while the reaction of the similar manganese complex **99a** with dimethyl telluride performed under relatively mild conditions affords the complex **79c**. When carbon monoxide is passed through a toluene solution of the complex **98c** at room temperature, the complex **79f** is produced.¹¹¹

The rhenium complexes **79e,f** are much more stable than the manganese analogues. Thus it has been found¹⁰⁸ that the manganese complex **79c** exists only in solution, the attempted isolation resulting in its complete decomposition.

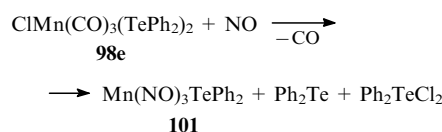
Study of the dimethyl chalcogenide ligand exchange in the rhenium complexes **98**¹¹¹ shows that the equilibrium in these reactions is shifted towards the formation of complexes containing heavier chalcogen atoms.¹¹¹



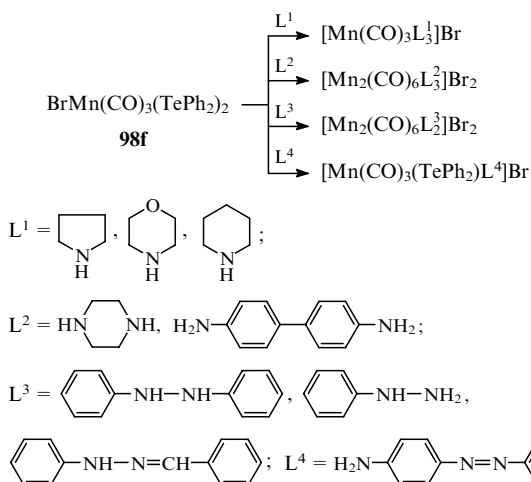
A new pathway to the iodo carbonyl complexes **79a,b** is based on the reaction of decacarbonyl-dimanganese and -dirhenium with dimethyltellurium diiodide.⁹⁸ The compounds **79a,b** were isolated by sublimation *in vacuo* at 60 °C. The reactions of other dialkyltellurium dihalides with the manganese and rhenium carbonyls have not been studied.



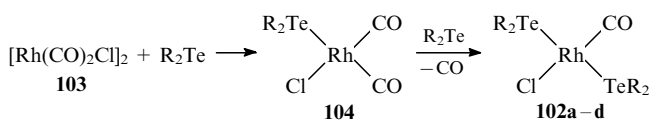
Passing NO through a benzene solution of the complex **98e** gives the nitrosyl complex **101**, which, however, has not been isolated in an analytically pure state.⁴⁸



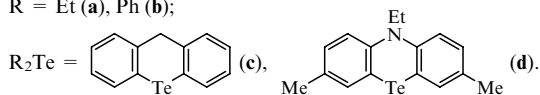
The reaction of the manganese complex **98f** with nitrogen-containing ligands results in the replacement of either or both diphenyl telluride ligands, depending on the nature of the reagent used.¹¹⁰



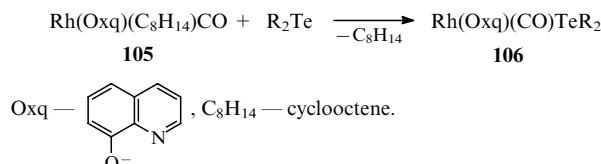
Both Rh(I)- and Rh(III)-containing complexes have been synthesised from rhodium halo carbonyls. Compounds of the former type (**102a–d**) were prepared by the reaction of di- μ -chlorobis[dicarbonylrhodium(I)] **103** with diorganyl tellurides,^{69, 114} including tellurium-containing heterocycles,¹¹⁵ at room temperature in pentane, hexane or toluene. According to IR spectroscopy, after the isolation of the complex with telluroxanthene **102c** (ν_{CO} 1967 cm^{-1}), the mother liquor contains the intermediate dicarbonyl complex **104** (ν_{CO} 2080, 2033 cm^{-1}), which has resulted from cleavage of the chloride bridges in the complex **103** by the tellurium-containing ligand.¹¹⁵



$\text{R} = \text{Et (a), Ph (b)};$

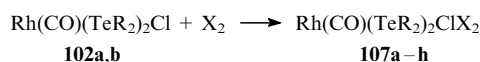


The reactions of $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ with tellurium-containing ligands generally resemble its reactions with triorganylphosphines. However, tellurium-containing ligands, in particular, telluroxanthene and 3,7-dimethyl-*N*-ethylphenotellurazine, are weaker donors than phosphines. Indeed, $\text{Rh}(\text{acac})(\text{CO})_2$ readily reacts with triphenylphosphine at room temperature to give $\text{Rh}(\text{acac})(\text{CO})\text{PPh}_3$ ^{116, 117} but does not react with telluroxanthene even at 80 °C.¹¹⁵ However, telluroxanthene and 3,7-dimethyl-*N*-ethylphenotellurazine replace the alkene ligand in the rhodium complex **105**, giving rise to complexes **106** with *trans*-arrangement of organic ligands.¹¹⁵

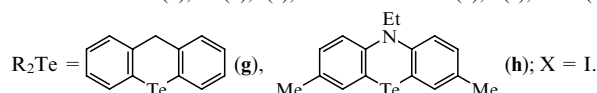


The weaker donor properties of diorganyl tellurides compared to those of tertiary phosphines account for the fact that telluride ligands in the complexes **102c,d** and **106** are readily substituted by triphenyl- and tributylphosphines.¹¹⁵

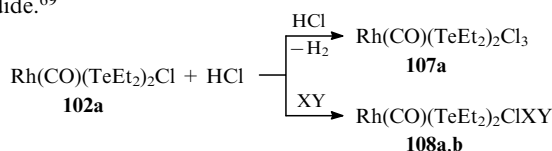
The rhodium carbonyl complexes **102a,b** undergo fast oxidative addition of halogens and thiocyanogen to give octahedral $\text{Rh}(\text{III})$ complexes **107a–c**,¹¹⁴ **107d–f**⁶⁹ and **107g,h**.¹¹⁵



$\text{R} = \text{Et}$: $\text{X} = \text{Cl}$ (**a**), Br (**b**), I (**c**); $\text{R} = \text{Ph}$: $\text{X} = \text{Br}$ (**d**), I (**e**), SCN (**f**);

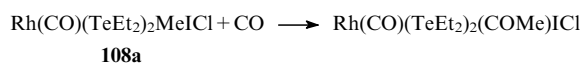


The complex **107a** was also prepared by the reaction of the diethyl ditelluride complex **102a** with hydrogen chloride;¹¹⁴ **102a** also adds several other reagents to give $\text{Rh}(\text{III})$ complexes **108a,b**.¹¹⁴ It is noteworthy that the diphenyl telluride analogue **102b**, unlike the compound **102a**, does not react with methyl iodide.⁶⁹



$\text{XY} = \text{MeI}$ (**108a**), PhSO_2Cl (**108b**).

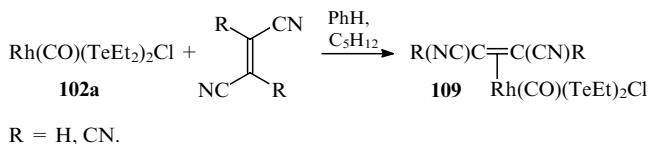
The complex **108a** easily reacts with carbon monoxide; the insertion of CO into the $\text{Rh}-\text{Me}$ bond gives rise to a rhodium(III) acyl derivative.¹¹⁴



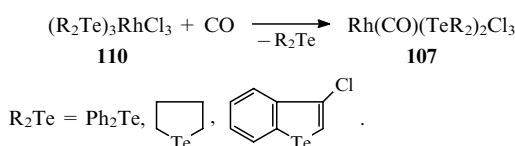
On passing from the planar rhodium(I) complexes **102** to the octahedral rhodium(III) complexes **107** and **108**, the ν_{CO} value increases by $\sim 100 \text{ cm}^{-1}$.^{69, 114, 115}

The CO stretching vibration frequencies in the spectra of the complexes **102c** ($1956, 1946 \text{ cm}^{-1}$), **102d** (1962 cm^{-1}), and the analogue of **102d** containing phenothiazine as a ligand (1966 cm^{-1})¹¹⁵ indicate that the π -donative transfer of electron density from the central atom to a carbonyl group is less significant in the complex with phenothiazine than in the complexes with telluroxanthene and tellurazine. A similar effect, although less pronounced, noted for diethyl chalcogenide complexes **102**,¹¹⁴ may be due to the enhancement of the σ -donor properties of chalcogen atoms in the series $\text{S} < \text{Se} < \text{Te}$. The substantial increase in ν_{CO} following the transition from the complexes **102c,d** to the phenothiazine complex attests that the $\text{Rh}(\text{I})-\text{S}$ bond is weaker than $\text{Rh}(\text{I})-\text{Te}$.¹¹⁵

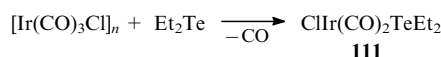
The complex **102a** not only enters into oxidative addition reactions but also reacts with tetracyanoethylene and fumaronitrile to give stable 1 : 1 adducts **109** in almost quantitative yields.¹¹⁸ In these complexes, the metal is coordinated to the double bond of the cyanoalkene. Similar complexes with acrylonitrile and cinnamitrile are not formed.¹¹⁸



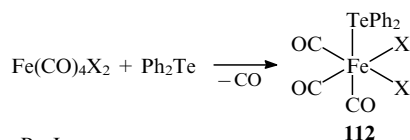
The rhodium(III) complexes **107** have also been obtained by replacement of one tellurium-containing ligand in complexes **110** by CO, which is attained by passing carbon monoxide through solutions of the complexes **110** in chloroform or toluene.^{69, 119}



Data on halo carbonyl complexes of iridium with diorganyl tellurides can scarcely be found in the literature. The only representative of this class of compound, complex **111**, has been synthesised by the reaction of polymeric iridium chloro carbonyl with diethyl telluride.¹²⁰

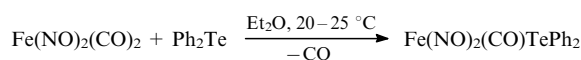


Only few representatives of complexes of diorganyl tellurides with iron⁴⁸ and ruthenium^{121, 122} halo carbonyls are known. Iron diphenyl telluride complexes **112** were prepared by substituting diphenyl telluride for one carbonyl group in tetracarbonyldihaloirons. The structure of these products was not specially studied; they were identified by analogy with other complexes.⁴⁸

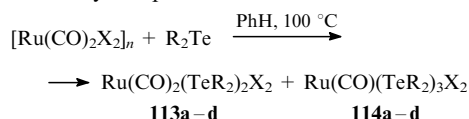


$\text{X} = \text{Br}, \text{I}$.

A mixed iron carbonyl nitrosyl complex was synthesised in a similar way.⁴⁸



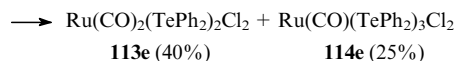
Complexes **113a–d**, containing two telluride ligands, were prepared by the reactions of polymeric ruthenium halo carbonyls with diorganyl tellurides.^{121, 122} These reactions also give small amounts of tritelluride complexes **114a–d**.¹²¹ They were not isolated in a pure state and their existence in solution was confirmed by IR spectra.



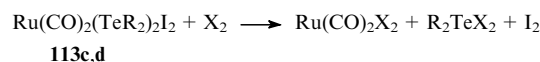
$\text{X} = \text{Br}$: $\text{R} = \text{Bu}$ (**a**), Ph (**b**); $\text{X} = \text{I}$: $\text{R} = \text{Bu}$ (**c**), Ph (**d**).

The mixture of the compounds **113e** and **114e**, resulting from the reaction of a CO-saturated alcoholic solution of $\text{RhCl}_3 \cdot \text{H}_2\text{O}$ with Ph_2Te , was successfully separated by fractional crystallisation.¹²¹



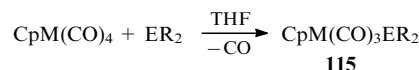


The reactions of complexes of the type **113** with halogens lead to the rupture of the Te–Ru bonds, unlike similar reactions of analogous complexes containing nitrogen and phosphorus ligands, in which less active halogens are replaced by more active ones.¹²¹



R = Bu (**c**), Ph (**d**); X = Cl, Br.

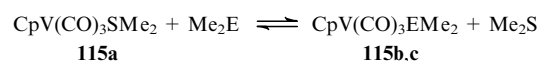
Of complexes of metal cyclopentadienyl carbonyls with diorganyl tellurides, compounds of Group V elements, vanadium^{123,124} and niobium,¹²⁵ have been described. These complexes, having the composition $\text{CpM(CO)}_3\text{TeR}_2$ **115**, are prepared by exposure of a solution of tetracarbonyl(cyclopentadienyl)-vanadium or -niobium and a large excess of a diorganyl telluride to UV or visible light. Complexes of the type **115** with other diorganyl chalcogenides have also been synthesised.



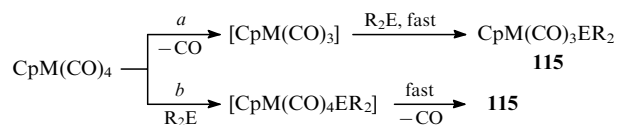
Compound 115	M	R ₂ E	Ref.
a	V	Me ₂ S	124
b	V	Me ₂ Se	124
c	V	Me ₂ Te	124
d	V	Ph ₂ S	123
e	V	Ph ₂ Se	123
f	V	Ph ₂ Te	123
g	Nb		125
h	Nb		125
i	Nb		125

When other solvents (toluene, heptane) are used instead of THF, the complexes **115g–i** substantially decompose and their yields diminish.¹²⁵ The low thermal stability of dimethyl chalcogenide complexes is the obstacle preventing large-scale preparation of these compounds.¹²⁴ Niobium complexes with tetrahydrochalcogenophenes are the most stable; they have been isolated as individual crystalline compounds. However, they are still fairly sensitive to air both in the crystalline state and especially in solutions.¹²⁵ All complexes of the type **115** tend to decompose in solution to give diorganyl chalcogenides and CpM(CO)_4 .^{124,125} The stability of the diorganyl chalcogenide complexes with the same metal increases in the series S < Se < Te.^{123–125} This stability series was attributed¹²⁵ to the increase in the σ-donor capacity on passing to heavier chalcogens. This is confirmed by IR spectra, which display a decrease in ν_{CO} in the order S > Se > Te both for the vanadium¹²⁴ and niobium¹²⁵ diorganyl chalcogenide complexes **115**.

The reaction of formation of the complexes **115a–c** is reversible, the equilibrium constant increasing in the order S < Se < Te (4.5×10^{-3} , 1.8×10^{-2} and 5.8×10^{-1} , respectively). The dimethyl sulfide ligand in the complex **115a** can be displaced by dimethyl selenide and dimethyl telluride ligands; the equilibrium constants for these reactions are 4.0 and 1.3×10^2 , respectively.¹²⁴

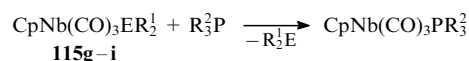


The reactions of tetracarbonyl(cyclopentadienyl)-vanadium and -niobium with diorganyl chalcogenides can occur by either dissociative (pathway *a*) or associative (pathway *b*) mechanism.¹²⁵



Kinetic measurements¹²⁵ indicate that the formation of the niobium complexes **115g–i** occurs according to both mechanisms.

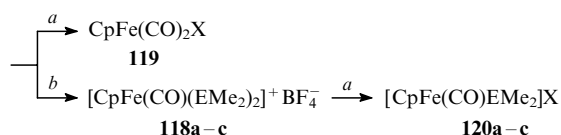
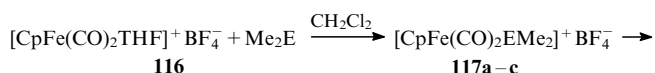
The tetrahydrochalcogenophene ligands in the complexes **115g–i** are easily replaced by various phosphine ligands.¹²⁵ The reaction rate increases in the series Te < Se < S, thus confirming the fact that on passing to heavier chalcogens, the complex stability increases, which has been repeatedly noted above.



R² = Bu, Ph, OPh.

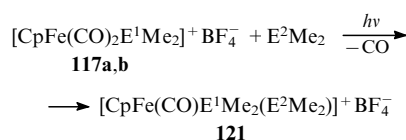
In addition to the neutral complexes of diorganyl tellurides with metal cyclopentadienyl carbonyls **115** described above, cationic cyclopentadienyl carbonyl complexes of iron^{126,127} and molybdenum¹²⁸ and anionic cyclopentadienyl carbonyl complexes of vanadium^{129,130} have been synthesised.

When dimethyl chalcogenides react with cationic complexes **116a–c** under mild conditions, they substitute the THF molecule, which results in the formation of cationic complexes **117a–c**, their yields exceeding 90%.¹²⁶ On UV irradiation of solutions containing the complexes **117a–c** and dimethyl chalcogenides, the latter replace a CO molecule to give cationic monocarbonyl complexes **118a–c** (yields 47%–82%).¹²⁶ The cationic complexes **117a–c** and **118a–c** react with salts containing nucleophilic anions (CN[–], I[–]) to give neutral complexes **119**, **120a–c**, in which X is cyano group or iodine.¹²⁶



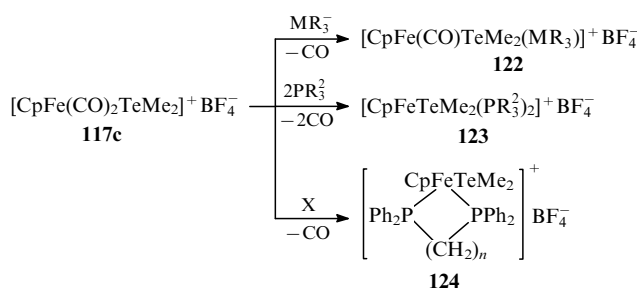
E = S (**a**), Se (**b**), Te (**c**); X = CN, M = K; X = I, M = Li;
(a) MX, CH₂Cl₂, ~20 °C, Ar; (b) Me₂E, CH₂Cl₂, *hν*.

Exposure of solutions of the complexes **117a,b** and dimethyl chalcogenides containing a heavier chalcogen to UV radiation leads to the displacement of a CO molecule and the formation of compounds **121**, which incorporate two different dimethyl chalcogenide ligands.¹²⁷



E¹ = S; E² = Se, Te; E¹ = Se, E² = Te.

Treatment of the complex **117c** with organoelement compounds of Group V elements results in the replacement of one or more CO ligands giving rise to compounds **122–124**.¹²⁷

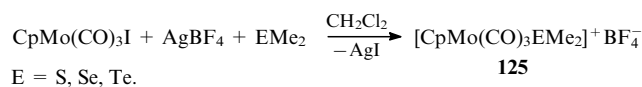


MR₃¹ = PMe₃, P(NMe₂)₃, PPh₃, AsPh₃, SbPh₃; R² = Me, OMe, OPh; X = Ph₂P(CH₂)_nPPh₂.

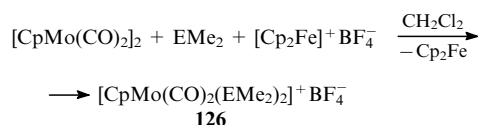
The molecular and crystal structures of the complex **117c** have been studied by X-ray diffraction analysis.¹³¹ In this compound, the iron atom is linked to two terminal carbonyl groups, one TeMe₂ ligand and one cyclopentadienyl ring, which form a pseudo-octahedral configuration. No tight contacts between the [CpFe(CO)₂TeMe₂]⁺ cations and the BF₄[−] anions were found in the crystals. The Fe–Te distance is 2.533 Å. The dimethyl telluride ligand occupies the *anti*-position in relation to the cyclopentadienyl ring, which minimises steric contacts. The Te–C bond length (2.107 Å) and the C–Te–C bond angle (93.1°) fall within the ranges of these values normal for organic tellurides.

The extended Hückel quantum-chemical calculations¹³¹ for the [CpFe(CO)₂EMe₂]⁺ cations confirmed the conclusion, based on the study of reactions of the cations **117**, that the stability of the Fe–E bond increases in the series S < Se << Te.

A different approach has been used to prepare molybdenum cyclopentadienyl carbonyl complexes **125**.¹²⁸ These monocarbonyl complexes were synthesised in 39%–91% yields by treatment of tricarbonyl(cyclopentadienyl)iodomolybdenum with silver tetrafluoroborate in the presence of the corresponding dimethyl chalcogenides (at a molar ratio of the reactants of 1 : 1 : 1).

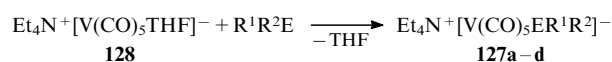


Dicarbonyl molybdenum-containing cations **126** were obtained in 86%–93% yields by oxidation of the dimer of dicarbonyl(cyclopentadienyl)molybdenum with ferrocenium tetrafluoroborate in the presence of dimethyl chalcogenides.¹²⁸ These compounds are formed as mixtures of *cis*- and *trans*-isomers the latter being formed in substantially larger amount.¹²⁸



E = S, Se, Te.

Anionic vanadium pentacarbonyl complexes **127**, containing diorganyl chalcogenides as ligands, have been synthesised by ligand exchange, namely, by the replacement of the THF molecule in the anionic complexes of vanadium **128** by diorganyl chalcogenide.^{129, 130}



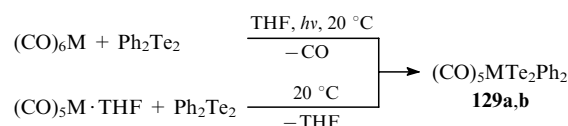
Compound 127	R ¹	R ²	E	Ref.
a	Ph	Ph	S	130
b	Ph	Ph	Se	129, 130
c	Ph	Ph	Te	129, 130
d	Me	Ph	S	129, 130

Among the synthesised compounds, only the tellurium complex **127c** is stable at room temperature.¹³⁰ The ⁵¹V NMR spectra

of the complexes **127a–c** demonstrate that the metal atom becomes more shielded with an increase in the size of the chalcogen atom. The δ_{51V} values for E = S, Se, Te are −1618, −1658 and −1753 ppm, respectively.¹³⁰

2. Complexes of diorganyl ditellurides

It has been shown in Section II that bi- and trinuclear iron, ruthenium and manganese carbonyls and molybdenum hexacarbonyl react with diaryl ditellurides with cleavage of the Te–Te bond to give complexes containing bridging ArTe ligands. However, when diphenyl ditelluride reacts with chromium and tungsten hexacarbonyls, the Te–Te bond is retained in the resulting complexes.^{15, 132} Depending on the ratio of the substrates, this gives either 1 : 1 (**129**)¹³² or 2 : 1 (**130**)¹⁵ complexes. Complexes of the former type are produced in 40%–60% yields on UV irradiation of tetrahydrofuran solutions of metal hexacarbonyls and diphenyl ditelluride at room temperature.¹³² The use of adducts of metal carbonyls with THF instead of hexacarbonyls makes it possible to prepare the complexes **129** in approximately the same yield without UV irradiation.¹³²



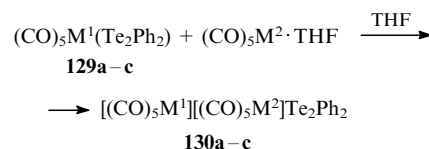
M = Cr (**a**), W (**b**).

The complexes **129a,b** are orange crystalline compounds, stable in air and readily soluble in organic solvents.¹³²

The structures of complexes of both types were studied by X-ray diffraction analysis.¹³² The metal atom is bound only to one tellurium atom; the coordination polyhedron is a slightly distorted octahedron. The Cr–Te and W–Te bond lengths are 2.679 and 2.810 Å, respectively. The complexation has only a slight effect on the Te–Te bond length in the ligand; in the complex **129a**, the length of this bond is 2.737 Å, and in **129b**, it is 2.718 Å (the Te–Te bond length in Ph₂Te₂ is 2.712 Å³²).

The ¹²⁵Te NMR spectra of the complexes **129** exhibit, in conformity with the structure proposed for them, two singlet signals due to ¹²⁵Te nuclei; for the chromium complex **129a**, they occur at 289 and 250 ppm (with respect to Ph₂Te₂), while for the tungsten complex, they are observed at 340 and 34 ppm.¹³² Since the positions and shapes of the ¹²⁵Te signals do not depend on the temperature, no exchange processes occur in solutions. It remains unknown why the difference between the chemical shifts of the two ¹²⁵Te nuclei in the tungsten complex **129b** (Δδ = 306 ppm) is much greater than that in the chromium derivative **129a** (Δδ = 39 ppm).

Heterometallic complexes **130a–c** have been prepared in 40%–55% yields by the reaction of equimolar amounts of **129a–c** with (CO)₅M²·THF.¹⁵



M¹ = M² = Cr (**a**), W (**b**); M¹ = Cr, M² = W (**c**).

The complexes **130a–c** can also be synthesised by UV irradiation of a mixture of metal hexacarbonyls and diphenyl ditelluride (taken in a molar ratio of 2 : 1) followed by evaporation of the reaction mixture *in vacuo*.¹⁵

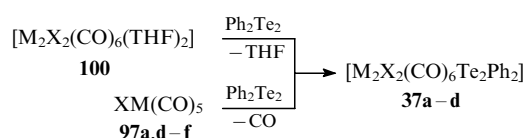
The compounds **130** form dark lilac crystals, readily soluble in aromatic and chlorinated solvents. They are fairly stable in air but gradually decompose in solutions. In coordinating solvents (acetonitrile, THF), especially in the light or on exposure to UV radiation, they decompose to give the complexes **129**.¹⁵

According to X-ray diffraction data,¹⁵ each metal atom in the complex **130a–c** is linked to one Te atom. The coordination polyhedron is a distorted octahedron. The Cr–Te bond in **130a** (2.656 Å) and the W–Te bond in **130b** (2.779 Å) are somewhat shorter than the corresponding bonds in the complexes **129**. However, the Te–Te bond lengths in the complexes **130a–c** (2.812, 2.808 and 2.828 Å, respectively) are markedly longer than the corresponding bonds in the complexes **129** and diphenyl ditelluride. The C₂Te₂ fragment is planar, the M(CO)₅ groups occupying *trans*-positions with respect to the Te–Te bonds.¹⁵

This molecular geometry implies one signal in the ¹²⁵Te NMR spectrum. For the complex **130b**, δ₁₂₅Te is 417. However, for the complexes **130a,c**, no signals for the ¹²⁵Te nuclei were detected; this was attributed¹⁵ to weakening of the Te–Te bond and its possible dissociation to give paramagnetic monomers. However, no evidence for such a homolytic bond cleavage (which could be provided, *e.g.*, by EPR spectroscopy) is presented in this study.

Thermal decomposition of the complexes **129a,b** and **130a–c** was studied by differential scanning calorimetry.¹⁵ The complexes **129a,b** decompose at 185–192 °C to give inorganic ditellurides CrTe₂ and WTe₂. The binuclear complexes **130a–c** lose the carbonyl and phenyl groups at 180–234 °C to yield, depending on the composition of the initial compound, CrTe, WTe and CrWTe₂.

Metal halo carbonyls, similarly to metal carbonyls, can react with diorganyl ditellurides both with rupture and with retention of the Te–Te bond. The reaction of *trans*-chlorocarbonylbis(triphenylphosphine)iridium **43** with di(4-ethoxyphenyl) ditelluride, accompanied by Te–Te bond rupture and giving the complex **44** with bridging ArTe ligands, was described above (see Section II).⁶⁸ Meanwhile, the reactions of the dimeric rhenium bromo carbonyl **100** (PhMe, room temperature) or pentacarbonyl(halo)manganese **97a,d** (Et₂O, PrⁱO, Δ)⁶⁴ and -rhenium **97e,f** (PrⁱO, Δ)⁶⁷ with Ph₂Te₂ give the binuclear complexes **37a–d** in which the Te–Te bond is retained. The dimeric octacarbonyl halo derivatives Mn₂X₂(CO)₈ are formed as intermediate compounds in the reactions of manganese complexes.⁶⁴ An intermediate with the same composition has been postulated for the reaction involving pentacarbonyl(iodo)rhenium.⁶⁷



M = Mn: X = Br (**37a, 97a**), I (**37b, 97d**);

M = Re: X = Br (**37c, 97e, 100**), I (**37d, 97f**).

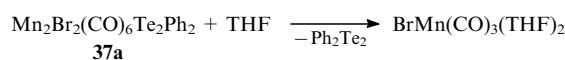
The complexes **37a–d** are red or red-brown crystalline compounds. The manganese complexes **37a,b** exist in air in the crystalline state only for several minutes; in solutions, they are fairly unstable thermally and photochemically unlike the rhenium complexes **37c,d**. Thermal decomposition of manganese complexes affords the complexes **24f** with bridging PhTe ligands (see Section II.3).

The molecular and crystal structures of the rhenium complex **37c** were studied by X-ray diffraction analysis.⁶⁷ The geometry of bonds about the rhenium atoms is a pseudo-octahedron, each rhenium atom being bound to three carbonyl groups, one tellurium atom of the ditelluride fragment and two bridging bromine atoms. The average length of the Te–Re bond is 2.760 Å, and the Te–Te bond length is equal to 2.794 Å, which is somewhat longer than this bond in diphenyl ditelluride (2.712 Å).³² The length of the bridging Re–Br bond is 2.642 Å; the Te···Br contact (3.674 Å) is almost 0.5 Å shorter than the sum of the van der Waals radii of the corresponding atoms (3.91 Å) and attests apparently to a weak interaction between them.⁸²

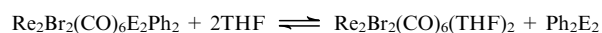
The fact that the IR spectra of the rhenium bromo carbonyl **37c** are similar to those of the iodo carbonyl **37d** suggests that they have similar structures.⁶⁷ The IR spectra of the complexes **37a–d**

and their sulfur and selenium analogues show a regular decrease in the ν_{CO} value following an increase in the atomic mass of the chalcogen. In the opinion of the researchers cited,⁶⁷ this regularity is largely due to the increase in the σ-donor capacity of chalcogens in the series S < Se < Te.

The diphenyl ditelluride ligand in the complexes **37a–d** can be substituted by other ligands under mild conditions. Thus, on dissolution in THF, the diphenyl ditelluride molecule is ejected to be replaced by a THF molecule.^{64,67} However, the adduct of bromo(tricarbonyl)manganese with THF, formed from the manganese complex **37a**, is unstable even at room temperature⁶⁴ and decomposes to give a mixture of non-identified products.



Dissolution of the rhenium complex **37c** and its S and Se analogues results in the equilibrium



E = S, Se, Te.

The equilibrium constants diminish in the series S (3.15) > Se (7.5 × 10^{–2}) > Te (5 × 10^{–4}).⁶⁴

The diphenyl ditelluride ligand in the complexes **37a,b** is replaced relatively easily at room temperature by carbon monoxide.⁶⁴



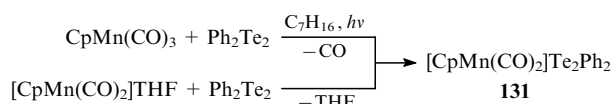
For the manganese complexes of diphenyl dichalcogenides Mn₂Br₂(CO)₆E₂Ph₂ (E = Se, Te), the rate of this reaction for E = Se is higher than that for E = Te, which reflects the increase in the bond strength in this series.⁶⁴

A ¹³C NMR study of the exchange of diphenyl dichalcogenide ligands in the reaction of rhenium complexes **37** enriched in ¹³C with diphenyl dichalcogenides showed that the strength of the Re–chalcogen bond increases on passing from Se to Te. The ligand containing a heavier chalcogen expels the ligand containing a lighter chalcogen from the complex.



E¹ = S, E² = Se; E¹ = Se, E² = Te.

Complexes of metal cyclopentadienyl carbonyls with diaryl ditellurides are relatively little studied.^{88,133} The dark lilac complex of diphenyl ditelluride with dicarbonyl(cyclopentadienyl)manganese **131** has been prepared in 70% yield by the reaction of tricarbonyl(cyclopentadienyl)manganese with diphenyl ditelluride in heptane on exposure to UV radiation.¹³³ This complex was also obtained by the reaction of diphenyl ditelluride with [CpMn(CO)₂]THF at room temperature.¹³³

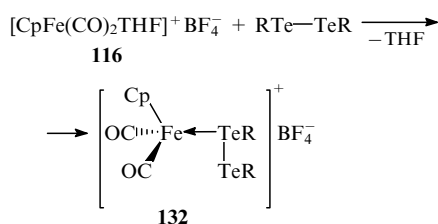


The complex **131** is fairly sensitive to air. It is readily soluble in THF, CH₂Cl₂ and in aromatic hydrocarbons and poorly soluble in alkanes. Its solution in THF does not exhibit signals in the EPR spectrum, and a toluene solution produces no signal in the ¹²⁵Te NMR spectrum.¹³³

The complex [MeCp(CO)₂Mn]₂(MesTe)₂ with a similar structure has been synthesised in 33% yield by the reaction of the adduct [MeCp(CO)₂Mn]THF with Mes₂Te.⁸⁸ It follows from X-ray diffraction data¹³³ that each CpMn(CO)₂ fragment in complex **131** is linked to one tellurium atom. The Mn–Te bond length is 2.486 Å. The metal atoms are in the *trans*-positions

relative to the Te–Te bond, the atoms in the Mn–Te–Te–Mn fragment thus formed lying in one plane. The coordination to the metal scarcely influences the Te–C bond length (2.128 Å) but substantially influences the Te–Te bond length, which is equal to 2.884 Å in the complex **131** and 2.712 Å in diphenyl telluride. The Te–Te–C bond angle also considerably changes — it is 88.4° in **131** and 97.4° and 100.3° in free Ph₂Te₂.³² This was interpreted¹³³ as being due to the additional dative interaction of the lone electron pairs of manganese with vacant *d* orbitals of tellurium.

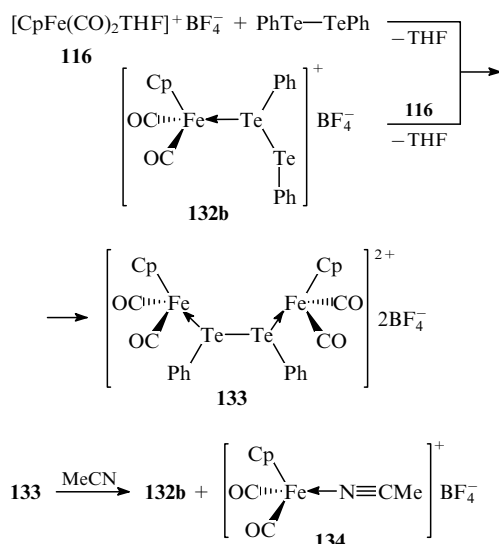
The Te–Te bond in diorganyl ditellurides is retained when they react with the cationic iron complex **116**. The reaction occurs under mild conditions (CH₂Cl₂, ~20 °C) and affords complexes **132a,b** in high yields (85%–98%).¹³⁴ The sulfur and selenium analogues of the complexes **132** were prepared in a similar way in 89%–98% yields.¹³⁴



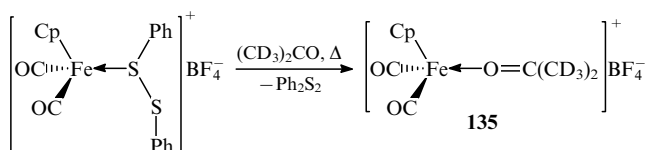
R = Me (**a**), Ph (**b**).

When diphenyl ditelluride reacts with two equivalents of the salt **116** or when the complex **132b** is treated with one equivalent of **116**, complex **133** is formed in 81% yield. Obviously, in this compound, diphenyl ditelluride acts as a bridging ligand, both its Te atoms being linked to iron atoms.¹³⁴ The sulfur and selenium analogues of **133** were synthesised in a similar way in 84% and 87% yields, respectively.¹³⁴

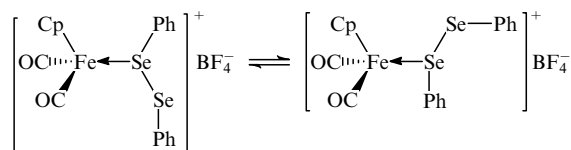
It should be noted that the complex **133** and its chalcogen analogues react with MeCN to give mixtures of complexes **132b** and **134**.



Diphenyl dichalcogenide complexes of the type **132** behave differently on heating in (CD₃)₂CO. In the sulfur complex, the solvent displaces the disulfide ligand, which leads to complex **135**.¹³⁴



In the case of the selenium analogue, the data of ¹³C NMR spectroscopy indicate the occurrence of a dynamic process, which was interpreted as a 1,2-shift of the CpFe(CO)₂ fragment.¹³⁴

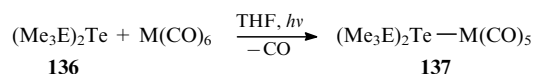


For the tellurium complex **132b**, no splitting of the ¹³C signals of the phenyl groups is observed even at 200 K.¹³¹

3. Complexes of metal carbonyls with compounds with tellurium – element bonds

The formation of complexes from metal carbonyls and compounds containing Te–element bonds can, in principle, involve coordination of the metal atom both to tellurium and to the other element.

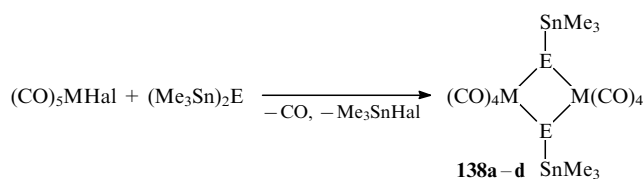
The interaction of metal hexacarbonyls with compounds (Me₃E)₂Te (**136**, E = Ge, Sn, Pb) gives rise to complexes **137**, their yields being 17%–45%.^{135, 136} The reactions proceed in THF on exposure to UV radiation.



M = Cr, Mo, W; E = Ge, Sn, Pb.

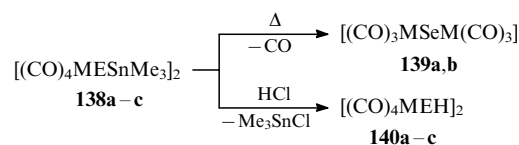
The complexes **137** are rather sensitive to moisture and atmospheric oxygen. Complexes with similar compositions and structures are formed when Cr, Mo and W hexacarbonyls are made to react with bis-element-substituted sulfides¹³⁷ and selenides.¹³⁵

The reactions of Mn(CO)₅Br and Re(CO)₅Cl with (Me₃Sn)₂E (E = Se, Te) afford binuclear complexes **138a–d**, which contain apparently bridging (Me₃Sn)E ligands.¹³⁸ Unlike the selenium derivatives **138a,b**, which are formed in high yields, the yields of their tellurium analogues **138c,d** are quite low. Thus the manganese complex **138c** was isolated in a yield of only 11%, and the formation of the rhenium derivative **138d** was judged only from the IR spectra of the reaction mixture.¹³⁸



E = Se: M = Mn (**a**), Re (**b**); E = Te: M = Mn (**c**), Re (**d**).

The complexes **138** can be transformed *via* two routes giving either compounds **139** or **140**.¹³⁸ The thermal transformation of **138** into **139** can be accomplished only for selenium-containing derivatives **138a,b**; the tellurium analogue could not be synthesised. On treatment with HCl, the complexes **138a–c** undergo destannylation to give the compounds **140a–c**.



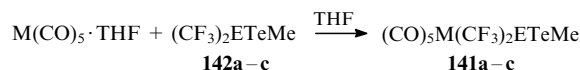
E = Se: M = Mn (**a**, 69%), Re (**b**, 66%); E = Te, M = Mn (**c**, 57%).

The proton signals of the EH groups in the ¹H NMR spectra of the complexes **140a–c** substantially shift upfield on passing from Se to Te. The chemical shifts of the SeH group in the spectra of **140a,b** are –6.20 and –4.13 ppm, respectively, whereas the signal for the TeH group in the spectrum of **140c** occurs at

–12.80 ppm.¹³⁸ For comparison, the chemical shifts of protons of the TeH groups in stable tellurols (Me₃Si)₃ETeH are –5.10 (E = C), –8.82 (E = Si), –9.02 (E = Ge).¹³⁹

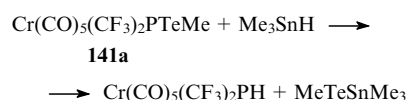
Unlike complexes formed by metal carbonyls with compounds containing Te—E bonds with Group IV elements, in which the tellurium atom acts as the coordination site, in the case of complexes in which E is a Group V element, both tellurium and this element can be involved in coordination.

The complexes **141a–c** have been prepared in relatively low yields (14%–27%) by reactions of metal carbonyls with compounds **142a–c** at room temperature.^{140, 141}


$$M = \text{Cr}; E = P(\mathbf{a}), \text{As}(\mathbf{b}); M = \text{Mo}, E = P(\mathbf{c}).$$

The complexes **141a,c** with phosphorus ligands are relatively stable in the light both in the solid state and in solutions in the absence of atmospheric oxygen. The arsenic analogue **141b** decomposes in solution over a period of several days even in the dark and under an inert atmosphere. Based on the spectroscopy data,^{140, 141} it was concluded that in phosphorus complexes, the metal is coordinated only to the P atom, while the arsenic complex exists as two isomers in which the metal is coordinated to either As or Te.

The reaction of the complex **141a** with trimethyltin hydride occurs with rupture of the P–Te bond.¹⁴²



A common drawback of studies describing metal carbonyl complexes with tellurium-containing ligands with Te–element bonds is that no X-ray diffraction data are presented.

IV. Conclusion

In the last 10–15 years, substantial progress has been achieved in the synthesis and study of complexes of metal carbonyls and cyclopentadienyl carbonyls with organic derivatives of tellurium(II). This includes synthesis of the complexes of metal carbonyls and cyclopentadienyl carbonyls with tellurocarbonyl compounds and triorganylphosphine tellurides, the use of organic derivatives of tricoordinated (diaryl telluroxides) and tetracoordinated (σ -telluranes) tellurium for the synthesis of Te(II) complexes and the possibility of thermolytic synthesis of metal tellurides. The reactions of bidentate N,Te-containing organic ligands also present interest; in particular, this refers to the synthesis of the first structurally characterised complex of benzochalcogenazoles with metal–tellurium coordination. It is significant that many types of complexes of organotellurium compounds considered here are more stable than complexes containing structurally related organic compounds of sulfur and selenium.

Further research in this field should be directed apparently along the following lines: (1) systematic studies of complexes with broad variation of the electronic and spatial structures of organotellurium ligands and metal carbonyls; (2) the search for new preparative methods for the synthesis of complexes of Te(II) organic derivatives using various compounds of tricoordinated (telluronium ylides, tellurimides, telluronium salts) and tetracoordinated (organyltellurium trihalides, aryltellurinic acid derivatives) tellurium as well as organyltellurenyl halides, organyl tellurocyanates, and telluroesters; (3) elucidation of the relationship between the structural and spectral characteristics of complexes and the structures of both initial components and elucidation of the influence of the nature of the chalcogen atom on the structure and reactivity of complexes containing similarly constructed organochalcogen ligands; (4) synthesis of complexes with various ambidentate tellurium-containing ligands; (5) pre-

paration of complexes with organotellurium ligands of various types containing bulky organic substituents (Me_3Si)₃E (E = C, Si, Ge) and the use of these complexes as initial compounds for low-temperature synthesis of metal tellurides.

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Methods for the synthesis of α,β -unsaturated trifluoromethyl ketones and their use in organic synthesis

V G Nenaidenko, A V Sanin, E S Balenkova

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Abstract. Published data on the methods of synthesis and properties of α,β -unsaturated trifluoromethyl-containing ketones are surveyed and described systematically. Primary attention is devoted to the use of these compounds in organic synthesis as useful building blocks for the preparation of various compounds bearing a trifluoromethyl group. The bibliography includes 133 references.

I. Introduction

Organofluorine chemistry has been vigorously developing during the last two decades. A large number of studies have been devoted to modification of natural products by introduction of a fluorinated or perfluorinated substituent.^{1–3} These fluorinated derivatives often exhibit biological activities; some heterocyclic compounds containing a trifluoromethyl group have already found wide use as medicines (for example, triflazine, trifluorothymidine).⁴ α,β -Unsaturated trifluoromethyl ketones (trifluoromethyl α,β -enones) are fairly convenient building blocks for preparing heterocycles with a trifluoromethyl group. Most of the known approaches to the synthesis of these heterocycles suffer from serious drawbacks, associated either with the fact that the initial compounds are rather difficult to obtain or with the fact that they are fairly toxic and inconvenient to work with.^{1–3} Thus, development of methods for the synthesis and study of properties of trifluoromethyl α,β -enones present substantial interest and have been in the centre of attention of many researchers in recent years.

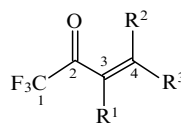
In this review, we survey methods for the synthesis of α,β -enones with a trifluoromethyl (perfluoroalkyl) substituent at the carbonyl group, because these enones are used in organic synthesis much more often than those containing a CF_3 group at other positions.^{5,6}

II. Methods for the synthesis of α,β -unsaturated trifluoromethyl ketones

Although the first α,β -unsaturated trifluoromethyl ketones were synthesised almost 40 years ago, the vigorous development of the methods for their synthesis has started only in the last decade. As a

rule, they cannot be prepared by the same procedures as non-fluorinated α,β -enones.

Five possible approaches to the construction of the carbon skeleton of trifluoromethyl α,β -enones can formally be proposed. Four approaches are based on the formation of $\text{C}(1)–\text{C}(2)$, $\text{C}(2)–\text{C}(3)$, $\text{C}(3)=\text{C}(4)$ and $\text{C}(4)–\text{R}^3$ bonds and one is based on transformations resulting in the appearance of a carbonyl group.



Analysis of published data shows that the following principal methods for the synthesis of trifluoromethyl α,β -enones exist.

— Trifluoroacetylation (for example, of alkenes, their organometallic derivatives or compounds generating alkenes *in situ*) to give a $\text{C}(2)–\text{C}(3)$ bond.

— Condensation of 1,1,1-trifluoroacetone and its derivatives with aldehydes and the formation of the $\text{C}(3)–\text{C}(4)$ double bond in an elimination reaction.

— Addition to alkynyl ketones (α,β -ynones) or to enones containing a β -substituent capable of being replaced (most often, an alkoxy group), and replacement of one carbonyl group in β -diketones containing a perfluoroalkyl substituent [formation of the $\text{C}(4)–\text{R}^3$ bond]. In this case, examples described in the literature include formation of both $\text{C}–\text{C}$ and $\text{C}–\text{heteroatom}$ bonds.

— Addition of perfluoroalkyl organolithium compounds to esters of acrylic acid to give the $\text{C}(1)–\text{C}(2)$ bond. This method is scarcely documented and has never been used for the preparation of trifluoromethyl α,β -enones. Apparently, this is due to the fact that synthesis of perfluorinated organolithium compounds requires the use of perfluoroalkyl iodides, which are toxic and difficult to work with (especially, trifluoromethyl iodide).³

— Oxidation of allyl alcohols, which are synthesised using perfluorinated or vinylic organometallic compounds, yielding a $\text{C}=\text{O}$ group. This approach also has not found wide use.

Below, we consider all the above methods for the synthesis of α,β -unsaturated trifluoromethyl ketones in the same order.

1. Trifluoroacetylation of alkenes

a. Trifluoroacetylation of electron-rich alkenes by trifluoroacetic anhydride

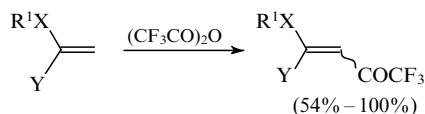
Trifluoromethyl α,β -enones are formed upon trifluoroacetylation of activated alkenes by trifluoroacetic anhydride (or other derivatives of trifluoroacetic acid) at room temperature or on

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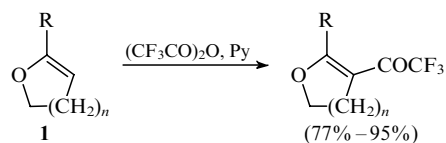
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cooling. The reaction is often carried out in the presence of pyridine, which increases the yield.

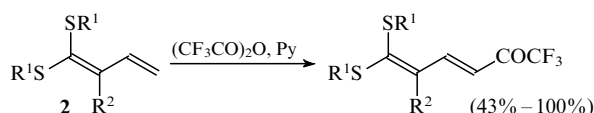


Y = H, Alk, Ar, SAR; X = O, S, Te, NSO₂R², NCOR³;
R¹, R², R³ = Alk, Ar.

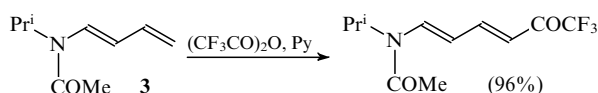
Activated alkenes can be represented by vinyl ethers⁷ (including cyclic ones such as **1**),^{8,9} vinyl sulfides,¹⁰ ketene dithioacetals,¹⁰ vinyl tellurides,¹¹ vinylamides,⁷ cyclic enamines^{12,13} and activated dienes such as 1,1-bis(alkylthio)alka-1,3-dienes **2** or *N*-acetyl-*N*-isopropyl-1-aminobuta-1,3-diene **3**.¹⁴



R = H, Me; n = 1, 2.

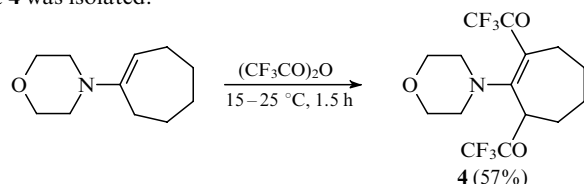


R¹ = Alk; R² = H, Et.

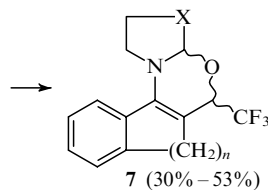
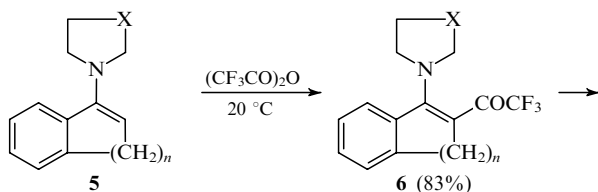


Trifluoroacetylation of vinyl ethers, vinylamides and 1,1-bis(alkylthio)alka-1,3-dienes **2** occurs stereospecifically yielding thermodynamically more favourable *E*-isomers of trifluoromethyl α,β-enones. Trifluoroacetylation of vinyl tellurides gives rise to *Z*-isomers, because they are stabilised by an O–Te coordinate bond (X-ray diffraction data¹¹). Vinyl sulfides are trifluoroacetylated non-stereoselectively. According to the ¹H NMR spectra and data on the reaction kinetics,^{15,16} this process follows an addition–elimination mechanism. Trifluoroacetylation of vinyl ethyl ether gives polymers as side products.¹⁶ In the absence of pyridine, the highest yield (59%) was attained when the reaction was carried out in chloroform.

Trifluoroacetylation of cyclic enamines, for example, 1-morpholinocyclopent-1-ene (or 1-morpholinocyclohex-1-ene), affords a complex mixture of products. In the case of less reactive 1-morpholinocyclohept-1-ene, doubly trifluoroacetylated product **4** was isolated.¹²

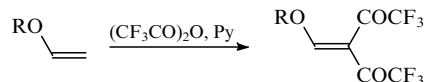


Enamines **5**, derived from indene, dihydronaphthalene and benzocycloheptene, react ambiguously with trifluoroacetic anhydride. Depending on the structure of the initial enamine, either trifluoromethyl enamino ketones **6** or products of their cyclisation, oxazine derivatives **7**, can be isolated.



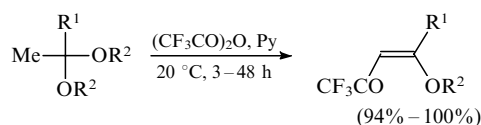
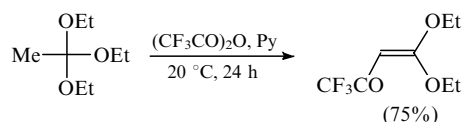
X = CH₂, (CH₂)₂, OCH₂; n = 1–3.

The reactions of vinyl ethers with a threefold excess of trifluoroacetic anhydride in the presence of pyridine result in the formation of 3-(alkoxymethylidene)-1,1,1,5,5,5-hexafluoropentane-1,3-diones in high yields.¹⁷

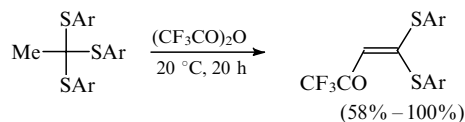


R = Et, Buⁱ.

Orthoacetates, acetals¹⁸ and trithioorthoacetates¹⁹ react with excess trifluoroacetic anhydride with elimination of alkyl or aryl trifluoroacetate (thioacetate) to give trifluoromethyl enones, *i.e.*, they are precursors of the corresponding activated alkenes. It should be noted that only trifluoroacetic and trichloroacetic anhydrides enter into this reaction, whereas acetic anhydride does not.

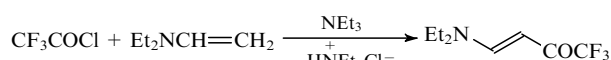
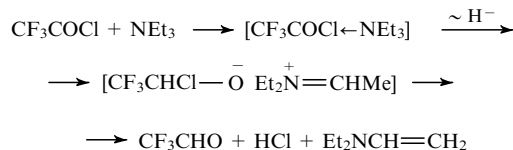


R¹ = Me, Ph; R² = Me, Et.



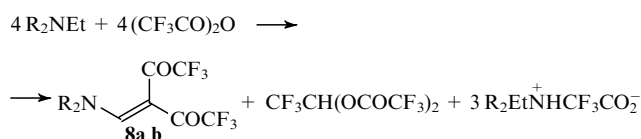
b. Trifluoroacetylation of tertiary amines

When trialkylamines are made to react with trifluoroacetic anhydride or trifluoroacetyl halides, β-dialkylamino-substituted trifluoromethyl enones are formed. The reaction of two equivalents of triethylamine with trifluoroacetyl chloride at –30 °C gives rise to 4-diethylamino-1,1,1-trifluorobut-3-en-2-one (in 18% yield based on the initial trifluoroacetyl chloride).²⁰ The reaction mechanism proposed in the study cited²⁰ includes oxidation of triethylamine by one equivalent of trifluoroacetyl chloride to give diethyl(vinyl)amine. Trifluoroacetyl chloride is reduced simultaneously to fluoral. The subsequent interaction of diethyl(vinyl)amine with a second equivalent of trifluoroacetyl chloride results in the formation of the corresponding enamino ketone.



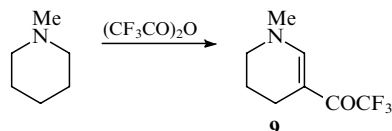
It has been found²¹ that the reaction of triethylamine or ethyldiisopropylamine with an equimolar amount of trifluoroacetic anhydride at 0 °C gives rise to doubly trifluoroacetylated

products **8a,b** (yield $\sim 25\%$), in conformity with the reaction stoichiometry



R = Et (**a**), Prⁱ (**b**).

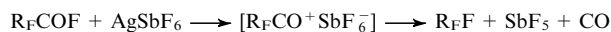
Cyclic amines react in a similar way. For example, *N*-methylpiperidine is converted into the corresponding enamine **9** in 96% yield (with allowance for the degree of conversion of the starting amine).



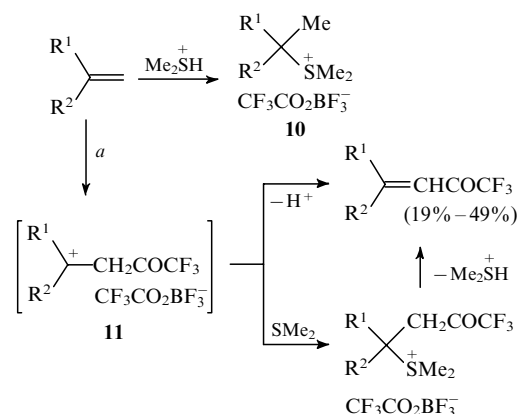
Some alkaloids containing tertiary nitrogen atoms enter into similar reactions with trifluoroacetic anhydride. They are oxidised and the resulting enamine fragment is then trifluoroacetylated.²²

c. Trifluoroacetylation of non-activated alkenes

The electrophilicity of trifluoroacetic anhydride and other derivatives of trifluoroacetic acid is insufficient for trifluoroacetylation of non-activated alkenes. The attempts to increase the reactivity of these reagents by complex formation with Lewis acids prove successful only for acylation of aromatic compounds. Unsaturated substrates undergo cationic polymerisation under these conditions. The use of acylium salts for the acylation of unsaturated compounds would permit conducting the reaction at low temperatures and thus diminish the probability of polymerisation and other side processes. Unfortunately, acylium salts with a perfluoroalkyl radical are unstable and decompose with decarbonylation during their attempted synthesis.^{23,24}

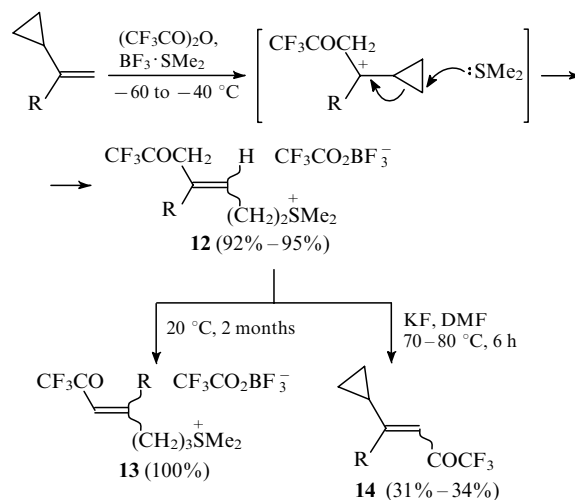


A new method for direct electrophilic trifluoroacetylation of non-activated alkenes has been proposed.²⁵ The method is based on the use of trifluoroacetic anhydride in the presence of a complex of dimethyl sulfide with boron trifluoride. This reagent is more electrophilic than trifluoroacetic anhydride, which reacts only with alkenes activated by a heteroatom at the double bond. However, the use of the complex $\text{BF}_3 \cdot \text{SMe}_2$ has a drawback; acylation of an equivalent of an alkene results in the liberation of protonated dimethyl sulfide, which then reacts with at least one more equivalent of the alkene to give sulfonium salt **10**. Consequently, the yield of vinyl trifluoromethyl ketones does not exceed 50%. This reaction proceeds with alkenes able to form benzylic, allylic or tertiary cations (of the type **11**); however, in the last-mentioned case, mixtures of α,β - and β,γ -enones are formed.^{26,27}



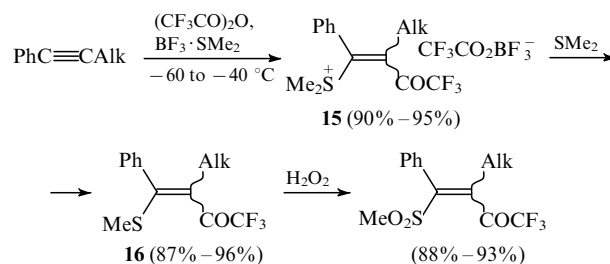
(a) $(\text{CF}_3\text{CO})_2\text{O}$, $\text{BF}_3 \cdot \text{SMe}_2$, -60 to -30°C .

Cyclopropyl-substituted alkenes enter into a similar reaction.^{28,29} The reaction of 2-cyclopropylpropene and 1,1-dicyclopropylethene with trifluoroacetic anhydride in the presence of $\text{BF}_3 \cdot \text{SMe}_2$ follows an unusual route and results in cyclopropane ring opening to give sulfonium salts **12**.²⁹ The salts **12**, which are β,γ -unsaturated ketones, rearrange spontaneously into α,β -enones **13** (2 months, $\sim 20^\circ\text{C}$) in a quantitative yield. In the presence of a base (KF, DMF), the sulfonium salts **12** undergo cyclisation in which the dimethylsulfonium group is intramolecularly substituted to give α,β -enones with a cyclopropyl substituent **14**.

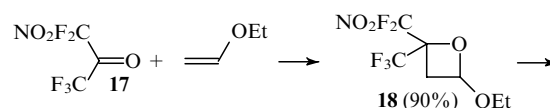


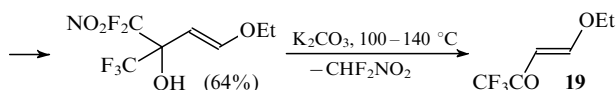
R = Me, cyclo- C_3H_5 .

In the presence of the complex $\text{BF}_3 \cdot \text{SMe}_2$, trifluoroacetic anhydride trifluoroacetylates alkynes with a phenyl substituent at the triple bond. The reactions afford sulfonium salts **15** as a result of conjugate addition of the CF_3CO group and dimethyl sulfide to the alkyne molecule.³⁰ The demethylation of these salts upon the reaction with dimethyl sulfide results in the formation of trifluoromethyl α,β -enones **16**. Oxidation of the enones **16** by hydrogen peroxide makes it possible to synthesise unsaturated compounds with two electron-withdrawing substituents at the double bond, namely, sulfonyl and CF_3CO groups.

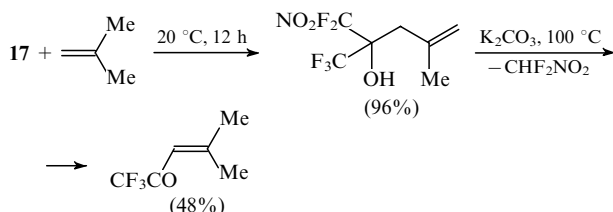


The reactions of pentafluoronitroacetone **17** with vinyl ethyl ether,³¹ ketene diethyl acetal³² or isobutylene³³ give rise to products similar to those formed upon trifluoroacetylation of alkenes with trifluoroacetic anhydride. The reaction with activated alkenes follows a cycloaddition pathway. Thus the compound **17** and vinyl ethyl ether react at $0-5^\circ\text{C}$ to give oxetane **18**. Opening of the oxetane ring and subsequent thermolysis of the resulting alcohols in the presence of catalytic amounts of K_2CO_3 affords 4-ethoxy-1,1,1-trifluorobut-3-en-2-one **19** (yield 96%). Ketene diethyl acetal enters into a similar reaction with the compound **17** (at -30°C), 4,4-diethoxy-1,1,1-trifluorobut-3-en-2-one being formed in 90% yield.



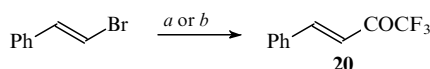


The reaction of pentafluoronitroacetone **17** with isobutylene yields an alcohol, which eliminates difluoronitromethane to give 4-methyl-1,1,1-trifluoropent-3-en-2-one.



d. Trifluoroacetylation of vinylic and allylic organometallic compounds

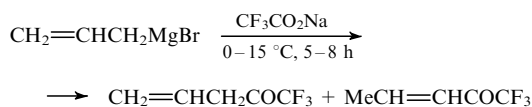
Trifluoroacetylated derivatives of non-activated alkenes can be prepared by acylation of vinylic organometallic compounds. The first trifluoromethyl-containing enone, 1,1,1-trifluoro-4-phenylbut-3-en-2-one **20**, was synthesised by the reaction of styrylmagnesium bromide with trifluoroacetic acid in 1959; however, the yield of the product was relatively low.³⁴ The subsequent studies showed that organolithium derivatives are better suited for the synthesis of trifluoromethyl enones; in this case, higher yields of the target products can be attained.³⁵ However, only one example of this type of synthesis is known to date; apparently, this is due to the fact that the corresponding vinyl lithium derivatives are difficult to obtain.



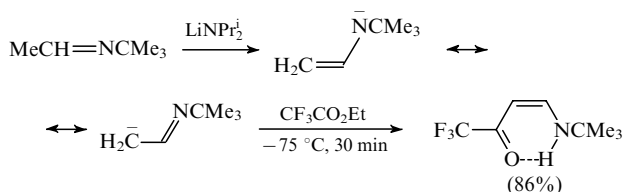
(a) Mg, Et₂O; CF₃COOH (yield 11%);

(b) Li, Et₂O; CF₃CON C_6H_{11} (yield 63%).

Trifluoromethyl α,β -enones can also be prepared from allylic organometallic compounds. For example, the reaction of allylmagnesium bromide with sodium trifluoroacetate gives a mixture of the corresponding α,β - and β,γ -enones (ratio ~1:1) in an overall yield of 37%.³⁶



When lithium diisopropylamide is made to react with *N*-ethylidene-*tert*-butylamine, a heteroallylic anion is formed; subsequent treatment of the anion with ethyl trifluoroacetate gives rise to 4-(*tert*-butylamino)-1,1,1-trifluorobut-3-en-2-one.³⁷



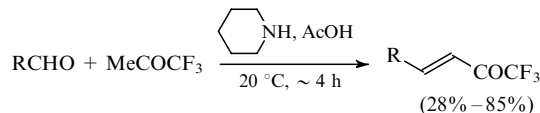
Reactions of other vinylic or allylic organometallic compounds with trifluoroacetic acid or its derivatives have not been studied.

Thus, trifluoroacetylation of alkenes is a convenient method for the synthesis of trifluoromethyl enones; however, it is applicable only to alkenes containing either an activating group (e.g., OR, SR, TeR, NR₂) or, at least, a phenyl, vinyl or

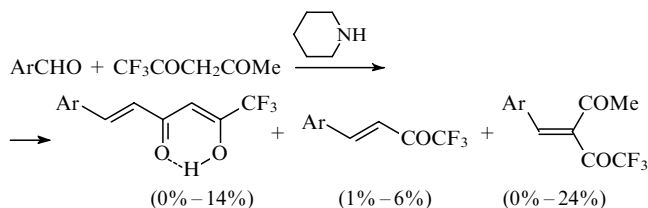
cyclopropyl substituent or two alkyl substituents (trifluoroacetylation in the presence of Me₂S·BF₃).

2. Condensation of 1,1,1-trifluoroacetone and its derivatives; construction of a double bond upon an elimination reaction

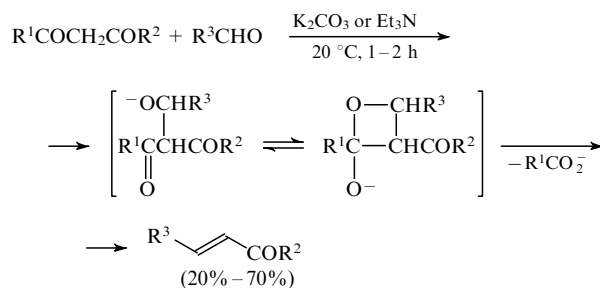
The condensation of 1,1,1-trifluoroacetone with aromatic or α,β -unsaturated aldehydes catalysed by the piperidine–acetic acid system in THF makes it possible to prepare trifluoromethyl-containing conjugated enones, dienones and polyenones (retinoids).^{38,39} The reaction is stereospecific and gives *E*-isomers of enones. A drawback of this method is self-condensation of 1,1,1-trifluoroacetone during the reaction; therefore, it should be taken in more than 10-fold excess.



α,β -Unsaturated ketones are often prepared by condensation of β -dicarbonyl compounds with aldehydes and ketones (Knoevenagel condensation). However, β -dicarbonyl compounds containing a perfluoroalkyl substituent enter into this reaction with difficulty. Thus the reaction of aromatic aldehydes with 1,1,1-trifluoroacetylacetone yields a mixture of products resulting from condensation at the methyl and methylene groups in a relatively low yield.⁴⁰ This fact was explained by assuming that the addition of amine, used as the catalyst, to the initial 1,1,1-trifluoroacetylacetone is the predominant reaction route.

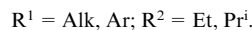


The reactions of β -diketones having one or two perfluoroalkyl groups with polyfluorinated aldehydes have also been studied.⁴¹ In the case of β -diketones with one perfluoroalkyl group, the carbonyl group adjacent to the perfluoroalkyl substituent, being more active, participates in the formation of the cyclic intermediate. As a consequence, the elimination of a carboxylate anion gives rise to β -unsaturated ketones with a non-fluorinated substituent at the carbonyl group.



R¹ = CF₃, H(CF₂)_{*n*}; R² = Me, Ph, CF₃, H(CF₂)_{*n*}; R³ = H(CF₂)_{*n*}.

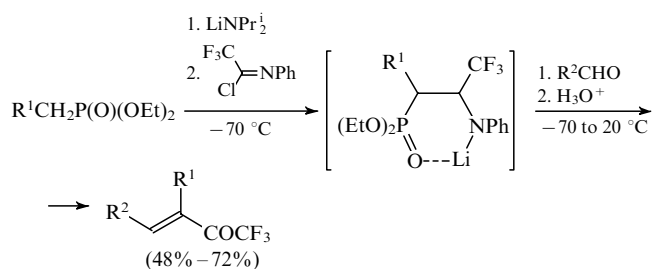
When esters of trifluoroacetic acid are made to condense with aldehydes in the presence of traditional catalysts such as piperidine–AcOH, the target products are formed in fairly low yields.⁴² Recently, it has been proposed to use functionalised silica gel [silica gel treated with (3-aminopropyl)triethoxysilane] as the catalyst with toluene-*p*-sulfonic acid being added subsequently to the reaction mixture. A mixture of *Z*- and *E*-isomers of alkoxy carbonyl-substituted trifluoromethyl α,β -enones was obtained in this way in a good yield.⁴²



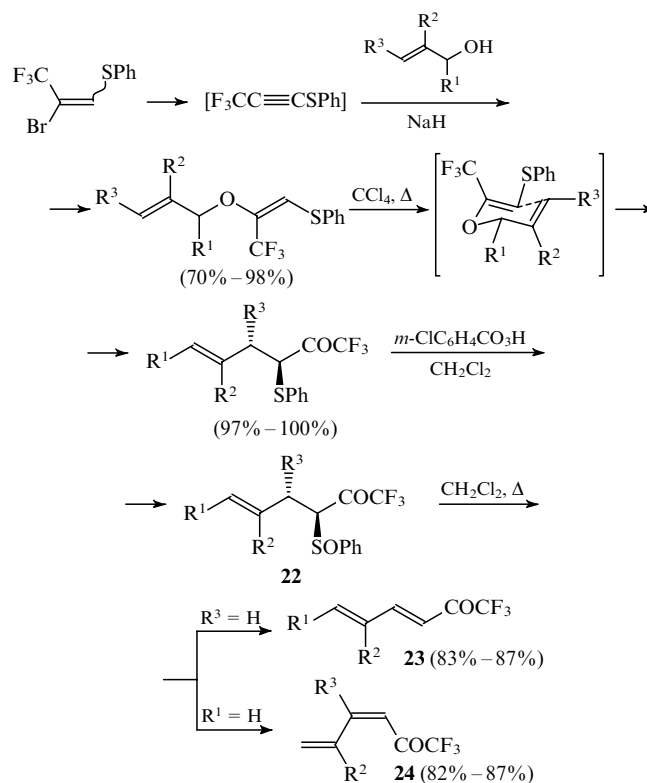
$$\text{R}_\text{F}\text{CF}_2\text{COCl} \xrightarrow[0-20^\circ\text{C}, 2\text{ h}]{\text{P(OEt)}_3} \left[\text{R}_\text{F}\text{CF}_2\text{C}(\text{O})(\text{OEt})\text{P(OEt)}_2 \right] \xrightarrow{\text{P(OEt)}_3}$$

$$\rightarrow \text{R}_\text{F}\text{C}(\text{F})=\text{C}(\text{OP(O)(OEt)}_2)\text{P(O)(OEt)}_2 \xrightarrow[2. \text{NH}_4\text{Cl (sat.)}]{1. \text{BuLi, CuI, THF}} \xrightarrow[-78^\circ\text{C}, 15\text{ min}]{} \text{R}_\text{F}\text{C}(\text{F})=\text{C}(\text{H})\text{P(O)(OEt)}_2 \xrightarrow[20^\circ\text{C}, 2\text{ h}]{\text{MeNH}_2} \text{R}_\text{F}\text{C}(\text{NMe})=\text{C}(\text{H})\text{P(O)(OEt)}_2 \xrightarrow[2. \text{RCHO}]{1. \text{B}} \text{R}_\text{F}\text{C}(\text{NMe})=\text{C}(\text{H})\text{CH}=\text{CH}\text{R} \xrightarrow{\text{H}_3\text{O}^+} \text{R}_\text{F}\text{COCH}=\text{CH}\text{R}$$

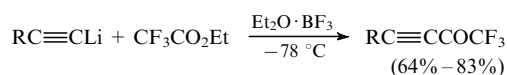
β -Iminophosphonate anions can also be obtained from diethyl alkylphosphonates and trifluoroacetimidoyl chloride. The synthesis is carried out as a one-pot procedure; first, diethyl alkylphosphonates are treated with two equivalents of lithium diisopropylamide and then with trifluoroacetimidoyl chloride; after that, the required aldehyde is added to the resulting β -iminophosphonate anion.⁴⁴



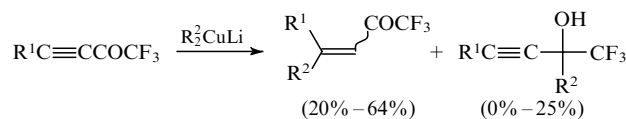
A method for the synthesis of substituted trifluoromethyl dienyl ketones with a particular configuration at the double bond has been reported.⁴⁵ Thus sulfoxides **22** were prepared from 1-trifluoromethyl-2-phenylthioacetylene *via* a four-stage procedure (Claisen rearrangement is the key stage of the process). Subsequent elimination of sulfinic acid from the sulfoxides **22** gave trifluoromethyl dienyl ketones **23** and **24** in high yields.



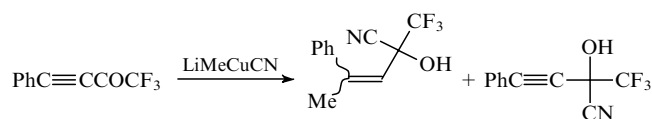
Alkynyl trifluoromethyl ketones are easily available compounds, readily formed upon acylation of lithium or magnesium acetylides (Iotsitch reagents) with trifluoroacetic acid or its derivatives.^{46–50} The best yields were attained in the reaction of lithium acetylides with ethyl trifluoroacetate in the presence of boron trifluoride etherate.⁵⁰



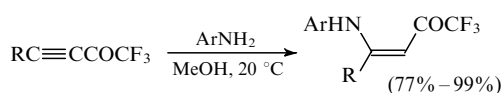
A method for the synthesis of trifluoromethyl α,β -enones is based on 1,4-addition of dialkylcuprates to acetylenic ketones. This reaction is highly regioselective but it is not stereoselective and gives products in moderate yields.^{50, 51}



The use of cyanocuprates results in higher yields and in a nearly 100% regioselectivity of the reaction. However, in some cases (for example, in the case of 1,1,1-trifluoro-4-phenylbut-3-yn-2-one), cyanohydrins are produced.⁵¹

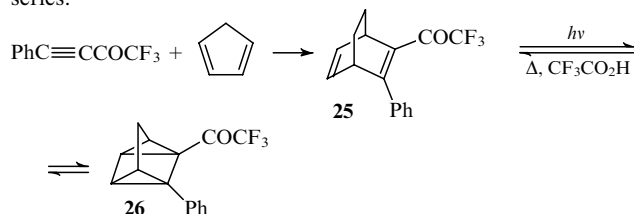


The reactions of alkynyl trifluoromethyl ketones with aromatic amines afford β -amino-substituted trifluoromethyl enones in good yields.⁵²



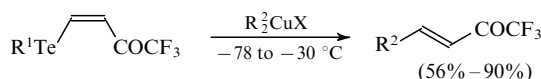
R = Alk, Ar.

Alkynyl trifluoromethyl ketones can act as dienophiles in the Diels–Alder reaction. 1,1,1-Trifluoro-4-phenylbut-3-yn-2-one reacts with cyclopentadiene to give bicyclic trifluoromethyl enone **25**, a norbornadiene derivative, which undergoes a reversible rearrangement to give compound **26** of the quadricyclane series.⁵³



4. Addition to enones containing a replaceable group in the β -position

A method for the synthesis of trifluoromethyl enones based on the reactions of various zinc dialkyl- and diaryl-cuprates with β -trifluoroacetylvinyl tellurides has been proposed.⁵⁴

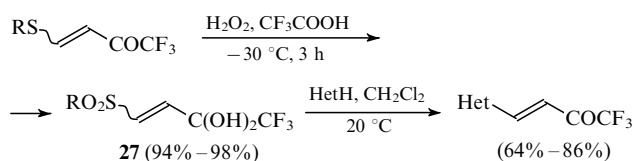


R¹ = Buⁿ, Buⁱ, Ph; R² = Ar, Alk; X = (CN)(ZnCl)₂, ZnCl.

However, in the case of zinc dialkylcuprates, the reaction is accompanied by side formation of the double addition products, Alk₂CHCH₂COCF₃, in 11%–19% yields. The necessity of using organotellurium compounds is also an obvious drawback of this method.

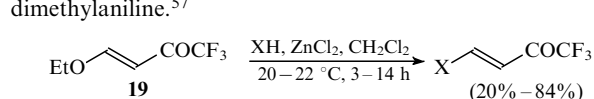
A new procedure for the synthesis of trifluoromethyl enones from β -trifluoroacetylvinyl sulfones **27** has been reported quite recently. The compounds **27** are formed as stable diols upon oxidation of trifluoroacetylated vinyl sulfides.⁵⁵

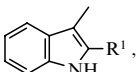
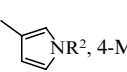
Thus β -trifluoroacetylvinyl sulfone **27** (R = Ph) reacts with electron-rich aromatic compounds (furans, indoles and pyrroles) to liberate sulfinic acid and to give aryl- and hetaryl-substituted trifluoromethyl α,β -enones.⁵⁵ The reaction is stereospecific yielding *E*-isomers of the enones.



R = Me, Ph.

β -Alkoxy-substituted trifluoromethyl enones (most often, 4-ethoxy-1,1,1-trifluorobut-3-en-2-one) are used as the starting compounds in a large number of syntheses. These compounds can be readily prepared by trifluoroacetylation of vinyl ethers.⁵⁶ Several studies consider the reactions of the enone **19** with diverse nucleophiles — electron-rich aromatic compounds, organometallic and organoboron compounds and amines. This reaction in the presence of zinc chloride can be carried out only for reactive aromatic compounds such as indoles, pyrroles^{57,58} and *N,N*-dimethylaniline.⁵⁷

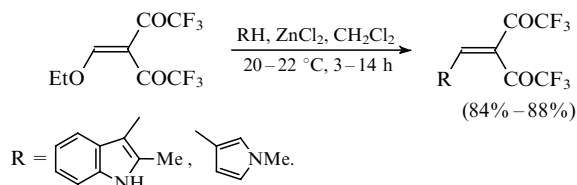


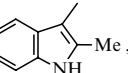
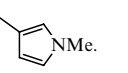
X = , , 4-Me₂NC₆H₄; R¹ = H, Me, Ph;

R² = H, Me.

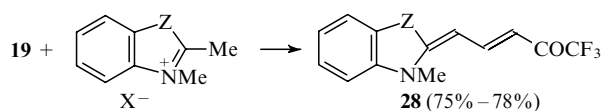
Less reactive compounds such as anisole do not enter into this reaction, and the use of other Lewis acids (BF₃ or TiCl₄) results in resinification.⁵⁷ The reactions of the enone **19** with other heterocyclic compounds such as furan, 2-methylfuran and thiophene under the same conditions do not lead to the desired result either.⁵⁸

The reaction of 3-ethoxymethylidene-1,1,1,5,5,5-hexafluoropentane-1,3-dione with indoles and pyrroles occurs faster and gives products in higher yields.⁵⁸

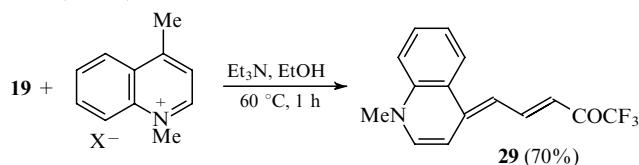


R = , .

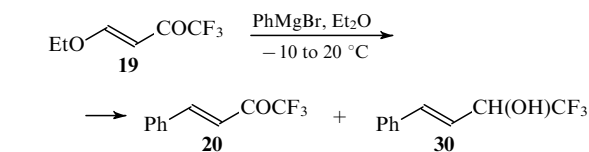
The enone **19** reacts with quaternary salts derived from nitrogenous heterocycles to give dienones — δ -trifluoromethylbutadienylmerocyanines **28** or **29**.⁵⁹



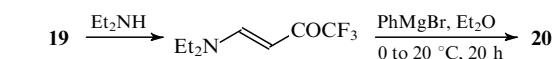
Z = S, Me₂C, CH = CH.



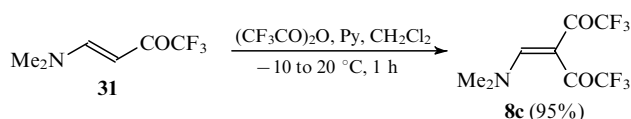
4-Butoxy-1,1,1-trifluorobut-3-en-2-one enters into a similar reaction. The enone **19** reacts with the phenylmagnesium bromide to give a mixture of β -trifluoroacetylstyrene **20** and allylic alcohol **30**, resulting from its reduction, in an overall yield of 40%–60%, the proportion of the alcohol **30** increasing with an increase in the reaction time.⁵⁷ The reaction of phenylmagnesium bromide with 4-diethylamino-1,1,1-trifluorobut-3-en-2-one, prepared from the enone **19**, occurs more unambiguously;⁵⁷ it gives only β -trifluoroacetylstyrene **20** in 53% yield.



Reaction time /h 2 20
The **20** : **30** ratio 1 : 1 1 : 7

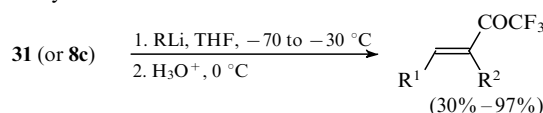


Recently, a new convenient and fairly versatile method for the synthesis of unsaturated trifluoromethyl ketones has been developed; this method is based on the reactions of various organolithium compounds with 4-dimethylamino-1,1,1-trifluorobut-3-en-2-one **31** and 3-(*N,N*-dimethylaminomethylidene)-1,1,1,5,5,5-hexafluoropentane-2,4-dione **8c**. The compound **8c** can be easily prepared by acylation of the enaminone **31** with trifluoroacetic anhydride in the presence of pyridine.⁶⁰



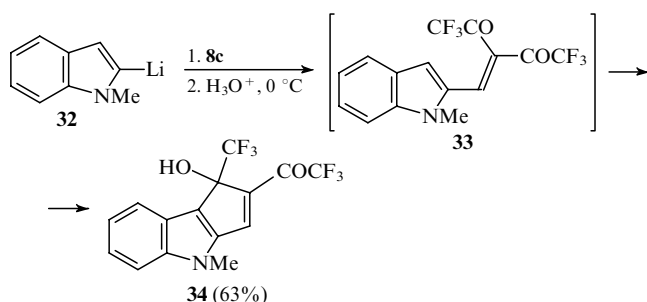
The reactions of the trifluoromethyl enaminones **31** and **8c** with organolithium compounds afford trifluoromethyl enones; in

the case of the enaminone **31**, the reactions are stereospecific and give only *E*-isomers of the enones.⁶⁰

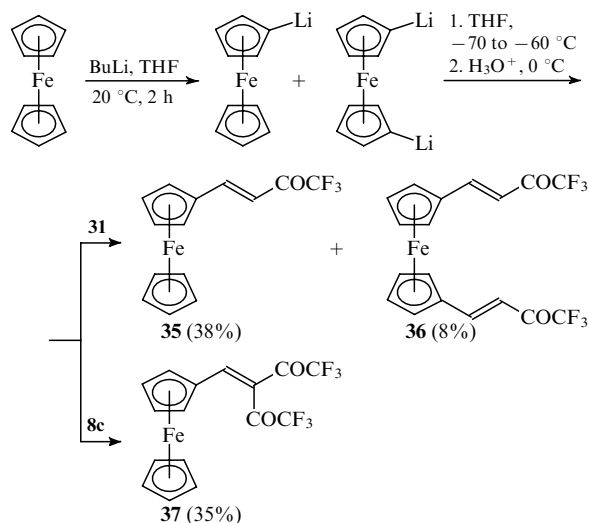


$\text{R}^1 = \text{Ar, Het}; \text{R}^2 = \text{H, COCF}_3$.

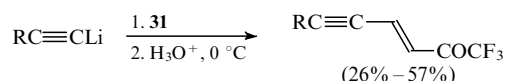
The reaction of enaminodione **8c** with 1-methyl-1*H*-2-indolyl lithium **32** gives rise to the corresponding enedione **33** but does not stop at this stage; the subsequent cyclisation yields cyclopenta[*b*]indole derivative **34**.⁶⁰



The same study⁶⁰ describes the reaction of the enaminone **31** with a mixture of lithiated ferrocenes, resulting in the formation of the corresponding mono- **35** and bis-enones **36**. In the case of the enaminodione **8c**, only the product of its interaction with monolithioferrocene, enedione **37**, was isolated.

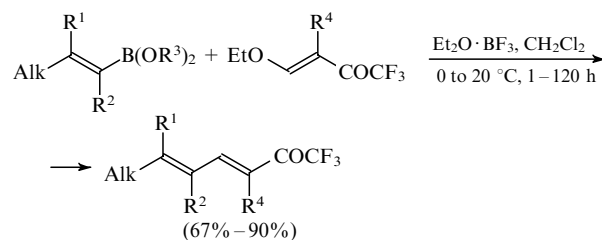


In order to synthesise conjugated trifluoromethyl enones containing an acetylenic fragment (enynones), which are promising from the synthetic point of view, a method based on the reaction of lithium acetylides with the enone **31** has been developed.⁶¹ The reaction is stereospecific giving *E*-isomers of substituted trifluoromethyl enynones.

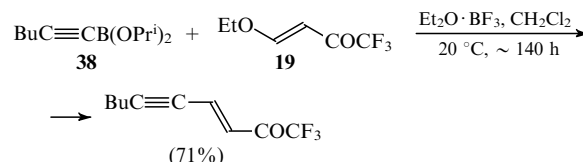


$\text{R} = \text{Alk, Ar, Me}_3\text{Si}$.

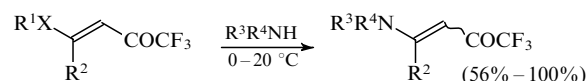
The reactions of various trifluoroacetylated vinyl ethers with organoboron compounds, which occur with high stereoselectivity (92% – 98%) to give the *E*-isomers of the corresponding dienones, have been studied.^{62, 63} Thus the reaction of alkenyldialkoxyboranes with substituted vinylic ethers in the presence of boron trifluoride etherate affords the corresponding trifluoromethyl dienones.⁶² Similarly, 6-butyl-1,1,1-trifluorohex-3-en-5-yn-2-one is formed in the reaction of alkynyldialkoxyborane **38** with the enone **19**.⁶³



$\text{R}^1 = \text{H, Me, Ph, Br}; \text{R}^2 = \text{H, Br}; \text{R}^3 = \text{Et, Pr}^i; \text{R}^4 = \text{H, Me, Ph}$.

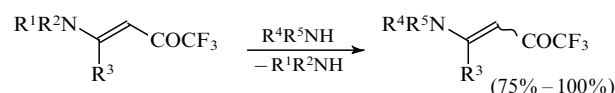


β -(Thio)alkoxy-substituted trifluoromethyl enones react with ammonia and primary and secondary amines (including aromatic ones) at room temperature to give β -amino-substituted enones (enaminones) in high (sometimes quantitative) yields.^{64, 65}



$\text{X} = \text{O, S}; \text{R}^1 = \text{Alk}; \text{R}^2 = \text{H, Me, Ph}; \text{R}^3 = \text{H, Alk}; \text{R}^4 = \text{H, Alk, Ar}$.

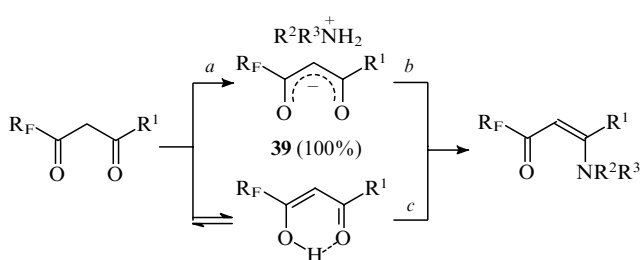
Diamines enter into a similar reaction. Thus symmetrical enaminones have been synthesised by the reaction of ethylenediamine and *o*-phenylenediamine with two molecules of β -ethoxy trifluoromethyl enone **19**.⁶⁴ The route of transamination in the series of β -amino-substituted enones does not depend on the nature of the solvent, being determined by the ratio of the initial reactants and the basicities of both the entering and leaving amines. The highest yields are attained when the amine entering into the reaction is more basic than the leaving one (for example, an amino group can easily be replaced by a dimethylamino or methylamino group but not *vice versa*). The reactions occur at room temperature and do not require a large excess of the amine used.^{65, 66}



$\text{R}^1 = \text{H, Alk}; \text{R}^2, \text{R}^3 = \text{H, Alk, Ph}; \text{R}^4 = \text{H, Alk}; \text{R}^5 = \text{Alk}$.

5. Preparation of trifluoromethyl ketones from β -diketones

Trifluoromethyl enaminones can be synthesised by the reaction of amines with β -diketones. When fluorinated β -diketones are made to react with ammonia,⁶⁷ ammonium acetate, ammonium hydrogen carbonate,⁶⁸ alkylamines or dialkylamines, stable salts **39** are initially formed. Refluxing of the salts **39** obtained from β -diketones having one trifluoromethyl (or perfluoroalkyl) substituent in benzene or toluene with azeotropic distillation of water affords β -amino-substituted enones in 12% – 76% yields.⁶⁷

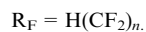
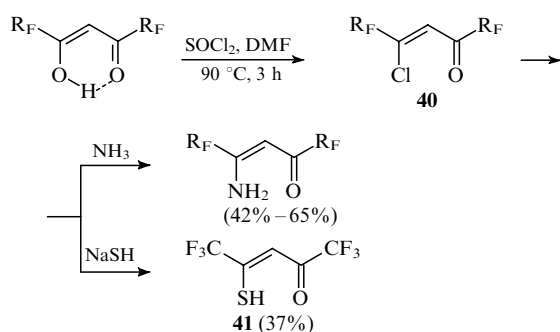


$\text{R}_F = \text{H}(\text{CF}_2)_n \text{ (} n = 2, 4\text{)}; \text{R}^1 = \text{Alk, Ar};$
 (a) $\text{R}^2\text{R}^3\text{NH} \text{ (} \text{R}^2, \text{R}^3 = \text{H, Alk} \text{), } 20^\circ\text{C};$ (b) PhH or PhMe, Δ ;
 (c) $\text{R}^2\text{R}^3\text{NH} \text{ (} \text{R}^2 = \text{Ph, R}^3 = \text{H} \text{), MeOH, } 20^\circ\text{C}.$

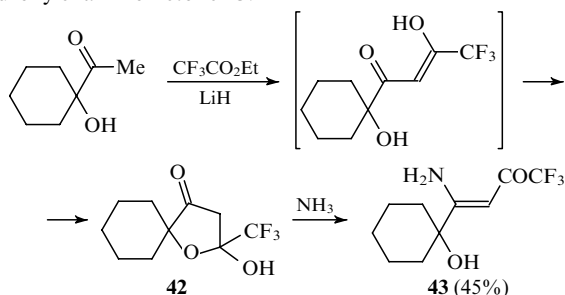
In the case of low-basicity aromatic amines (*e.g.*, aniline), salts are not formed and the corresponding enamines are obtained by prolonged keeping of the initial compounds in polar solvents such as methanol at room temperature (yields 70%–90%).⁶⁷

As a rule (or always if $R^1 = \text{Alk}$), this reaction gives enamines in which the amino group is removed from the perfluoroalkyl substituent. Apparently, the electron-withdrawing influence of this group stabilises the *gem*-amino-alcoholic fragment and hampers elimination of water in the case where the amine has added at the carbonyl group adjacent to the perfluoroalkyl substituent.

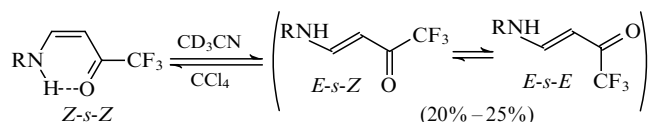
β -Diketones having two perfluoroalkyl substituents react with amines, including aromatic ones, to give stable salts, which cannot be converted into the corresponding amino-substituted enones.⁶⁹ However, these enones can be obtained by the reaction of ammonia or aliphatic amines with fluorine-containing β -chlorovinyl ketones **40**.^{70,71} The compounds **40** are formed in the reaction of polyfluorinated β -diketones with SOCl_2 in the presence of DMF as a catalyst or with the Vilsmeier reagents [$\text{DMF} - \text{POCl}_3$ or $\text{DMF} - (\text{COCl})_2$].^{71–74} This approach has also been used to synthesise hexafluoromonothioacetylacetone **41**, which exists in the enol form.⁷²



Similarly, treatment of hydroxytetrahydrofuranone **42** — the hemiketal form of a diketone — with ammonia is accompanied by opening of the furan ring and gives rise to the corresponding hydroxy enamino ketone **43**.⁷⁵



The structure and the stereochemistry of β -amino-substituted trifluoromethyl enones were studied by NMR and IR spectroscopy.^{64,76} The configuration of their molecules was found to depend on the nature of the amino substituent. Trifluoromethyl enamines with NH_2 , AlkNH or ArNH groups in non-polar solvents or neat exist entirely as *Z*-isomers, which is apparently due to the presence of an intramolecular hydrogen bond. In polar solvents such as acetonitrile, an equilibrium between the *Z*- and *E*-isomers is established.

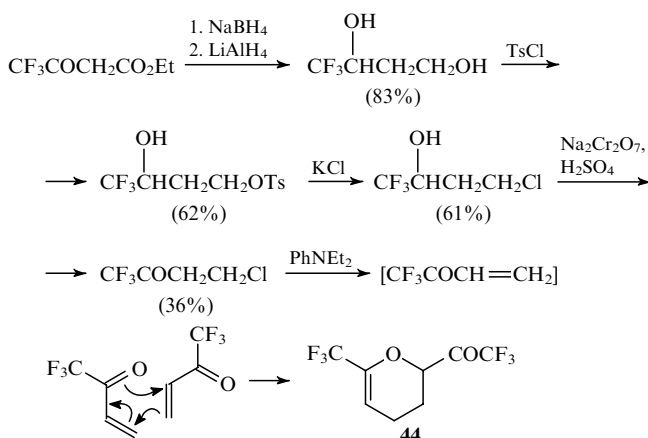


β -Dialkylamino-substituted enones always exist as *E*-isomers. Their ^1H NMR spectra exhibit two pairs of signals corresponding

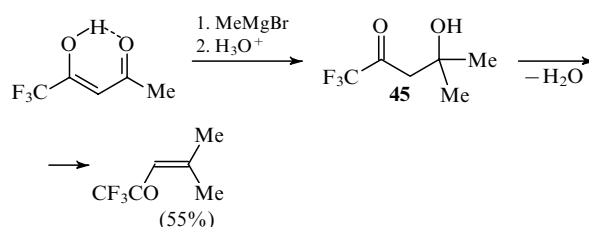
to the diethylamino group, which seems to be due to the hindrance of its rotation around the $\text{C}(4) - \text{N}$ bond caused by conjugation.⁶⁴



An attempt has been made⁷⁷ to prepare unsubstituted perfluoroalkyl enone — trifluoromethyl vinyl ketone — from ethyl trifluoroacetoacetate. The researchers found that this enone (like other unsubstituted perfluoroalkyl vinyl ketones) dimerises spontaneously at temperatures above -30°C to give dihydropyran derivative **44**.

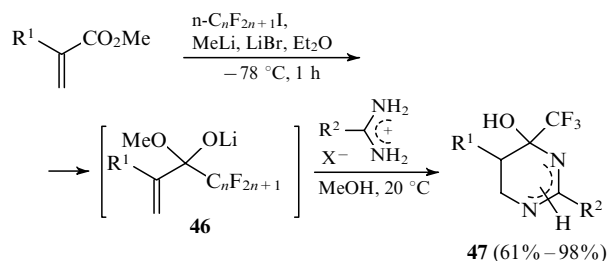


When two moles of methylmagnesium bromide are made to react with one mole of trifluoroacetylacetone, methylmagnesium bromide adds to the trifluoroacetylacetone anion formed initially (mostly at the carbonyl group further removed from the CF_3 substituent). The resulting tertiary alcohol **45** is readily dehydrated (to a large extent, during the hydrolysis) to give 1,1,1-trifluoro-4,4-dimethylbut-3-en-2-one.⁷⁸



6. Addition of perfluoroalkyl organolithium compounds to acrylic esters

Perfluoroalkyl organolithium compounds, generated by the reaction of perfluoroalkyl iodides with methyl lithium (transmetalation reaction), react with methyl acrylate or methyl methacrylate to give perfluoroalkyl enones, which exist in the reaction medium as anions of the corresponding hemiacetals **46**. Perfluoroalkyl α,β -enones having no substituents at the β -position are unstable and readily dimerise to give dihydropyran derivatives. Therefore, the hemiacetals **46** were introduced without isolation in reactions with isothiuronium salts or amidines, giving 4-perfluoroalkyltetrahydropyrimidines **47** in good yields.⁷⁹

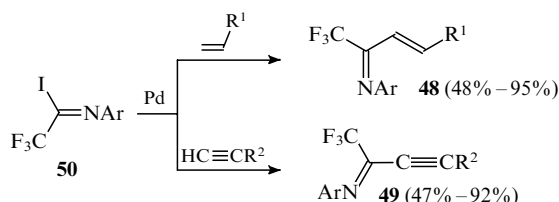


$R^1 = \text{H, Me; } R^2 = \text{AlkS, Me, Ph; } X = \text{I, Cl; } n = 2, 4, 6, 8.$

This method has not been used to prepare trifluoromethyl enones, probably, because trifluoromethyl iodide is a toxic gaseous compound, inconvenient to work with.³

7. Palladium-catalysed reactions

Imino-derivatives of alkenyl (**48**) and alkynyl (**49**) trifluoromethyl ketones can be synthesised by condensation of trifluoroacetimidoyl iodides **50** with various alkenes and alkynes in the presence of a palladium catalyst; no elimination of fluorine, typical of this type of reaction, occurs.⁸⁰ The reaction is carried out under mild conditions, alkynes reacting much faster and at lower temperatures than alkenes.

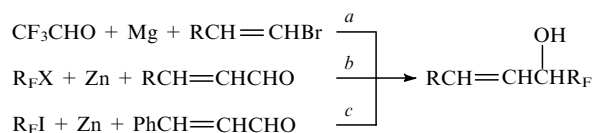


$R^1 = \text{CO}_2\text{Me}, \text{Ph}, \text{CN}, \text{SO}_2\text{Ph}, \text{C}_6\text{H}_{13}$;

$R^2 = \text{Ph}, \text{CO}_2\text{Me}, \text{CO}_2\text{Et}, \text{C}_6\text{H}_{13}, \text{CH}_2\text{OCOPh}$.

8. Oxidation of allyl alcohols

Perfluoroalkyl-containing allyl alcohols can be synthesised in two ways, namely, by the addition of vinyl-containing organometallic reagents to fluoral⁸¹ or to another perfluorinated aldehyde or by the addition of perfluoroalkyl organometallic compounds to α,β -unsaturated aldehydes.^{82,83} In both cases, the corresponding halide and the metal are directly introduced in the reaction, because perfluoroalkyl organometallic compounds are unstable and vinyl organometallic compounds are usually formed in low yields. To increase the yield of perfluoroalkyl-containing allylic alcohols, ultrasonic treatment (yield 40%–70%)^{82,83} and catalysis by palladium or nickel complexes (yield 19%–62%)⁸³ have been employed.

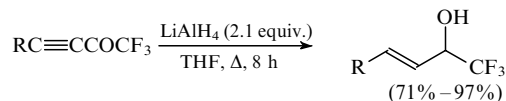


$R = \text{H}, \text{Me}, \text{Ph}, \text{Me}_3\text{Si}$; $R_\text{F} = \text{CF}_3, \text{C}_2\text{F}_5, \text{C}_3\text{F}_7$; $X = \text{Br}, \text{I}$;

(a) ultrasound, THF, 20 °C, 3 h; (b) ultrasound, DMF, 100 °C, 1 h;

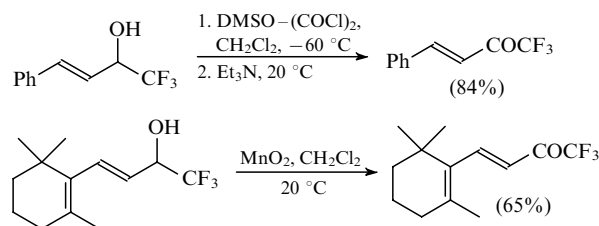
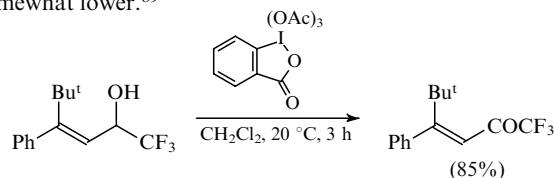
(c) $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ or $(\text{Ph}_3\text{P})_2\text{NiCl}_2$, DMF, 20 °C, 3–4 h.

In addition, trifluoromethyl-containing allylic alcohols have been prepared by the reduction of alkynyl ketones with lithium tetrahydroaluminate.⁸⁴ The reaction is stereospecific and gives the alcohols as *E*-isomers.



$R = \text{C}_n\text{H}_{2n+1}$ ($n = 4-16$), $\text{Ph}(\text{CH}_2)_2\text{CH}(\text{OSiMe}_2\text{Bu}^t)$.

Trifluoromethyl-containing allylic alcohols can be oxidised into the corresponding enones on treatment with the Dess–Martin reagent^{84–87} or Swern reagent⁸⁸ (DMSO–oxalyl chloride–triethylamine). Manganese dioxide in CH_2Cl_2 was also used for this purpose; however, in this case, the yield of the product was somewhat lower.⁸⁹



Thus, despite the high yields of the target enones, this method is limited due to the poor accessibility of the initial allylic alcohols and has not found wide use.

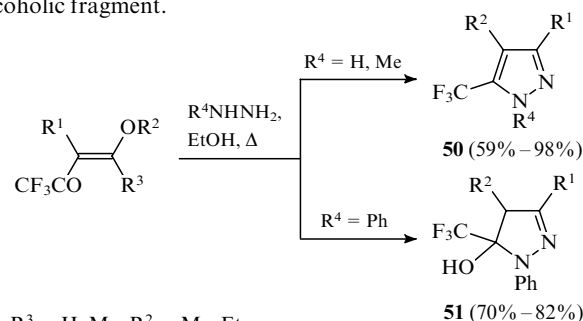
III. The use of α,β -unsaturated trifluoromethyl ketones in organic synthesis

The first example of using a trifluoromethyl enone (β -trifluoroacetylstyrene) for the synthesis of pyrazolines dates back to 1959;³⁴ however, vigorous studies along this line started in the last decade. Trifluoromethyl α,β -enones are usually employed to prepare heterocyclic compounds. Attempts to use them for other purposes, for example, as protective reagents in peptide synthesis, have also been made (see below). All trifluoromethyl enones can be divided into two main types: (a) enones containing a group capable of being substituted (*e.g.*, OR, SR, NR₂) in the β -position and (b) enones without such group. β -Alkoxy- and β -amino-substituted trifluoromethyl enones as well as alkynyl trifluoromethyl ketones (α,β -ynones) have found the widest application. Below we consider the use of these compounds in organic synthesis, except for their use to prepare trifluoromethyl-containing enones from acetylenic ketones and enones of type (a), which is described in Section II.3.

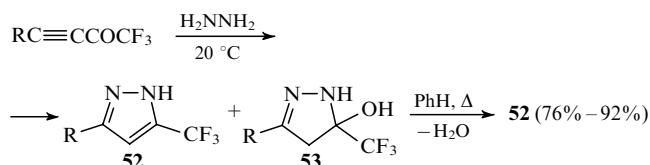
1. Reactions of β -alkoxy-substituted enones and acetylenic ketones

Enones containing a β -alkoxy group (trifluoroacetylated vinyl ethers) and alkynyl trifluoromethyl ketones are readily available reagents (see Sections II.1 and II.3). Their reactions with various nucleophiles are widely used to synthesise five-, six- and seven-membered heterocycles and other compounds containing a CF_3 group.

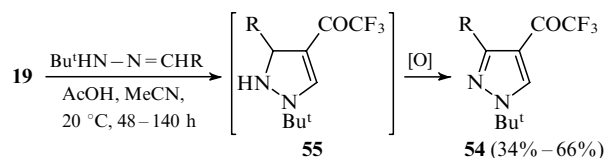
Hydrazine and methylhydrazine react with β -alkoxy-substituted trifluoromethyl enones to give trifluoromethyl-containing pyrazoles **50**.^{61,90} The reaction of trifluoromethyl enones with phenylhydrazine affords pyrazolines **51**. On treatment with sulfuric acid, the compounds **51** are not dehydrated.⁹⁰ Apparently, the conjugation of the nitrogen lone electron pair with the benzene ring hampers aromatisation. In addition, the electron-withdrawing influence of the CF_3 group stabilises the *gem*-amino-alcoholic fragment.



The reaction of alkynyl trifluoromethyl ketones with hydrazine at room temperature gives rise to a mixture of pyrazoles **52** and pyrazolines **53**. Subsequent refluxing of the reaction mixture in benzene with azeotropic distillation of water affords only pyrazoles **52** in good yields.⁹¹



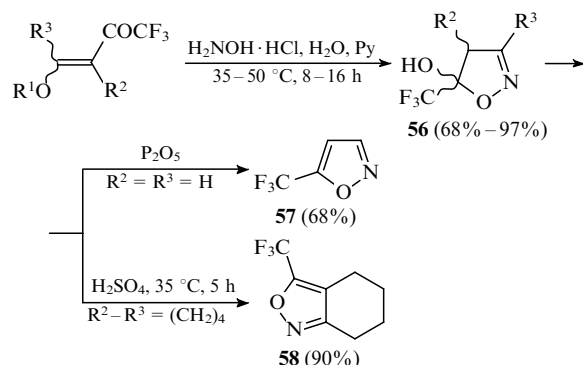
tert-Butylhydrazones of aldehydes react with β -ethoxy enone **19** giving rise to 4-trifluoroacetylpyrazoles **54**. A possible mechanism of this reaction includes replacement of the ethoxy group by the hydrazone. The subsequent cyclisation affords pyrazoles **55**, which are oxidised to pyrazoles by atmospheric oxygen.⁹²



R = Et, Ar.

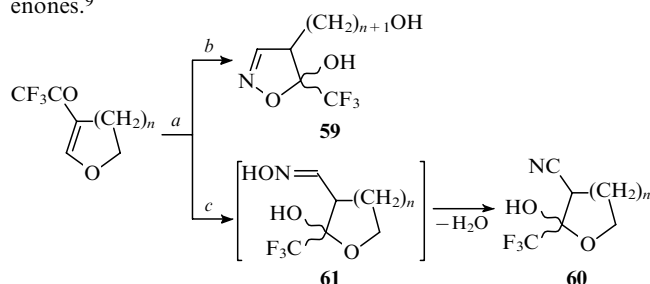
It is noteworthy that the reactions of aldehyde methylhydrazones do not give the corresponding pyrazoles. In all probability, the bulky *tert*-butyl group favours cyclisation resulting in the formation of intermediate **55**. When the pyrazoles **54** are heated with 90% sulfuric acid, the *tert*-butyl group is removed, which gives *N*-unsubstituted 4-trifluoroacetylpyrazoles in high yields.

The reactions of β -alkoxy-substituted enones with hydroxylamine follow different pathways, depending on the structure of the initial enone. Thus acyclic enones and enones containing no oxygen atom in the ring are converted into isoxazolines **56**,^{9,64,93} which are dehydrated on treatment with P_2O_5 (followed by distillation of the reaction mixture)⁶⁴ or concentrated H_2SO_4 ⁹³ to give the corresponding isoxazoles **57** or **58**.



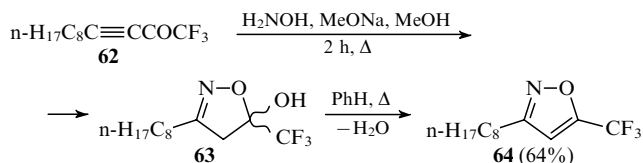
R¹ = Me, Et; R², R³ = H, Me; R²–R³ = (CH₂)₄.

Cyclic enones prepared by trifluoroacetylation of 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran are converted in a similar way at 0–20 °C into isoxazolines **59**, which result from opening of the furan or pyran ring. However, when the reaction is carried out at higher temperatures, it gives rise to tetrahydrofuran and tetrahydropyran derivatives **60**, formed apparently upon dehydration of aldehyde oximes **61**, resulting from recyclisation of the starting enones.⁹

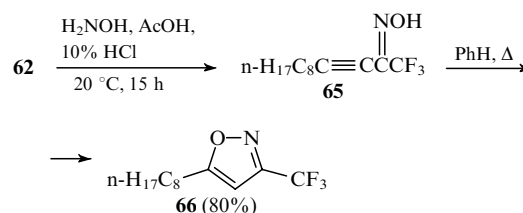


n = 1, 2; (a) $\text{H}_2\text{NOH}\cdot\text{HCl}$, H_2O , Py; (b) 0–20 °C, 5–170 h; (c) 65–85 °C, 30–170 h.

Isoxazolines and isoxazoles were also obtained in good yields in the reaction of alkynyl ketones with hydroxylamine, the regioselectivity of the reaction being dependent on the reaction conditions.⁹¹ Thus ketone **62** reacts with hydroxylamine in an alkaline medium to give isoxazoline **63**; on refluxing in benzene with azeotropic distillation of water, this product undergoes dehydration to give the corresponding isoxazole **64**.

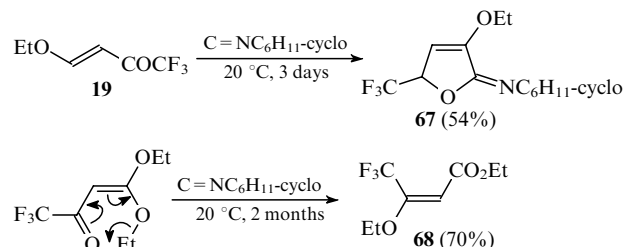


This reaction performed in an acid medium gives initially oxime **65**, which cyclises on refluxing in benzene giving rise to isoxazole **66**, isomeric to the isoxazole **64**.

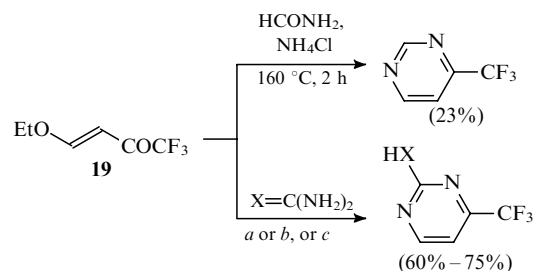


This reaction pathway may be due to the fact that in an acid medium, dehydration is possible, which shifts the equilibrium towards the oxime. In an alkaline medium, the formation of isoxazoline, which exists as the anion under these conditions, appears to be thermodynamically more favourable.

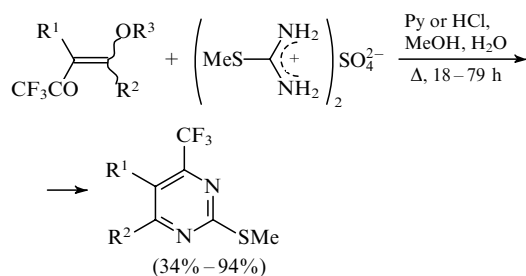
The reactions of some β -alkoxy-substituted trifluoromethyl enones with isocyanides have been studied.⁹⁴ β -Ethoxyvinyl trifluoromethyl ketone **19** reacts with cyclohexyl isocyanide to give 2,5-dihydrofuran derivative **67**, whereas β,β -diethoxyvinyl trifluoromethyl ketone isomerises under the same conditions to ester **68**.



When β -alkoxy-substituted enones are made to react with formamide in the presence of NH_4Cl , with compounds of the urea series⁹⁵ or with isothiuronium salts,⁹⁶ trifluoromethylpyrimidines are formed. In the last-named case, the reaction is carried out in the presence of an acid or a base.

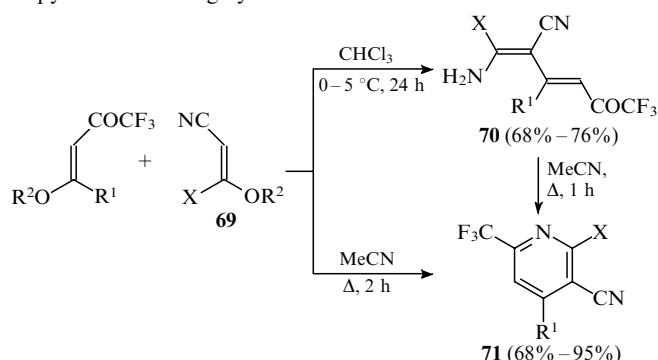


(a) HCl , EtOH, 20 °C, 48 h (X = O, S); (b) PhH, Δ , 6 h (X = NH); (c) AcONa, AcOH, 100 °C, 2 h (X = *p*-NSO₂C₆H₄NHCOMe).



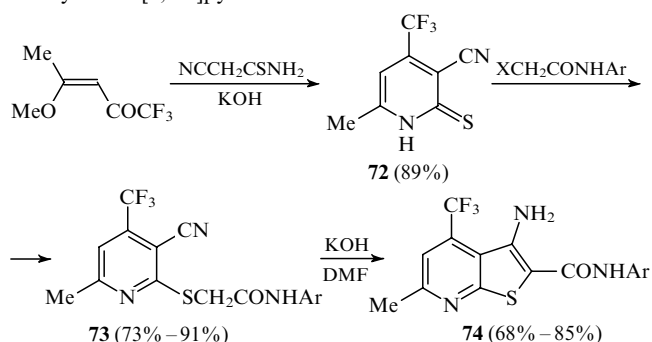
$R^1, R^2 = \text{H, Me; } R^3 = \text{Me, Et; } R^1-R^2 = (\text{CH}_2)_2, (\text{CH}_2)_3$.

The reactions of β -alkoxy-substituted enones with enamino nitriles **69** result in the formation of pyridine derivatives containing a CF₃ group. Acyclic adducts **70** are formed as intermediates. For $R^1 = \text{H}$, they can be isolated in good yields on cooling. At room temperature, mixtures of the adducts **70** and cyanopyridines **71** are formed; refluxing of initial compounds in acetonitrile leads to pyridines **71** in high yields.⁹⁷



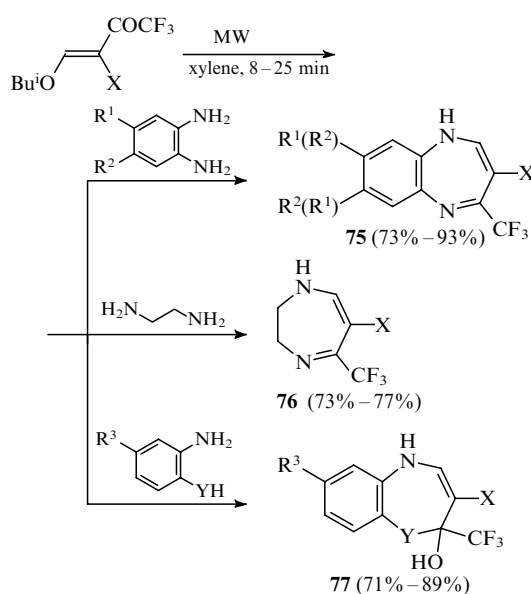
$X = -\text{N}(\text{CH}_2)_2-, -\text{N}(\text{CH}_2)_3-, \text{Y} = \text{O, NMe, NCOOEt}$.

Unlike reactions of enamino nitriles with alkoxyenones, which give 2-trifluoromethylpyridines, the reaction of 1,1,1-trifluoro-4-methoxypent-3-en-2-one with cyanothioacetamide results in the regioselective formation of 4-trifluoromethylpyridinethione **72**, the structure of which was proved by X-ray diffraction analysis.⁹⁸ The alkylation of the pyridinethiones **72** obtained by *N*-arylchloro(iodo)acetamides followed by cyclisation of the resulting compounds **73** in an alkaline medium affords 3-amino-4-trifluoromethylthieno[2,3-*b*]pyridinecarboxamides **74**.



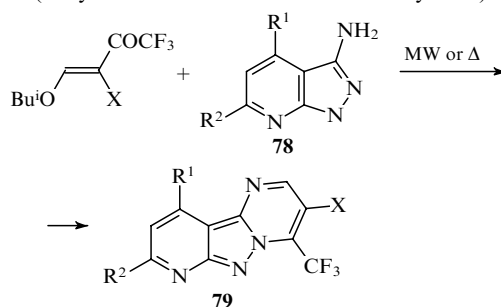
$X = \text{Cl, I; Ar} = \text{Ph, 4-MeC}_6\text{H}_4, 3\text{-BuOC}_6\text{H}_4$.

The reaction of the butoxy-substituted trifluoromethyl enone, prepared by trifluoroacetylation of vinyl isobutyl ether, with 1,2-diamines (*o*-phenylenediamine or 1,2-ethylenediamine) gives rise to 1,5-diazepine **75** or **76**, while the reactions with *o*-aminophenols or *o*-aminothiophenol yield 1,5-oxazepines or 1,5-thiazepines **77**, respectively. The bis(trifluoroacetyl) derivative was also introduced into this reaction. Good yields were attained by using microwave (MW) radiation, whereas conducting the reaction in boiling xylene resulted in a complex mixture of products (Scheme 1).^{99, 100}



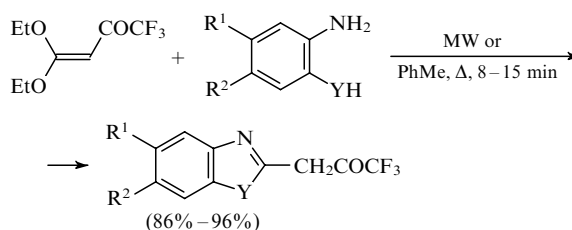
$X = \text{H, COCF}_3; R^1 = \text{H, Me; } R^2 = \text{H, Me, Cl, NO}_2, \text{COPh; } R^3 = \text{H, Cl; Y} = \text{O, S}$.

3-Aminopyrazolo[3,4-*b*]pyridine derivatives **78** enter into a similar reaction as nucleophiles. On exposure to microwave radiation, trifluoromethyl-substituted derivatives of pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidine **79** are formed in 62%–78% yields (the yield in the thermal reaction is only 20%).¹⁰¹



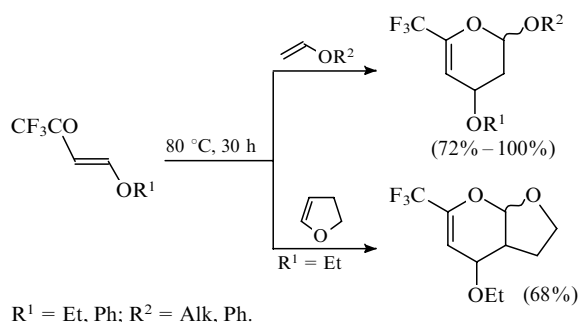
$X = \text{H, COCF}_3; R^1 = \text{Me, CF}_3; R^2 = \text{Me, Ar}$.

4,4-Diethoxy-1,1,1-trifluorobut-3-en-2-one reacts with *o*-phenylenediamines, *o*-aminophenols and *o*-aminothiophenol to give five-membered heterocycles — benzimidazoles, benzoxazoles and benzothiazoles — in high yields, the reaction occurring both on refluxing in toluene and on exposure to microwave radiation.¹⁰⁰

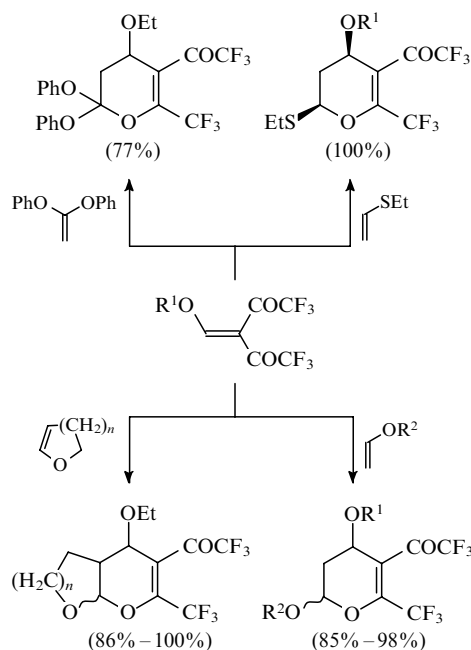


$Y = \text{O, S; } R^1 = \text{H, Cl; } R^2 = \text{H; Y} = \text{NH; } R^1, R^2 = \text{H, Me}$.

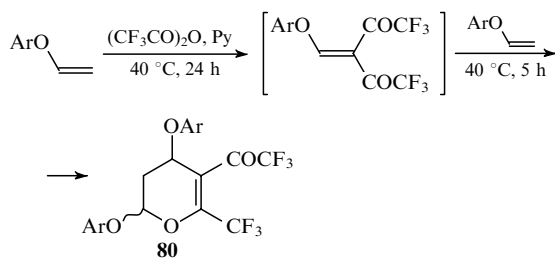
The reaction of β -ethoxy(phenoxy)-substituted enones with vinyl ethers affords 3,4-dihydro-2*H*-pyrans in good yields; thus, these enones are efficient heterodienes in the hetero-Diels–Alder reaction.¹⁰²



This reaction proceeds especially easily for β -alkoxy-substituted bis(trifluoromethyl) enones. The presence of the second strong electron-withdrawing group, COCF_3 , increases the reactivity of trifluoromethyl enones as heterodienes. The reaction occurs at room temperature to give 5-trifluoroacetyl-3,4-dihydro-2H-pyrans in high yields.¹⁷

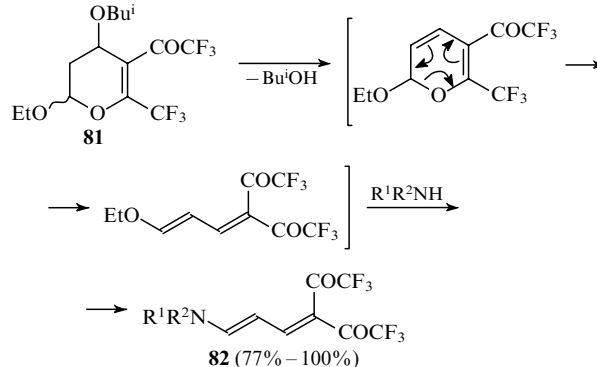


Aryl vinyl ethers react with trifluoroacetic anhydride to give the corresponding bis(trifluoroacetyl) derivatives. It was found¹⁷ that these compounds are unstable and cannot be isolated in a pure state; however, they can be introduced without isolation in the reaction with a second equivalent of aryl vinyl ether. Aryloxy-substituted 5-trifluoroacetyl-3,4-dihydro-2H-pyrans **80** were obtained in this way in 50%–68% yields. In some cases, these products are formed directly in trifluoroacetylation of aryl vinyl ethers.¹⁷



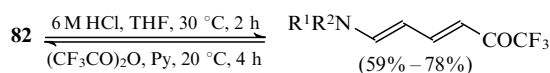
Ring opening in 5-trifluoroacetyl-3,4-dihydro-2H-pyrans **81** induced by secondary amines in acetonitrile gives rise to 1-amino-4,4-bis(trifluoroacetyl)buta-1,3-dienes **82**. The mechanism pro-

posed for this reaction includes elimination of isobutanol, electrocyclic ring opening and nucleophilic substitution of the amine for the ethoxy group. It is of interest that no reaction of this type occurs in the series of non-fluorinated analogues of pyrans **81**.¹⁰³

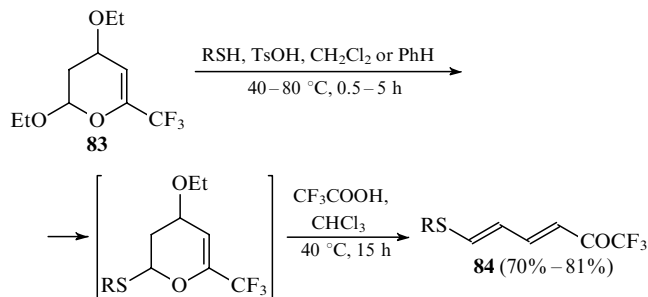


$R^1 = \text{Alk, Ph}; R^2 = \text{Alk.}$

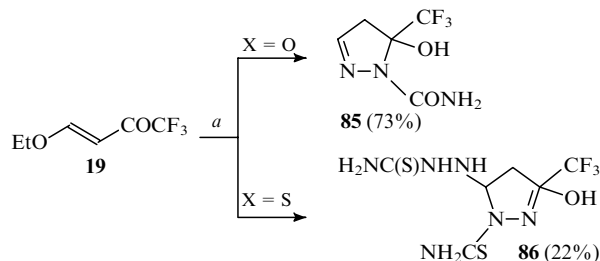
One trifluoroacetyl group in bis(trifluoroacetyl)-substituted dienes **82** can be eliminated in an acid medium; this gives 1-amino-4-trifluoroacetylbuta-1,3-dienes, which can be acylated by trifluoroacetic anhydride in the presence of pyridine to give the initial compounds **82**.¹⁰³



3,4-Dihydro-2H-pyran **83**, prepared by hetero-Diels–Alder reaction of β -ethoxy trifluoromethyl enone with vinyl ethyl ether, enters into a similar reaction. The dihydropyran ring opening induced by thiols in an acid medium is stereospecific and gives (*E*)-1-alkylthio-4-trifluoroacetylbuta-1,3-dienes **84** in good yields.¹⁰⁴



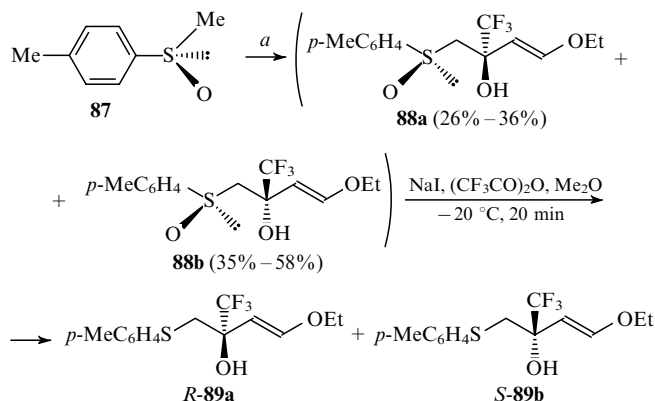
The reactions of β -ethoxy enone **19** with semicarbazide and thiosemicarbazide result in the formation of 2-pyrazoline-1-carboxamide **85** and 5-(1-thiosemicarbazido)-2-pyrazoline-1-thiocarboxamide **86**, respectively.¹⁰⁵



(a) $\text{H}_2\text{NCXNHNH}_2$, EtONa, EtOH; NH_4Cl , H_2O .

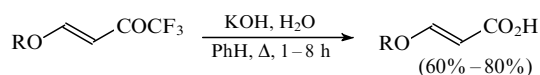
Apart from the synthesis of heterocycles, β -alkoxy-substituted enones have been used to prepare acyclic compounds. Thus the reaction of the lithium salt of (*R*)-methyl 4-tolyl sulfoxide **87** with the enone **19** (or some other perfluoroalkyl-containing enone) gives a mixture of two diastereoisomers of β -hydroxy sulfoxides **88a,b** in a ratio of $\sim 1:1$. These diastereoisomers were separated by chromatography; their configurations were determined by

X-ray diffraction analysis. The subsequent reduction of the sulfoxide group permits the preparation of two enantiomers of chiral allylic alcohols **89a,b** with known absolute configurations in a pure state (overall yield 40%–94%).¹⁰⁶

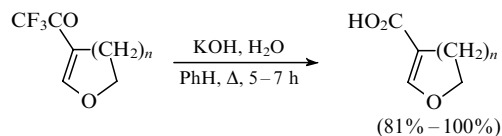


(a) LiAlH_4 , $-78\text{ }^\circ\text{C}$; $\text{EtOCH}=\text{CHCOCF}_3$ (**19**).

Trifluoroacetylated vinyl ethers (including cyclic ones) readily undergo haloform cleavage induced by KOH in boiling benzene in the presence of a small quantity of water to give α,β -unsaturated acids.⁸

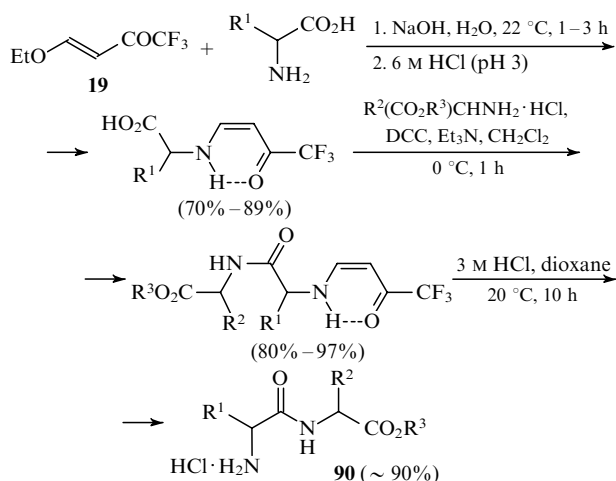


$\text{R} = \text{Et}, \text{Bu}^n, \text{Bu}^i, \text{Ph}$.



$n = 1, 2$.

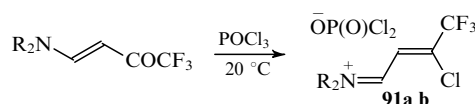
The replacement of the alkoxy group in β -alkoxy enones on treatment with amines occurs with high yields and the resulting enaminones are readily hydrolysed. Therefore, these enones can be used as protective reagents in peptide synthesis. Thus the β -ethoxy enone **19** reacts with amino acids in the presence of an equivalent of a base at room temperature to give the corresponding enaminones. The amino acids protected in this way were used to synthesise dipeptides **90**. The protective group can be easily removed on treatment with 3 M HCl in dioxane at room temperature.¹⁰⁷



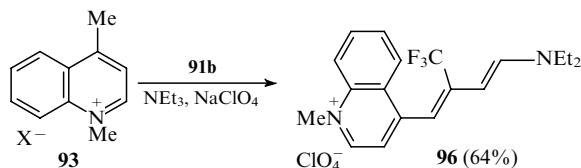
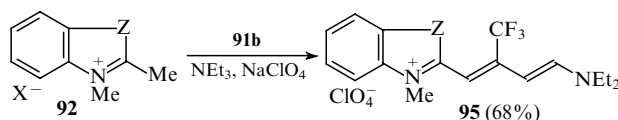
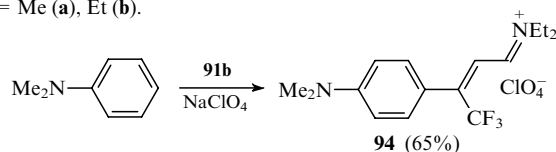
$\text{R}^1 = \text{Me}, \text{Pr}^i, (\text{CH}_2)_2\text{CO}_2\text{Me}, (\text{CH}_2)_2\text{CO}_2\text{Bu}^i, \text{PhCH}_2$; $\text{R}^2 = \text{H}, \text{Pr}^i, \text{PhCH}_2$; $\text{R}^3 = \text{Et}, \text{Bu}^i, \text{Me}$; DCC is dicyclohexylcarbodiimide.

2. Reactions of β -amino-substituted trifluoromethyl enones

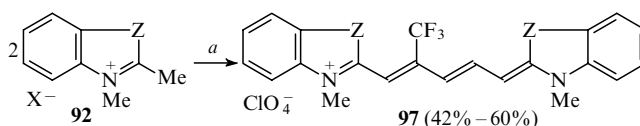
In addition to β -alkoxy-substituted trifluoromethyl enones, their β -dialkylamino-substituted analogues, readily prepared by treatment of β -alkoxy enones with dialkylamines, are also used for the synthesis of various trifluoromethyl-containing heterocyclic compounds. Since enaminones are less reactive in nucleophilic substitution than β -alkoxy enones, they are activated by virtue of POCl_3 or trifluoromethanesulfonic anhydride. Thus the reactions of enaminones with POCl_3 afford iminium salts **91a,b**, vinylogues of the Vilsmeier complexes. Despite the fact that these salts are less reactive than the complex $\text{DMF} \cdot \text{POCl}_3$, they are still able to aminoformylate ($\sim 20\text{ }^\circ\text{C}$, 1 h), e.g., *N,N*-dimethylaniline or quaternary salts of nitrogenous heterocycles **92** and **93**. These reactions yield hemicyanines **94–96**, respectively, which are valuable intermediates in the synthesis of cyanine dyes.⁵⁹



$\text{R} = \text{Me}$ (a), Et (b).

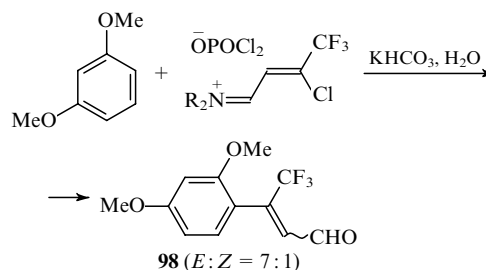


When two equivalents of the quaternary salt **92** react with one equivalent of triethylamine and with the iminium salt **91**, dicarbo-cyanines **97** are formed.⁵⁹



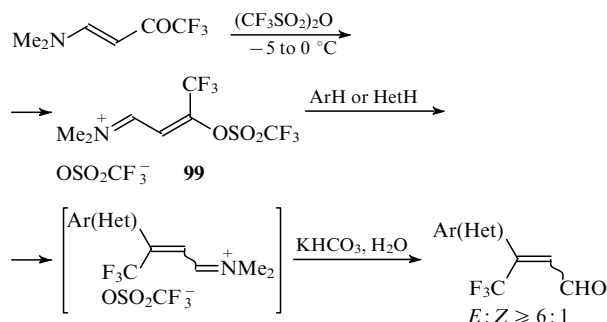
$\text{Z} = \text{S}, \text{CM}_2, \text{CH}=\text{CH}$; (a) **91**, NEt_3 , NaClO_4 , $20\text{ }^\circ\text{C}$, 30 min.

The electrophilicity of iminium salts proves to be insufficient for them to react with aromatic compounds less reactive than *N,N*-dimethylaniline. Thus quenching with a solution of KHCO_3 of the reaction mixture obtained upon the reaction between the complex of 4-dimethylamino-1,1,1-trifluorobut-3-en-2-one with POCl_3 and 1,3-dimethoxybenzene gave α,β -unsaturated aldehyde **98** in 7%–12% yield,¹⁰⁸ more than 80% of the initial 1,3-dimethoxybenzene being recovered unchanged.

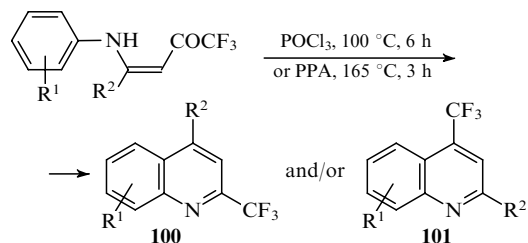


Due to the low electrophilicity of the iminium salts obtained by the reaction of enaminones with POCl_3 it has been proposed to

use more reactive salt **99**, formed from enaminone and trifluoromethanesulfonic anhydride and containing a better leaving group (OSO_2CF_3). The reactions of this compound with electron-donating aromatic or heteroaromatic compounds under mild conditions give rise to α,β -unsaturated trifluoromethyl-containing aldehydes.¹⁰⁸ The reaction is stereoselective giving mainly *E*-isomers of the aldehydes; it occurs for relatively reactive compounds such as indoles, pyrroles, furans and 1,3-dimethoxybenzene, whereas thiophene and anisole do not enter into this reaction, even when it is carried out under more rigorous conditions.

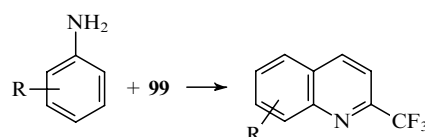


β -Arylamino-substituted trifluoromethyl enones cyclise on treatment with acids giving rise to 2-trifluoromethyl- (**100**) and 4-trifluoromethylquinolines (**101**).^{37, 52, 109, 110} As catalysts, POCl_3 , ZnCl_2 and polyphosphoric acid (PPA) were used. Quinolines **101** are the products of 'normal' cyclisation, while the mechanism of formation of 2-trifluoromethylquinolines **100** needs to be further investigated. The ratio of the reaction products depends on the acidic catalyst used and the structure of the initial enone. Cyclisation of enones with $\text{R}^2 = \text{H}$ gives only 2-trifluoromethylquinolines **100**,^{37, 52} and when $\text{R}^2 = \text{Alk}$ or Ph , 4-trifluoromethylquinolines **101** are formed predominantly.⁵² The presence of electron-donating substituents in the *meta*-positions of the aromatic amine substantially facilitates cyclisation and increases the total yield.



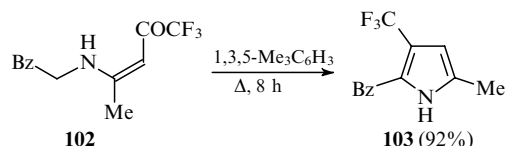
$\text{R}^1 = \text{Me}, \text{OMe}, \text{Hal}; \text{R}^2 = \text{H}, \text{Alk}, \text{Ph}; \text{PPA}$ is polyphosphoric acid.

The reactions of aniline derivatives with the iminium salt **99** afford 2-trifluoromethylquinolines and no 4-trifluoromethyl-derivatives.¹¹¹



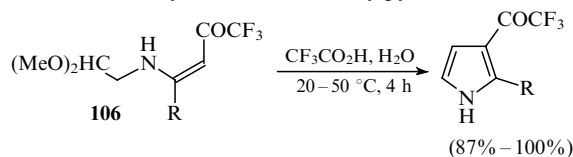
$\text{R} = \text{Me}, \text{OMe}, \text{SMe}, \text{OCF}_3, \text{Cl}, \text{OH}.$

Enaminone **102** cyclises on refluxing in a high-boiling solvent to give substituted 3-fluoromethylpyrrole **103**.¹¹²



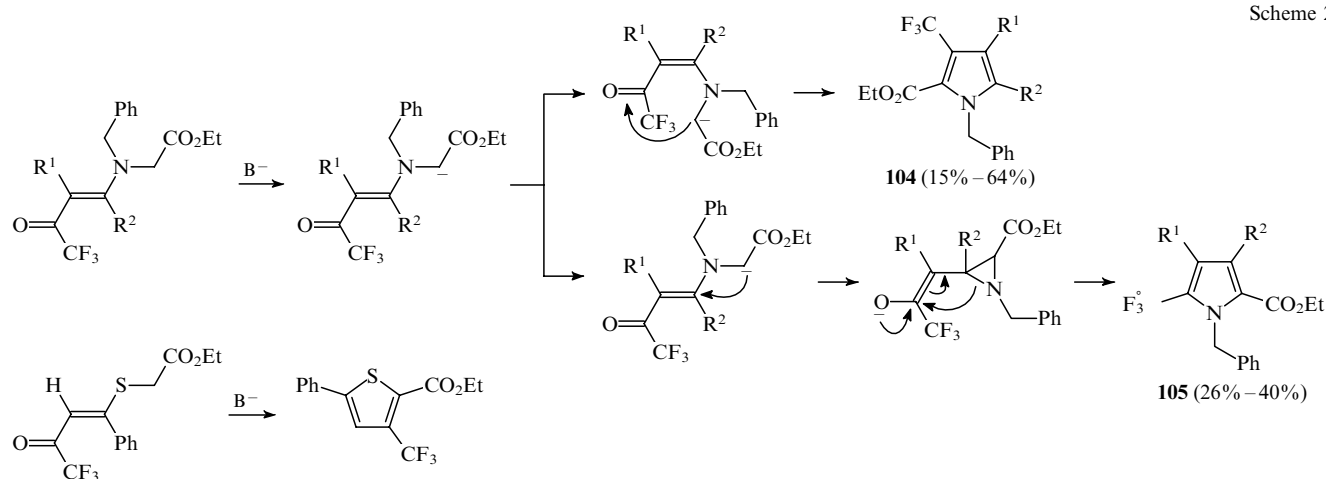
A detailed study of the mechanism of cyclisation of such enamino ketones in the presence of a base demonstrated that the transformations of trifluoromethyl-containing ketones include not only 5-*exo*-trigonal cyclisation to give 3-trifluoromethylpyrroles **104** but also previously unknown 3-*exo*-trigonal cyclisation, giving 2-trifluoromethylpyrroles **105**. Similarly, in the case of sulfide derivatives of enones, 3-trifluoromethylthiophenes were isolated in addition to 2-trifluoromethylthiophenes (Scheme 2).¹¹³

Meanwhile, enaminones **106** cyclise in the presence of trifluoroacetic acid to yield 3-trifluoroacetylpyrroles.^{112, 114}

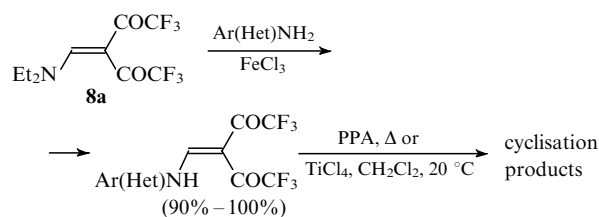


$\text{R} = \text{H}, \text{Me}, \text{Ph}.$

Reactions of 3-(diethylaminomethylidene)-1,1,1,5,5,5-hexafluoropenta-2,5-dione **8a** (enaminodione, whose electrophilicity is enhanced by the presence of the second trifluoroacetyl group) with various nucleophiles have been studied.¹¹⁵ When the enaminodione **8a** reacts with aromatic amines in the presence of catalytic amounts of FeCl_3 , the diethylamino group is substituted to give *N*-aryl-substituted enaminodiones, which cyclise on treatment with PPA or TiCl_4 , the yields of the reaction products being substantially higher in the case of TiCl_4 .

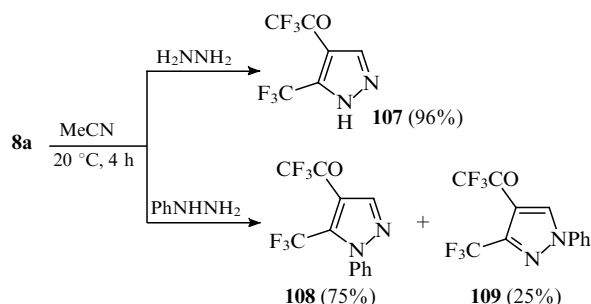


Scheme 2

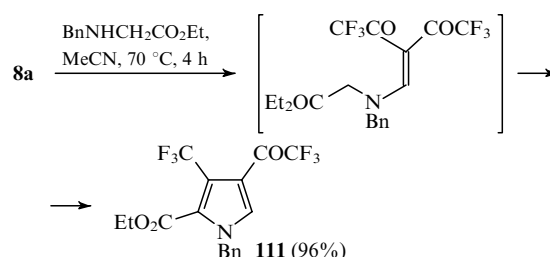
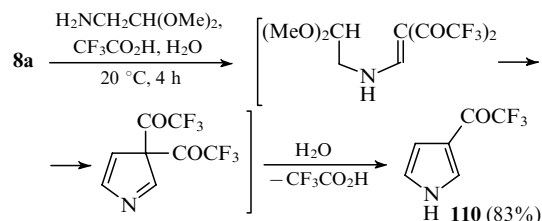


Ar(Het)NH	Cyclisation product	Yield (%)	
		PPA	TiCl ₄
		10	96
		0	90
		15	0
		—	100
		25	60
		0	25

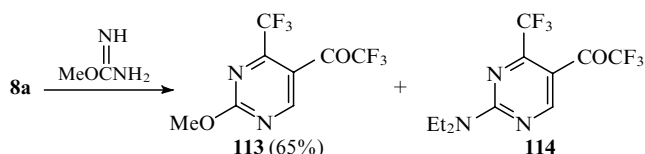
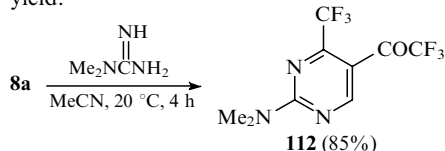
The reactions of the enaminodione **8a** with bifunctional nucleophiles occur similarly to the reactions of β -alkoxy-substituted enones. Thus the reaction of the compound **8a** with hydrazine gives rise to trifluoromethyl-substituted pyrazole **107**, while its reaction with phenylhydrazine yields a mixture of regioisomers **108** and **109** in 1 : 3 ratio.¹¹⁵



The reactions of the enaminodione **8a** with α -aminocarbonyl compounds (or their acetals) — 2,2-dimethoxyethylamine or ethyl *N*-benzylglycinate — result in the corresponding pyrroles **110** and **111**.¹¹⁵ In the reaction with 2,2-dimethoxyethylamine, for aromatisation to occur one molecule of $\text{CF}_3\text{CO}_2\text{H}$ is eliminated; this is the pathway to 3-trifluoroacetylpyrrole **110**.¹¹⁴



The enaminodione **8a** has also been introduced in reactions with compounds of the urea series. The reaction of **8a** with guanidine affords pyrimidine **112** in a good yield.¹¹⁵ The reaction with *O*-methylisourea affords two products — 1-methoxypyrimidine **113** and 1-diethylaminopyrimidine **114** — because diethylamine formed in the reaction reacts with methoxypyrimidine **113**. Optimisation of the reaction conditions (MeCN, 65 °C, 4 h) makes it possible to prepare the target compound **113** in 65% yield.

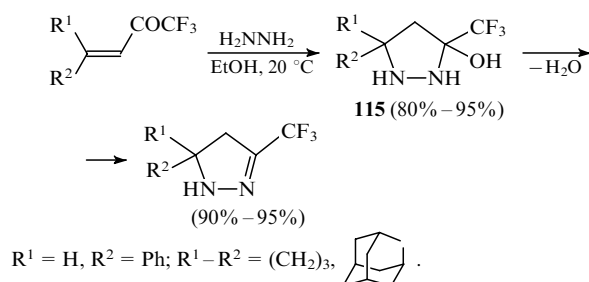


Thus, the enaminodione **8a** is a readily available reagent, widely used for the synthesis of various heterocyclic compounds containing both trifluoromethyl and trifluoroacetyl groups.

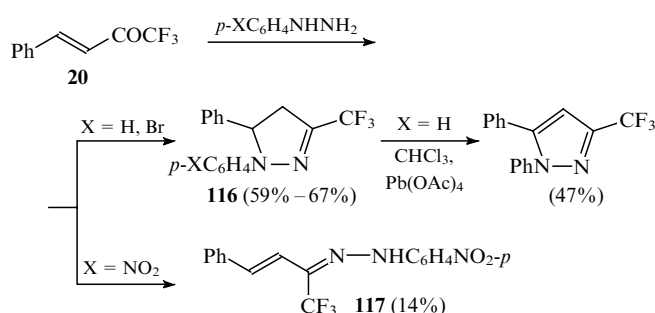
3. Reactions of trifluoromethyl enones containing no replaceable group

Trifluoromethyl enones containing no β -substituents able to be replaced are less available compounds than β -alkoxy- or β -amino-substituted enones; therefore, their reactions have not been studied so extensively. However, in the early 1990s, new methods for the synthesis of these compounds were developed (*e.g.*, trifluoroacetylation of alkenes in the presence of the complex of dimethyl sulfide with boron trifluoride^{25,26}). This stimulated vigorous studies of their synthetic potential.

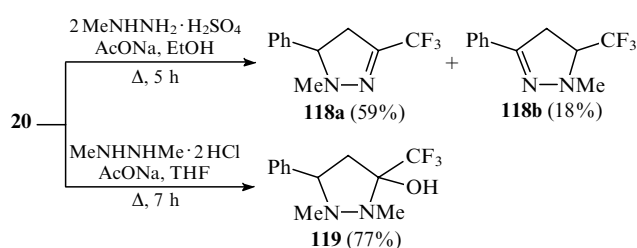
Trifluoromethyl enones containing no replaceable substituents readily react with various bifunctional nucleophiles. Thus the reactions of phenyl-, cyclobutyl- or adamantyl-substituted enones with hydrazine result in the formation of pyrazolidines **115**, which contain a *gem*-amino-alcoholic fragment, stabilised by the electron-withdrawing influence of the CF_3 group. Dehydration of the pyrazolidines **115**, which occurs either during the reaction, or on prolonged storage, or on refluxing in benzene in the presence of a catalytic amount of toluene-*p*-sulfonic acid (depending on the nature of substituents R^1 and R^2) gives the corresponding pyrazolines.¹¹⁶



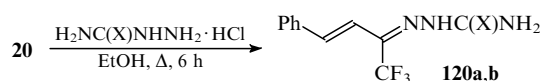
β -Trifluoroacetylstyrene **20** reacts with substituted aryl- or alkyl-hydrazines. Thus the reaction with *p*-bromophenyl- and phenyl-hydrazines affords pyrazolines **116**. Oxidation of the compound **116** with $X = H$ by lead tetraacetate affords the corresponding pyrazole in a moderate yield.³¹ The reaction with *p*-nitrophenylhydrazine does not give pyrazoline; in this case, β -trifluoroacetylstyrene *p*-nitrophenylhydrazone **117** is formed in a low yield.



When β -trifluoroacetylstyrene **20** is made to react with methylhydrazine, a mixture of isomeric pyrazolines **118a,b** (in $\sim 1:3$ ratio) is formed, which is apparently due to the fact that the nucleophilicities of the nitrogen atoms in methyl hydrazine are close. The reaction with 1,2-dimethylhydrazine gives pyrazolidine **119**, apparently due to the fact that elimination of water yielding a $C=C$ bond is substantially hampered.¹¹⁶

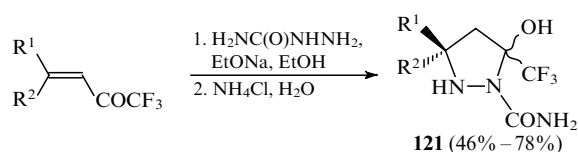


The enone **20** reacts with semicarbazide or thiosemicarbazide in an acid medium to afford semicarbazone **120a** or thiosemicarbazone **120b**. These compounds are stable both in acid and alkaline media and do not tend to cyclise.¹⁰⁵



$X = O$ (**120a**, 91%), S (**120b**, 93%).

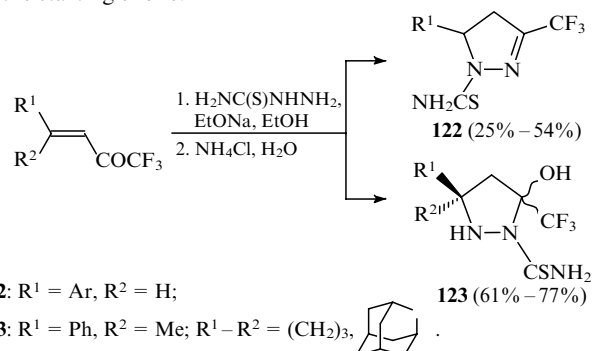
Conversely, the reaction with semicarbazide carried out in the presence of an equimolar amount of sodium ethoxide gives a cyclic compound, 5-trifluoromethylpyrazolidine-1-carboxamide **121**.¹⁰⁵



$R^1 = Ar, R^2 = H; R^1-R^2 = (CH_2)_3, \text{ bicyclic system}.$

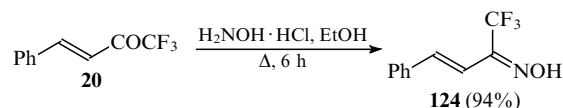
The reaction occurs regio- and stereoselectively, yielding predominantly one diastereoisomer. The bulky substituents R^1 and R^2 occupy pseudo-equatorial positions, *i.e.* thermodynamically the most favourable isomers are produced.¹⁰⁵

When trifluoromethyl-containing enones react with thiosemicarbazide under the same conditions, either 3-trifluoromethyl-2-pyrazolinethiocarboxamides **122** or 5-trifluoromethyl-2-pyrazolinethiocarboxamides **123** are obtained, depending on the structure of the starting enone.¹⁰⁵

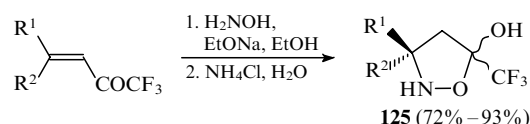


Unlike pyrazolidines **115**, pyrazolidine-1-carboxamides and -thiocarboxamides cannot be converted into the corresponding pyrazolines.¹⁰⁵

The reaction of β -trifluoroacetylstyrene **20** with hydroxylamine in an acid medium gives rise to oxime **124**, which does not tend to cyclise in either acid or alkaline medium.¹¹⁷



Meanwhile, the reactions of trifluoromethyl enones with hydroxylamine in the presence of an equimolar amount of sodium ethoxide give isoxazolidines **125** in good yields.¹¹⁷



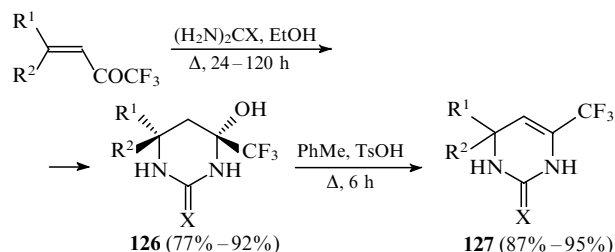
$R^1, R^2 = Ar, \text{ Het, Alk}.$

The attempts to carry out dehydration of isoxazolidines **125** to isoxazoles were unsuccessful. Refluxing of these compounds in toluene with azeotropic distillation of water in the presence of toluene-*p*-sulfonic acid gives rise to the corresponding oxime, the initial enone being formed as a side product. At the same time, β -alkoxy enones or alkynyl ketones are converted into isoxazoles, which are dehydrated in an acid medium to give isoxazoles.^{63,93} Thus, the possibility of aromatisation has the crucial influence on the reaction route.

The isoxazolidines **125** are fairly interesting from the stereochemical viewpoint. They exist in solutions at room temperature as equilibrium mixtures ($\sim 1:1$) of diastereoisomers. The energy barrier to nitrogen inversion in the compound **125** is almost a half that in the isoxazolidines described previously by Kostyanovsky *et al.*,^{118,119} however, it is still high enough ($51-55 \text{ kJ mol}^{-1}$)¹¹⁷ to retard nitrogen inversion. Therefore, the signals in the ^1H and ^{13}C NMR spectra recorded at room temperature are broadened, and when the temperature decreases, the conformation becomes 'frozen' and signals for four diastereoisomers are observed (due to the chirality of the nitrogen atom).

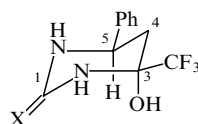
The reactions of trifluoromethyl enones with compounds of the urea series afford tetrahydropyrimidines **126** in high yields.¹²⁰ The compounds **126** are easily dehydrated on refluxing in toluene in the presence of catalytic amounts of toluene-*p*-sulfonic acid

[unlike cyclohexane derivatives containing a $C(OH)CF_3$ fragment]¹²¹ giving rise to dihydropyrimidines **127**.¹²⁰



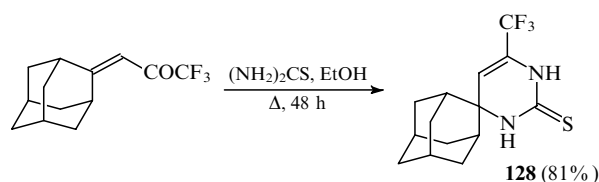
$R^1 = H, R^2 = Ph; R^1-R^2 = (CH_2)_3; X = O, S.$

In the case of β -trifluoroacetylstyrene **20**, the reaction occurs stereoselectively, yielding predominantly ($\geq 95\%$) one of the two possible diastereoisomers of **126**. The configuration of the major diastereoisomer was established by X-ray diffraction analysis. This was found to be the thermodynamically more favourable *trans*-isomer (regarding the arrangement of the Ph and OH groups), in which the bulkiest substituents, Ph and CF_3 , occupy equatorial positions.

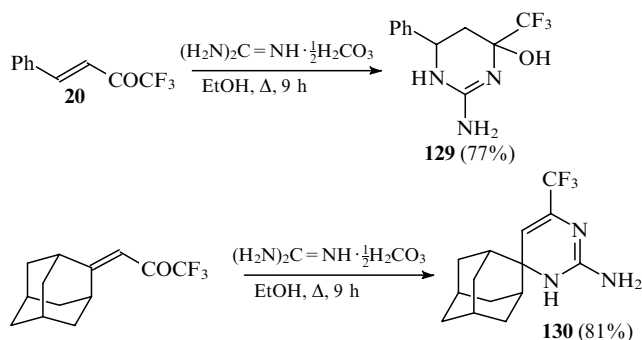


It should be noted that such stereochemistry has also been observed for cyclohexane derivatives with the same substituents at the 3- and 5-positions;¹²¹ this may be due to the relatively large effective size of the trifluoromethyl group[†] and to the high electron density on this group.

The reaction of a sterically hindered trifluoromethyl enone having an adamantane fragment with thiourea gives dihydropyrimidine **128**.¹²⁰

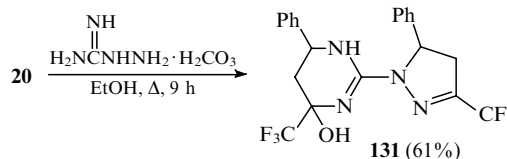


The reactions of phenyl- and adamantyl-substituted trifluoromethyl enones with guanidine occur in a similar way giving rise to the corresponding aminopyrimidines **129** and **130**.

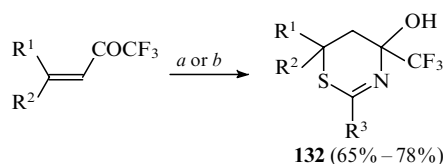


β -Trifluoroacetylstyrene **20** reacts with aminoguanidine to give compound **131**, resulting from addition of two enone molecules to an aminoguanidine molecule and containing two heterocyclic moieties (tetrahydropyrimidine and pyrazoline).¹²⁰

In this case, water is eliminated only from the five-membered ring, which is consistent with the general rule according to which trifluoro-substituted pyrazolidines are dehydrated more readily than tetrahydropyrimidines.^{116, 120}



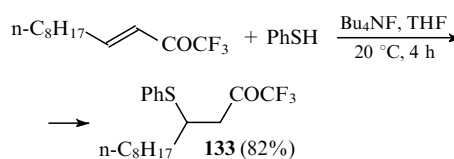
The reactions of trifluoromethyl enones with thiourea and thioacetamide in an acid medium afford dihydrothiazines **132**.¹²³ Both reactions are regiospecific and give one isomer, formed upon the addition of sulfur at the double bond and nitrogen at the carbonyl group. This reaction route was interpreted¹²³ in terms of the principle of hard and soft acids and bases.



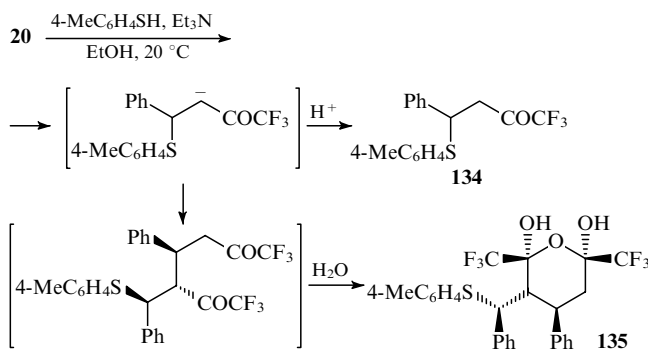
$R^1 = H, R^2 = Ph; R^1-R^2 = (CH_2)_3;$

(a) $(H_2N)_2CS, HCl, EtOH, \Delta$ ($R^3 = NH_2$);
(b) $MeC(S)NH_2, EtOH, \Delta$ ($R^3 = Me$).

The reactions of some trifluoromethyl enones with thiols have been studied. Thus 1,1,1-trifluorodec-3-en-2-one reacts with benzenethiol to give β -oxo sulfide **133**.^{86, 124}



As opposed to this, the reaction of the enone **20** with 4-methylthiophenol gives rise to two products, β -oxo sulfide **134** and pyran **135**. The compound **134** results from Michael addition, while the pyran **135** is formed upon interaction of two molecules of the ketone with one molecule of the thiol and one water molecule.¹²⁴

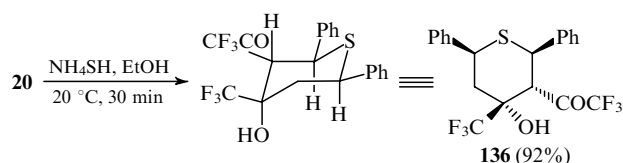


The reaction is stereospecific, the compound **135** being formed as one diastereoisomer of the 16 possible isomers (the molecule has five asymmetric centres); the bulkiest phenyl, trifluoromethyl, and (4-methylphenylthio)phenylmethyl substituents occupy equatorial positions. The relative configuration of the carbon atom located outside the ring and bearing the phenyl and 4-methylphenylthio substituents is also fixed. Thus, effective asymmetric 1,2-induction takes place.¹²⁴

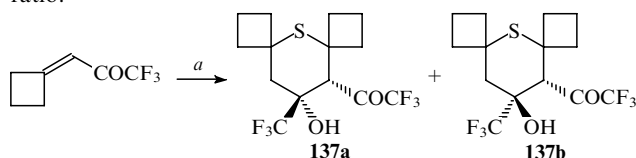
The reactions of trifluoromethyl enones with ammonium hydrogen sulfide have been studied.¹²⁵ The reaction pathway depends on the structure of the initial enone. For instance, the

[†] The energy required for substituents to pass from an equatorial to an axial position (conformational energy) was reported¹²² to increase in the sequence $Me < Pr^i < CF_3 < Bu^i$.

enone **20** reacts stereospecifically yielding tetrahydropyran **136** as one diastereoisomer of the eight possible isomers.¹²⁵

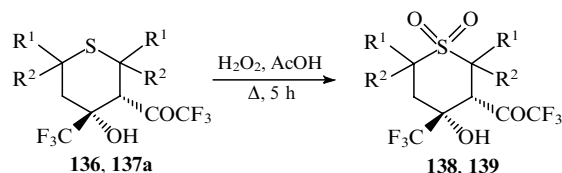


The reaction of ammonium hydrogen sulfide with cyclobutyl-substituted enone affords a mixture of *cis*- and *trans*-diastereoisomers of tetrahydrothiopyran **137a,b** (total yield 90%) in 1 : 1 ratio.¹²⁵



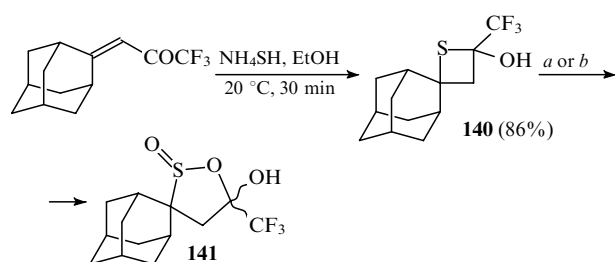
(a) NH_4SH , EtOH, 20 °C, 3 min.

The tetrahydrothiopyrans **136** and **137a** are oxidised with retention of configuration, giving the corresponding sulfones **138** and **139** in almost quantitative yields.



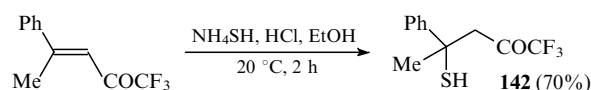
$\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$ (**136**, **138**); $\text{R}^1 - \text{R}^2 = (\text{CH}_2)_3$ (**137a**, **139**).

The reaction of ammonium hydrogen sulfide with adamantylidenemethyl ketone follows an unusual route and affords compound **140**, containing a four-membered thietane ring, as the only product. On treatment with hydrogen peroxide in acetone or acetic acid, this product is oxidised to give 1,3-sultine **141** as a mixture of diastereoisomers.¹²⁵

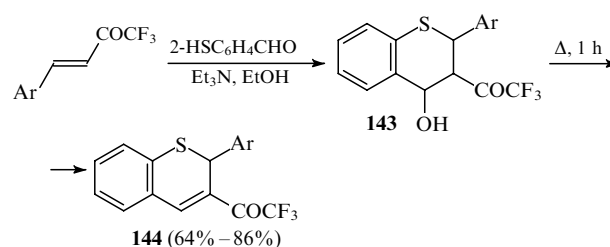


(a) H_2O_2 , Me_2CO , Δ , 24 h (92%); (b) H_2O_2 , AcOH, Δ , 1 min (61%).

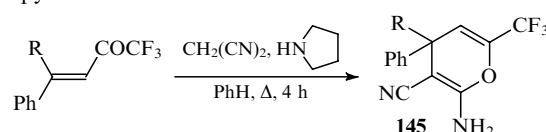
1,1,1-Trifluoro-4-phenylpent-3-en-2-one with three substituents at the double bond reacts with ammonium hydrogen sulfide to yield β -sulfanyl ketone **142**.¹²⁵



Aryl-substituted trifluoromethyl enones were found to react with 2-sulfanylbenzaldehyde at room temperature in ethanol in the presence of a basic catalyst (triethylamine). This gives a mixture of two compounds, thiochromanes **143** and 2*H*-thiochromenes **144**, resulting from dehydration of **143**. When the reaction mixture is refluxed for 1 h, the compounds **144** are formed in good yields. The intermediate thiochromane **143** (Ar = Ph) can be isolated in 65% yield only when the starting enone is β -trifluoroacetylstyrene **20**.¹²⁴

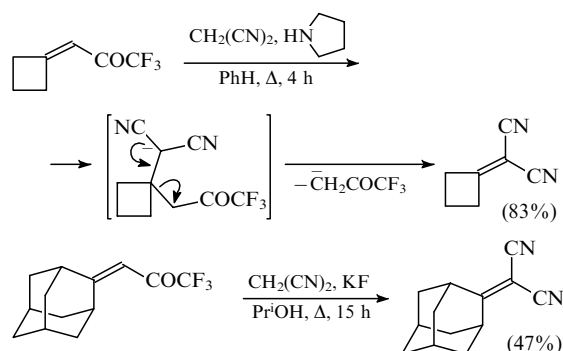


The reactions of trifluoromethyl enones with malonodinitrile and cyanoacetamide in protic (ethanol, propan-2-ol) and aprotic (benzene) solvents in the presence of various basic catalysts (triethylamine, pyrrolidine, calcined potassium fluoride) have been studied.¹²⁶ The reaction route depends on the reaction conditions and on the structure of the initial ketone.¹²⁶ On refluxing in benzene with malonodinitrile in the presence of pyrrolidine as a catalyst, β -aryl-substituted enones are converted into pyrans **145**.¹²⁶

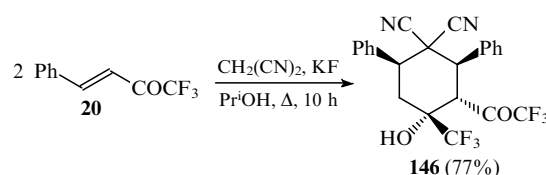


$\text{R} = \text{H}$, Me.

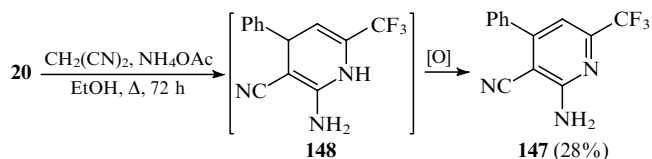
Under the same conditions, cyclobutylidenemethyl trifluoromethyl ketone is converted into cyclobutylidenemalonodinitrile, while adamantylidenemethyl trifluoromethyl ketone reacts in the presence of a stronger base (calcined potassium fluoride) to give adamantylidenemalonodinitrile. Apparently, in the case of ketones with an exocyclic double bond, the initial Michael addition of malononitrile is not followed by cyclisation to give pyran derivatives; instead, elimination of trifluoroacetone enolate occurs. The researchers cited suggest¹²⁶ that otherwise, cyclisation products would contain a spiro-fused fragment and, as a consequence, the ring would be more strained.



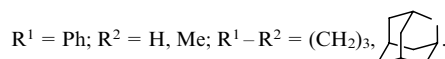
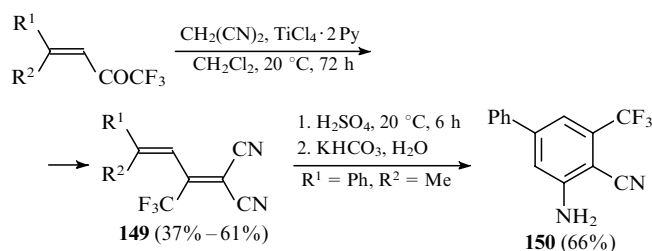
The reaction of malonodinitrile with two equivalents of β -trifluoroacetylstyrene **20** in the presence of potassium fluoride in isopropanol affords substituted cyclohexanol **146**, the product of addition of two molecules of the ketone to malonodinitrile and the subsequent intramolecular aldol condensation. The compound **146** is formed in a good yield as a single diastereoisomer of the eight possible isomers; the bulky substituents (Ph, CF_3 , COCF_3) occupy energetically more favourable equatorial positions.¹²⁶



The reactions of trifluoromethyl enones with malonodinitrile in the presence of ammonium acetate occur ambiguously. Only in the case of the enone **20**, was pyridine derivative **147**, resulting from oxidation of the corresponding dihydropyridine **148** with atmospheric oxygen, isolated in a low yield.

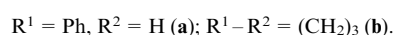
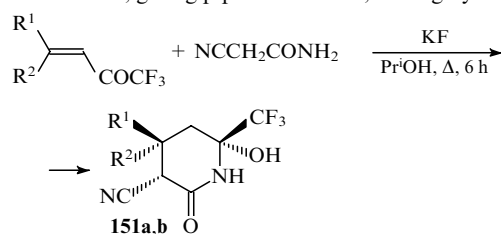


1,1-Dicyanobuta-1,3-dienes **149**¹²⁶ were synthesised by Knoevenagel condensation of trifluoromethyl enones with malonodinitrile in the presence of the complex $\text{TiCl}_4 \cdot 2\text{Py}$ in dichloromethane.

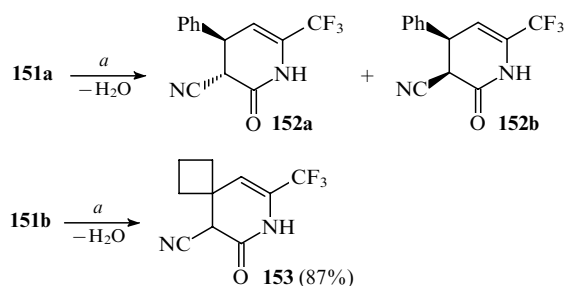


An attempt to carry out cyclisation of the compounds **149** in an acid medium was undertaken. When 1,1-dicyano-4-phenyl-2-trifluoromethylpenta-1,3-diene was treated with concentrated sulfuric acid, substituted benzonitrile **150** was obtained; in other cases, such cyclisation did not occur.

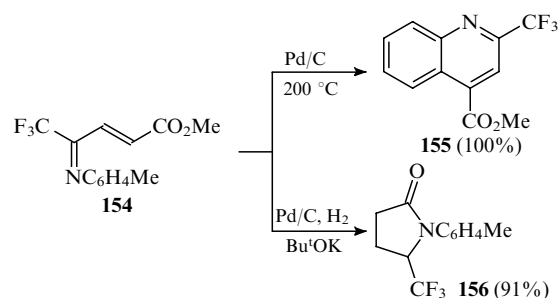
It was found that on refluxing of benzylidene- and cyclobutylidene-methyl trifluoromethyl ketones with cyanoacetamide in isopropanol in the presence of calcined KF, a stereospecific reaction occurs, giving piperidines **151a,b** in high yields.¹²⁶



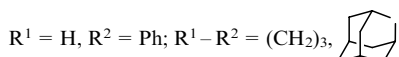
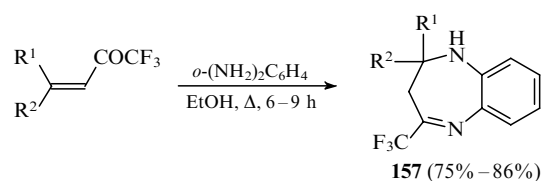
Dehydration of the piperidines **151a** and **151b** gives dihydropyridines **152a,b** (a mixture of diastereoisomers in ~2:1 ratio) and spiro compound **153**, respectively.



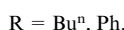
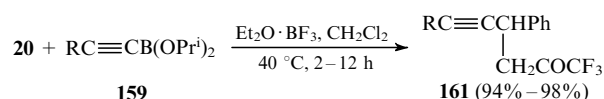
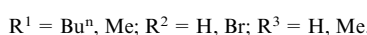
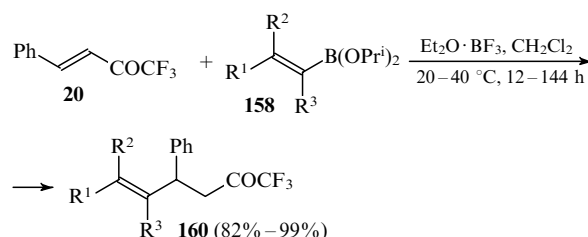
Imino-derivatives of unsaturated trifluoromethyl-containing ketones **154** cyclise in the presence of palladium supported on carbon to give, depending on the reaction conditions, either 2-trifluoromethylquinoline derivative **155** or 5-trifluoromethylpyrrolidone derivatives **156**.⁸⁰



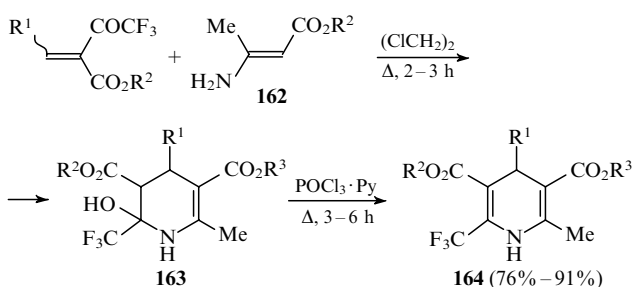
The reactions of trifluoromethyl enones with *o*-phenylenediamine afford 2,3-dihydro-1,5-benzodiazepines **157**.¹²⁷ The compounds **157** undergo spontaneous dehydration, apparently, due to the fact that this enables the energetically favourable conjugation of the resulting C=N bond with the benzene ring.



γ,δ -Unsaturated trifluoromethyl-containing ketones **160** and **161** have been prepared by the reactions of β -trifluoromethylstyrene **20** with alk-1-enyl- (**158**)¹²⁸ and alk-1-ynyl-diisopropoxyboranes (**159**)⁶² in the presence of boron trifluoride etherate.

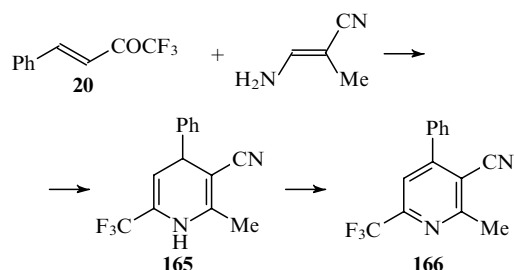


α -Alkoxy carbonyl-substituted trifluoromethyl α,β -enones, prepared by condensation of ethyl trifluoroacetoacetate with aldehydes, react with enamino esters **162** to afford fairly stable hydroxypyridines **163**, whereas their non-fluorinated analogues are converted directly into 1,4-dihydropyridines. The hydroxypyridines **163** were dehydrated in the presence of a number of catalysts; the best yields were attained when the complex $\text{POCl}_3 \cdot \text{Py}$ adsorbed on silica gel was used.¹²⁹

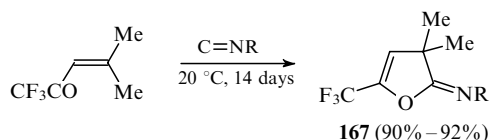


The reaction of the enone **20** with β -aminocrotononitrile results in the formation of 6-trifluoromethylpyridine **165** in a low

yield; oxidation of this product leads to the corresponding aromatic derivative **166**.¹³⁰

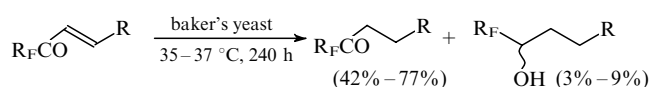


The reactions of 1,1,1-trifluoro-4-methylpent-3-en-2-one with isocyanides occur at room temperature without catalysts to give stable 1,4-cycloaddition products, namely, substituted dihydrofurans **167**.¹³¹



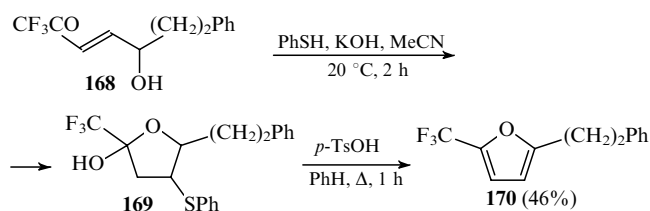
R = Bu^t, cyclo-C₆H₁₁.

Treatment of perfluoroalkyl α,β -enones with reagents that are widely used for asymmetric reduction of non-fluorinated ketones (e.g., Binal-H, Darvon-red)¹³² results in racemic alcohols.¹³³ The microbial reduction of perfluoroalkyl enones by baker's yeast was studied; however, the corresponding saturated ketones rather than alcohols were formed as the major reaction products. The alcohols were formed with high enantioselectivities (*ee* 77%–85%) but in very low yields.



R_F = CF₃, C₂F₅, n-C₄F₉; R = Me, Ph.

The reaction of γ -hydroxy enone **168**, synthesised by oxidation of the corresponding protected allyl alcohol by the Dess–Martin reagent, with benzenethiol affords a tetrahydrofuran derivative — hemiacetal **169**. On refluxing in benzene in the presence of sulfuric acid with azeotropic distillation of water, the compound **169** eliminates water and benzenethiol being thus converted into the corresponding furan **170**.⁸⁴



IV. Conclusion

The data presented in this review can be summarised by stating that development of facile methods for the synthesis of trifluoromethyl α,β -enones remains a topical task. Trifluoromethyl enones containing no RO, RS or R₂N groups are not very easy to synthesise; nevertheless, they are highly reactive compounds possessing great synthetic potential.

A remarkable feature of trifluoromethyl enones is their high reactivity towards nucleophiles combined with regio- and stereoselectivity of the corresponding reactions. Similar reactions of their non-fluorinated analogues with nucleophiles occur non-selectively giving products in low yields or do not occur at all. Another significant feature that distinguishes trifluoromethyl α,β -enones from non-fluorinated enones is their ability to form

compounds incorporating a stable hemiacetal or hemiaminal fragment, CF₃C(OH)O or CF₃C(OH)NH.

Thus, α,β -unsaturated trifluoromethyl-containing ketones are fairly convenient 'building blocks' for the synthesis of diverse CF₃-derivatives; further research into their properties and the ways of using them in organic synthesis appears quite promising.

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Bipyrroles, furyl- and thienylpyrroles

S E Korostova (deceased), A I Mikhaleva, B A Trofimov

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Abstract. Data on the methods of preparation of bipyrroles and furyl-, thienyl- and selenienylpyrroles are summarised and described systematically. The reactivity and the prospects of application of these compounds are discussed. Particular attention is paid to a new convenient one-step method for the synthesis of hetaryl-substituted pyrroles starting from alkyl hetaryl ketoximes and acetylene. The bibliography includes 191 references.

I. Introduction

Derivatives of five-membered aromatic heterocycles (pyrrole, furan, thiophene and selenophene) are, as a rule, endowed with high biological activity and other useful properties and find ever-increasing uses in medicine, agriculture and technology.^{1–11}

Of five-membered aromatic heterocycles, pyrrole possesses the highest reactivity and most diverse chemical properties. It is not accidental that it is pyrrole that Nature has 'chosen' for constructing the 'vital pigments' chlorophylls and hemoglobin, as well as other vitally important supramolecular structures (various porphyrins, chlorins, prodigiosins, vitamin B₁₂, etc.). For this reason, amongst all five-membered aromatic heterocycles the molecules containing the pyrrole nucleus attract the greatest attention of researchers and are studied in most detail.

The chemistry of bipyrroles as well as of pyrroles with furan, thiophene and selenophene substituents is a very recent field in the chemistry of heterocyclic compounds. Until recently, no sufficiently efficient and general methods of their preparation existed; therefore, these compounds remained attractive but hard to access and little studied subjects. The development of this field began in the 1970s, when new methods for pyrrole synthesis appeared or the existing procedures were modified to allow for linking five-membered aromatic heterocycles to the pyrrole ring. A very simple and versatile method based on the reaction of ketoximes with acetylene (the Trofimov reaction) has been developed, which allows the synthesis not only of hetarylpyrroles non-substituted at the nitrogen atom but also their 1-vinyl derivatives from accessible alkyl hetaryl ketoximes. This also stimulated studies of

reactivity, structure, biological activity and of other useful properties of hetarylpyrroles.

Some aspects of the chemistry of pyrroles with furyl, thienyl and selenienyl substituents have been presented in monographs,^{4, 12} reviews,^{5, 6, 13–21} the US physical and technical encyclopedia (chapter 'Acetylene'),²² and Ph.D. and D.Sc. theses.^{23–27} Nevertheless, generalising papers that summarise the progress in the chemistry of hetaryl-substituted pyrroles are missing. We have attempted to fill this gap by generalising and systematising the currently available literature on the methods of synthesis, reactivity, biological and other properties of pyrroles linked to five-membered aromatic heterocycles.

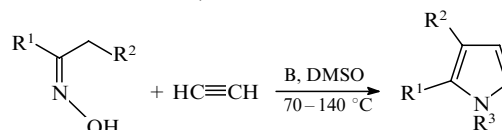
II. Methods of synthesis

Conventional methods for the synthesis of pyrroles — the Knorr, Hantzsch, Piloty, Yuriev (except for the Paal–Knorr synthesis) reactions — have not found wide use for the preparation of pyrroles bound to other five-membered heterocycles. This goal can be reached most efficiently using the method based on the reaction of alkyl hetaryl ketoximes with acetylene (the Trofimov reaction), which is carried out in one step using accessible initial compounds.

New methods have been developed for the preparation of hetarylpyrroles based on activated acetylenes, *e.g.*, by condensation of hetarylacetylenes with trimethylsilyl cyanide, as well as those with the use of isocyanides, other cyano compounds, azides, *etc.*

1. Synthesis from ketoximes and acetylene (the Trofimov reaction)

In the early 1970s, heterocyclisation of ketoximes with acetylene in a superbasic system (strong base–polar aprotic solvent) was discovered, which yielded in one step 1*H*- and 1-vinylpyrroles (the Trofimov reaction).^{4, 5, 14–20, 23, 24, 26}



R¹ = Alk, Ar, Het; R² = H, Alk, Ar; R¹–R² = (CH₂)_n; n = 3–5; B = MOH, MOR, MON = $\langle$; M is alkali metal; R³ = H, CH = CH₂.

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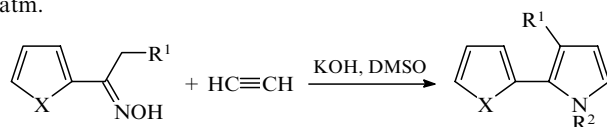
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Later it was established that this reaction is of a general character and embraces virtually all ketoximes that have at least

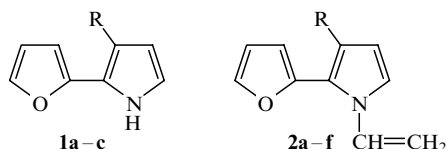
one CH₃ or CH₂ group in the α -position relative to the oxime function and contain no groups unstable in the presence of strong bases. This finding has led to successful syntheses of pyrroles and 1-vinylpyrroles with alkyl, alkenyl, cyclopropyl, aryl and hetaryl substituents in the ring; condensed pyrrole systems of the type of cycloheptano[*b*]pyrrole, dihydrobenzo[*g*]indole and 5-azaindoles including stable free radicals with the NO $\cdot$ group at position 5, *etc.*^{13–24, 26, 28–33}

Synthesis of hetarylpyrroles with furyl and thienyl substituents by this method was first described by Trofimov *et al.*^{34–36} 2-(2-Furyl)-3-methyl-1-vinyl- and 3-ethyl-2-(2-furyl)-1-vinylpyrroles were synthesised from the corresponding ketoximes and acetylene in yields up to 85%.³⁵ An analogous approach was used to prepare 2-(2-thienyl)- and 2-(2-thienyl)-1-vinylpyrroles in 60% and 50% yields, respectively.³⁶ The reactions were carried out in an autoclave under an initial pressure of acetylene from 6 to 16 atm.



R¹ = H, Me, Et; R² = H, CH=CH₂; X = O, S.

Subsequently, this method has successfully been used for the preparation of 3-alkyl-2-(2-furyl)pyrroles **1a–c** and their 1-vinyl derivatives **2a–f**.³⁷



Compound	R	Yield (%)	Compound	R	Yield (%)
1a	H	36	2c	Et	85
1b	Me	23	2d	Pr ⁿ	77
1c	Et	39	2e	Pr ⁱ	81
2a	H	80	2f	Bu ⁿ	76
2b	Me	92			

Under conditions close to those established⁴ earlier for aliphatic ketoximes [100 °C, ketoxime:KOH = 5:3 (w/w), excess of acetylene, pressure 10–16 atm.], the reaction of 2-furyl methyl ketoxime with acetylene produces a mixture consisting of 1*H*- (**1a**) and 1-vinyl-2-(2-furyl)pyrroles (**2a**) in the ratio of *ca* 1:4 and an overall yield of 71% (16% and 55%, respectively).³⁷

Under analogous conditions 2-(2-furyl)-3-methyl-1-vinylpyrrole (**2b**, 57% yield) and the corresponding pyrrole **1b** (8% yield) are formed from ethyl 2-furyl ketoxime. At a higher temperature (130 °C) and an equimolar ketoxime:KOH ratio this reaction proceeds selectively with the formation of vinylpyrrole alone (**2b**, 92% yield).

The yield of furylpyrroles **1a** and **2a** upon the reaction of 2-furyl methyl ketoxime and acetylene depends on the reaction temperature (Table 1). At temperatures below 100 °C, the rate of ketoxime cyclisation into pyrrole **1a** and vinylation of the latter to vinylpyrrole **2a** is too low (the ketoxime conversion does not exceed 40%). At 130–150 °C, one observes resinification that decreases the yield of 1-vinylpyrrole **2a**. In addition, at a high temperature the process of deoximation of the initial oxime to 2-acetylfuran becomes noticeable. The optimal conditions for the synthesis of 3-alkyl-2-(2-furyl)-1-vinylpyrroles are as follows: 110–130 °C, 3 h, excess of acetylene (initial pressure 10–14 atm) and equimolar ratio ketoxime:KOH).

It should be pointed out that lithium hydroxide, which catalyses selectively the stage of heterocyclisation in an analogous reaction with methyl phenyl and benzyl phenyl ketoximes,^{38,39} is

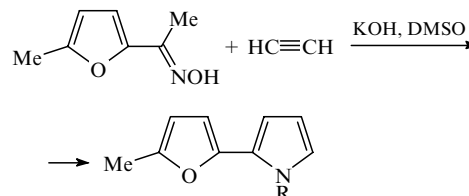
Table 1. Dependence of the yield of 2-(2-furyl)- (**1a**) and 2-(2-furyl)-1-vinylpyrroles (**2a**) on the reaction temperature (molar ratio ketoxime:KOH = 1:1, C₂H₂ pressure 10–14 atm, 3 h).³⁷

Temperature / °C	Yield of mixed products (%)	Composition of mixture (%) ^a			Ketoxime conversion (%)
		ket-oxime	compound 1a	compound 2a	
70	85	60	26	14	40
90	82	20	24	56	80
110	70	traces	39	71	~100
120	65	"	15	85	~100
130	46	undetected	traces	~100	~100
150	21	"	"	~100	~100

^a According to ¹H NMR data.

not selective in this case: even at 100 °C a mixture of 1*H*- (**1a**) and 1-vinylpyrroles (**2a**) is formed in the ratio 15:1, while the total yield of pyrroles is lower than with KOH (~50% instead of 72%, GLC).

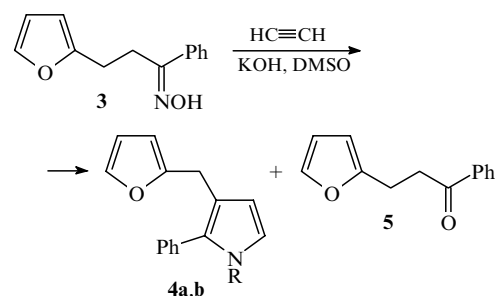
The corresponding pyrrole is also readily formed from methyl (5-methyl-2-furyl) ketoxime and acetylene.⁴⁰



R = H (53%), CH=CH₂ (62%).

Under atmospheric pressure (100 °C, 5 h, equimolar ratio ketoxime:KOH) the yield of 2-(5-methyl-2-furyl)pyrrole is 53% and the conversion of ketoxime is 80%. Under these conditions 2-(5-methyl-2-furyl)-1-vinylpyrrole is formed in a rather low yield (15%). Under acetylene pressure of 12 atm (90 °C, 3 h, molar ratio ketoxime:KOH = 1:2), the same reaction produces vinylpyrrole in 62% yield, though being accompanied by resinification. According to GLC data, no more than ~3% of the corresponding 1*H*-pyrrole remains unconsumed under these conditions.⁴⁰

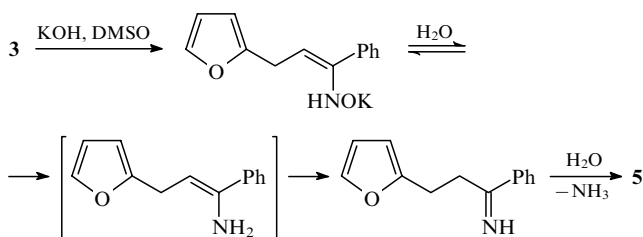
It is known that even at 50–60 °C and atmospheric pressure alkyl phenyl ketoximes react readily with acetylene to form the corresponding pyrroles in yields up to 83%.⁴¹ The reaction of ethyl 2-furyl ketoxime with acetylene under a pressure of 10 atm and 100 °C produces 2-(2-furyl)-3-methyl- and 2-(2-furyl)-3-methyl-1-vinylpyrroles in yields of 8% and 57%, respectively.³⁷ Quite unexpectedly, in the condensation of the oxime **3** with acetylene (10 atm, 100 °C) the conversion of oxime **3** was no more than 65%, while the yield of pyrrole **4a** was as low as 30%. The reaction is accompanied by considerable resinification.



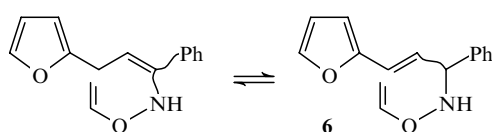
R = H (**a**), CH=CH₂ (**b**).

A decrease in the reaction temperature to 75–80 °C did not lead to higher yield of compound **4a**, because even at this

temperature ketoxime **3** seems to undergo deoxygenation to the ketone **5**.



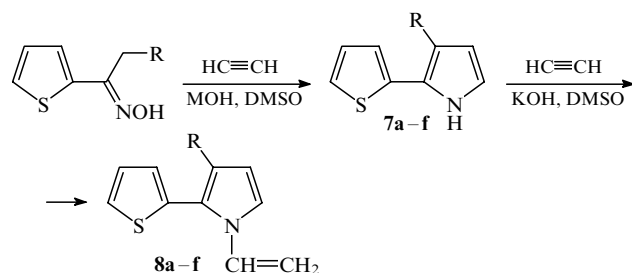
Vinylpyrrole **4b** was detected in the reaction mixture only by GLC.⁴⁰ Low yield of pyrroles **4a,b** was explained by the decrease in the reactivity of ketoxime **3** due to the presence of bulky phenyl and furyl groups preventing the approach of oximate anion to the triple bond. An intermediate formed from ketoxime **3** isomerises easily into a substituted vinylfuran **6**, which cannot undergo the [3,3]-sigmatropic shift and, consequently, the pyrrole formation.



These two side reactions seem to account for resinification and formation of by-products, which prevent isolation of pure pyrroles **4a,b**. Additional difficulties appear to be associated with oligomerisation of acetylene, which occurs in the NH_3 (amine)–KOH–DMSO systems.⁴²

Condensation of alkyl 2-thienyl ketoximes with acetylene catalysed by superbases (MOH–DMSO) produced 1*H*- (**7a–f**) (50%–60%) and 3-alkyl-2-(2-thienyl)-1-vinylpyrroles (**8a–f**) (in 60%–70% yields).^{43,44} The reaction proceeds smoothly at 100–130 °C and may be carried out under both elevated (10–16 atm) and atmospheric pressures of acetylene.

The effect of reaction conditions (temperature, acetylene concentration, addition of water, the nature of cation in the alkali metal hydroxide) on the ratio of pyrroles to their vinyl derivatives formed in the same synthesis was studied in the example of methyl 2-thienyl ketoxime.



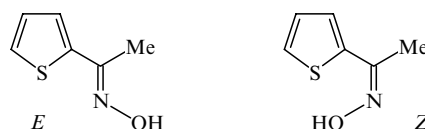
R = H (**a**), Me (**b**), Et (**c**), Prⁿ (**d**), Buⁿ (**e**), n-C₆H₁₃ (**f**); M = Li, K.

Synthesis of 2-(2-thienyl)-1-vinylpyrrole (**8a**) is best carried out in an autoclave, at 120 °C for 3 h under elevated acetylene pressure, 17 mass.%–30 mass.% of KOH with respect to the ketoxime.^{26,37} The increase in the reaction time to 5 h and more as well as in the temperature to 140–150 °C lead to more pronounced resinification and a lower product yield. 2-(2-Thienyl)pyrrole (**7a**) free of its vinyl derivative is produced in > 60% yield with the use of a superbasic pair LiOH–DMSO (100 °C, 3 h, 10–16 atm) which, as in the case of condensation of methyl phenyl ketoxime with acetylene,^{38,39} catalyses the stage of pyrrole ring formation and is virtually inactive in the stage of vinylation. The amount of lithium hydroxide added is ~ 18 mass.% with respect to the ketoxime. The same pyrrole was obtained in 47% yield under atmospheric pressure (130–140 °C, 7 h, 30% LiOH). The addition of water to DMSO (10%–15%) and the use of KOH (equimolar ratio of KOH to the

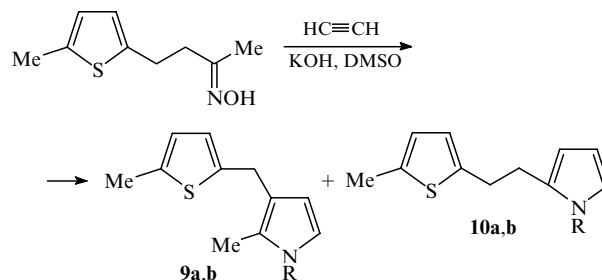
oxime) inhibit the vinylation process and make possible the preparation of 2-thienylpyrrole (**7a**) in 53% yield. Heating of propyl 2-thienyl ketoxime with acetylene (100–120 °C, 0.8 mol KOH, 11% H₂O, 7 h) leads to the formation of 3-ethyl-2-(2-thienyl)pyrrole (**7c**) also in 53% yield.

The length of the carbon chain of the alkyl radical in the original alkyl 2-thienyl ketoxime does not exert any noticeable effect on the composition and yield of the final products.

The starting ketoximes are a mixture of *E*- and *Z*-isomers. It was established that only the *anti*-isomer participates in the reaction with acetylene, while the *syn*-isomer is recovered unaltered after the reaction. It could be supposed that the oximes with a large content of *anti*-isomer would give thienylpyrroles in higher yields. This is not the case because of easy *syn*–*anti*-isomerisation. This was demonstrated for methyl thienyl ketoximes, where pure *syn*- and *anti*-isomers isolated by preparative TLC were used in the reaction with acetylene.²⁶

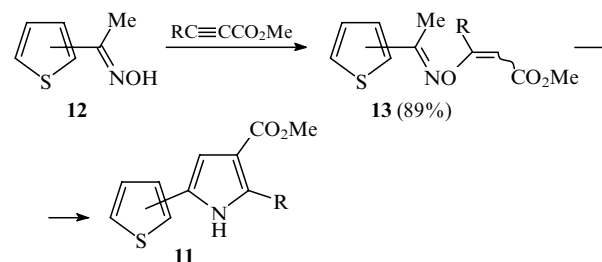


Like in the case of alkyl methyl⁴⁵ and alkyl benzyl ketoximes,⁴⁶ the reaction of (*E*)-methyl 2-(5-methyl-2-thienyl)ethyl ketoxime with acetylene involves the methylene group in the *anti*-position relative to the hydroxy group.⁴⁰ At 95 °C and atmospheric pressure, the ratio of structurally isomeric pyrroles **9a** and **10a** is 33 : 1 [yields 46% and 1.4%, respectively (GLC)], whereas vinylpyrrole **10b** was detected in the reaction products only in trace amounts. Despite a rather high total yield of pyrroles **9** and **10** (61%), their isolation from the reaction mixture proved to be problematic due to the presence of a number of unidentified by-products. More drastic conditions (120 °C) favour the increased proportion of the reaction products formed with the participation of the methyl group and also the vinylation of pyrroles **9a** and **10a**; the ratios of pyrroles **9a** : **10a** and **9b** : **10b** become equal to 24 : 1 and 5 : 1, respectively.⁴⁰



R = H (**a**), CH=CH₂ (**b**).

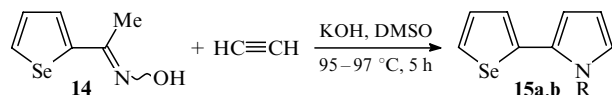
2-(2-Thienyl)- and 2-(3-thienyl)pyrroles **11** were synthesised recently using a modification of the Trofimov reaction consisting in the addition of methyl 2-thienyl and methyl 3-thienyl ketoximes **12** to methyl propiolate and dimethyl acetylenedicarboxylate.⁴⁷



R = H, CO₂Me.

The reaction is conducted in two stages: intermediate *O*-vinylloximes **13** are transformed into thienylpyrroles **11** on boiling in xylene.

Selenienylpyrroles have remained virtually unstudied until now since no efficient methods for their synthesis had been developed. Mikhaleva *et al.*⁴⁸ have shown the possibility of preparing the corresponding pyrroles from methyl 2-selenienyl ketoxime (**14**) by its reaction with acetylene at 95–97 °C: 2-(2-selenienyl)pyrrole (**15a**) and -2-(2-selenienyl)-1-vinylpyrrole (**15b**) were produced in yields of 10% and 2%, respectively.



R = H (a), CH=CH₂ (b).

Ketoxime **14** was used in this reaction as a mixture of *E*- and *Z*-isomers (1 : 1). Under these conditions, the *Z*-isomer reacted predominantly (or exclusively), which correlates with the results of the analogous reaction with methyl 2-thienyl ketoxime⁴³ and 2-benzimidazolyl methyl ketoxime.⁴⁹

The low yield of pyrrole **15a** is explained by its instability in the KOH–DMSO system.⁴⁸ Further temperature increase to 110–120 °C results only in a lower yield and resinification. Apparently, the C–Se bond is less stable and more sensitive to the attack by a strong base compared with the C–O and C–S bonds (as mentioned above, under the same conditions the total yield of furyl and thienyl analogues reaches 80%–90%).

a. 1,2-Dichloroethane as an acetylene equivalent

The reaction of alkyl hetaryl ketoximes **16** with 1,2-dichloroethane (DCE), which is a synthetic equivalent of acetylene under the conditions of the Trofimov reaction, is a version of the synthesis of furyl- and thienylpyrroles.⁵⁰

The ratio of the reaction products [hetarylpyrroles **1** and **7**, 1-vinylhetarylpyrroles **2** and **8**, intermediate *O*-2-chloroethyl (**17**) and *O*-vinyl (**18**) hetaryl ketoximes] and by-products, *viz.* 1,2-bis(hetarylalkylideneiminoxy)ethanes (**19**), depends on many factors: reaction temperature and time, the nature of the hydroxide cation, its concentration and the presence of water in the catalytic system (Scheme 1).

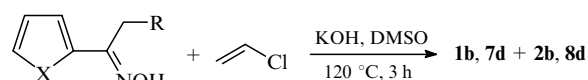
An advantage of this version consists in the substitution of acetylene by a more accessible, safe and handling-convenient DCE. The synthesis can be performed in a trivial apparatus under atmospheric pressure and in the temperature range 100–135 °C.⁵⁰ The highest yields of furyl- and thienylpyrroles were attained at 120 °C (6–9 h, molar ratio ketoxime : NaOH : DCE = 1 : 2 : 7). When KOH was used as a base, better results were obtained upon addition of 5%–10% of water (120 °C, 7 h, molar ratio ketoxime : KOH : DCE = 1 : 2 : 10); however, in this version the yields of 2-(2-furyl)- and 2-(2-thienyl)-1-vinylpyrroles did not exceed 25%. In the presence of lithium hydroxide, the yields of pyrroles were lower (18%). In an NaOH–DMSO + 10% H₂O system, the reaction stops at the stage of intermediates **18**, *viz.*, *O*-methyl 2-thienyl *O*-vinylketox-

imes (R = H, yield 43%) or 2-furyl methyl *O*-vinylketoximes (R = H, yield 6%).⁵⁰

The detection of *O*-vinylketoximes **18** and methyl 2-thienyl *O*-(2-chloroethyl)ketoximes **17** (X = S, R = H, yield 24%) among the main reaction products has made it possible to suggest⁵⁰ that in the case of DCE, two alternative pathways of the formation of pyrroles and 1-vinylpyrroles are realised. According to the first pathway,⁴ in a strongly basic medium DCE serves as the source of acetylene, and the reaction proceeds as usual (see Section II.1). The second pathway consists in the nucleophilic substitution of one chlorine atom in DCE by the oximate anion with the formation of *O*-(2-chloroethyl)ketoximes **17** with subsequent elimination of HCl to afford *O*-vinylketoximes (**18**). Intermediates **18** undergo cyclisation into the corresponding pyrroles, which react with DCE to form, apparently, 1-(2-chloroethyl)pyrroles **20**. These are further transformed into *N*-vinylpyrroles upon elimination of HCl.⁵⁰ The possibility of formation of 1-(2-chloroethyl)pyrroles **20** under these conditions is in accord with the data reported in Ref. 51.

b. Vinyl chloride as an acetylene equivalent

A simple and industrially acceptable method of synthesis of furyl- and thienylpyrroles is based on the reaction of the corresponding ketoximes with vinyl chloride in a KOH–DMSO suspension.²⁶ The condensation is carried out at 120 °C with a sixfold excess of KOH relative to the ketoxime. This results in the formation of a mixture of pyrroles and their 1-vinyl derivatives. In this modification of the Trofimov reaction, vinyl chloride serves as the acetylene equivalent.

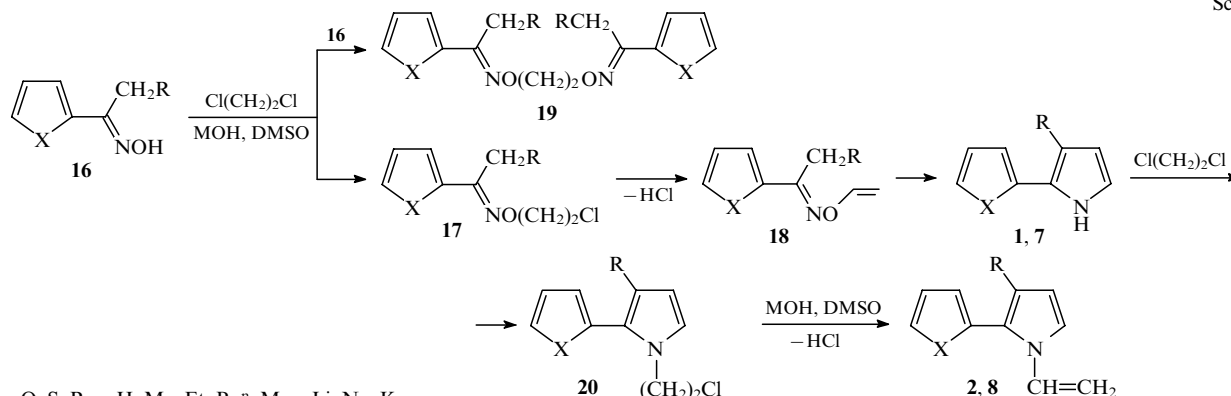


Compound	X	R	Yield (%)
1b	O	Me	40
2b	O	Me	36
7d	S	Pr ⁿ	46
8d	S	Pr ⁿ	26

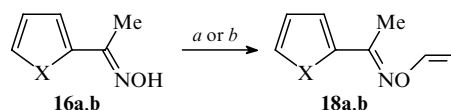
c. Intermediates and the reaction mechanism

Systematic studies on the synthesis of pyrroles from hetaryl ketoximes and acetylene in the superbasic KOH–DMSO medium have allowed not only identification of the reaction intermediates, such as *O*-vinylketoximes or 3*H*-pyrroles, but also the development of methods for their preparation.^{43, 50, 52–55} For instance, 2-furyl methyl (**18a**) and methyl 2-thienyl (**18b**) *O*-vinylketoximes were obtained in yields of 38% and 32%, respectively, by the reaction of 2-furyl methyl (**16a**) and methyl 2-thienyl ketoximes (**16b**) with acetylene in the KOH–DMSO system (initial pressure 12 atm, 3 h, 50–60 °C).^{52–54}

Scheme 1



X = O, S; R = H, Me, Et, Buⁿ; M = Li, Na, K.

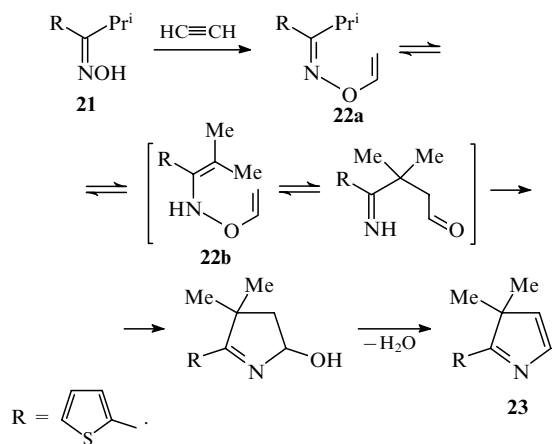


X = O (a), S (b); (a) $\text{HC}\equiv\text{CH}$, MOH , DMSO , H_2O ; (b) $\text{Cl}(\text{CH}_2)_2\text{Cl}$, MOH , DMSO , H_2O ; M = K, Li.

Upon addition of 4% of water to the KOH – DMSO system, the yield of *O*-vinylketoxime **18b** increased to 44%.⁵⁴ Under similar conditions, the yield of the corresponding furyl derivative **18a** did not exceed 13%.⁵⁴ Under atmospheric pressure of acetylene, the synthesis of *O*-vinylketoximes is less efficient. 1,2-Dichloroethane is also suitable for the preparation of ketoximes **18a,b**. The optimal conditions for the synthesis of compound **18b** are the use of LiOH – DMSO system and addition of 10% of water (100 °C, 4 h, yield 43%).⁵⁰ In the NaOH – DMSO system containing 10% of water, *O*-vinylketoxime **18b** is not formed, whereas the yield of *O*-vinylketoxime **18a** is as low as 6%.⁵⁰

Ketoximes **18a,b** are transformed upon thermolysis into the corresponding pyrroles as do alkyl aryl *O*-vinylketoximes,⁵⁶ methyl (1-methyl-2-pyrrolyl) *O*-vinylketoxime⁵⁷ or *O*-vinylketoximes formed upon heating of *O*-(2-iodoethyl)ketoximes with Bu^tOK in Bu^tOH .⁵⁸ Thus, heating of 2-furyl methyl and methyl 2-thienyl *O*-vinylketoximes (100 °C) in the KOH – DMSO system led to 2-(2-furyl)- and 2-(2-thienyl)pyrroles in yields of 60% and 50%, respectively.⁵⁶ 2-(2-Thienyl)- and 2-(3-thienyl)-4-methoxycarbonyl- and -4,5-di(methoxycarbonyl)pyrroles **13** were obtained by heating of the corresponding *O*-vinylketoximes **12** in xylene⁴⁷ (see Section II.1).

The reaction of isopropyl 2-thienyl ketoxime (**21**) with acetylene afforded 3,3-dimethyl-2-(2-thienyl)-3*H*-pyrrole (**23**), the yield of which depended on the reaction conditions and in the best case (addition of Al_2O_3 to the catalytic system) reached 43% with respect to the consumed ketoxime.⁵⁵



The formation of the pyrrole **23** from the oxime **21** indicates that the reaction pathway includes the stage of prototropic isomerisation of *O*-vinylketoxime **22a** into *O,N*-divinylhydroxyamine **22b**.

This scheme of the formation of pyrroles from oximes is also supported by the identification^{59,60} of other reaction intermediates (hydroxypyrrolines) and their transformation into the corresponding pyrroles upon condensation of alkyl aryl ketoximes with acetylene.⁴¹ The fact that pyrroles cannot be synthesised from *O*-alkyl ketoximes under the conditions of the Trofimov reaction,²⁴ as well as the predominant formation of β -phenylpyrroles in the case of phenylacetylene⁶¹ support the proposed reaction scheme.

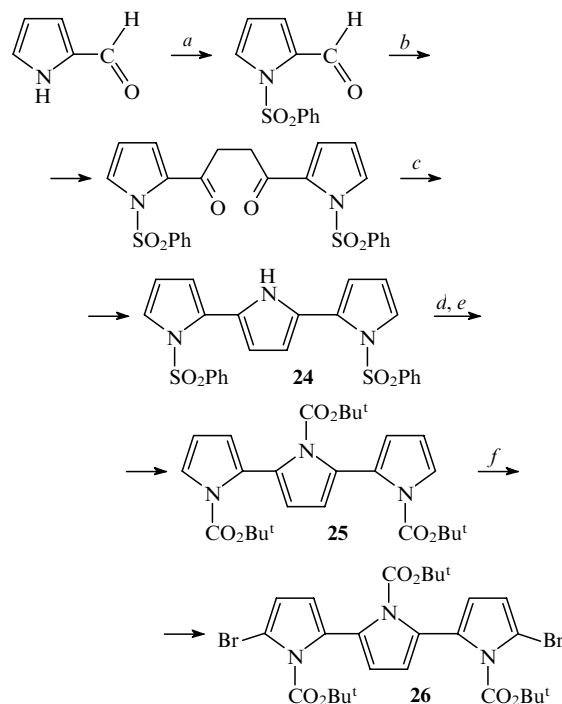
2. The Paal–Knorr synthesis

The Paal–Knorr synthesis is widely used for the preparation of pyrrolyl-, furyl- and thienylpyrroles. As a rule, it is carried out under mild conditions and provides for high yields of the target

products in the final stage. However, the preparation of the initial 1,4-diketones and/or amines with furyl and thienyl substituents remains a challenge: their synthesis includes several stages which do not always give high yields, which restricts substantially the applicability of this method.

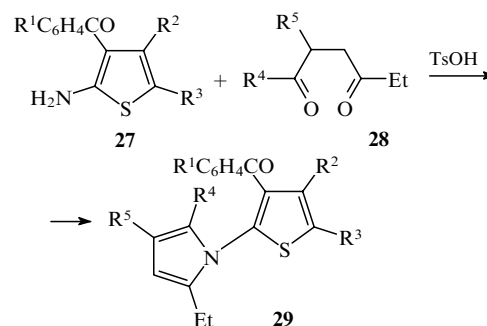
N,N',N''-Tris(*tert*-butoxycarbonyl)-5,5''-dibromo-2,2':5',2''-terpyrrole (**26**) was obtained from 2-formylpyrrole⁶² in several steps (Scheme 2). In the intermediate disulfone **24**, two sulfonyl groups were substituted by *tert*-butoxycarbonyl protective groups. Simultaneously, the third pyrrole ring was *N*-protected; the totally protected terpyrrole **25** was then selectively brominated with *N*-bromosuccinimide (NBS) to pyrrole **26**.

Scheme 2



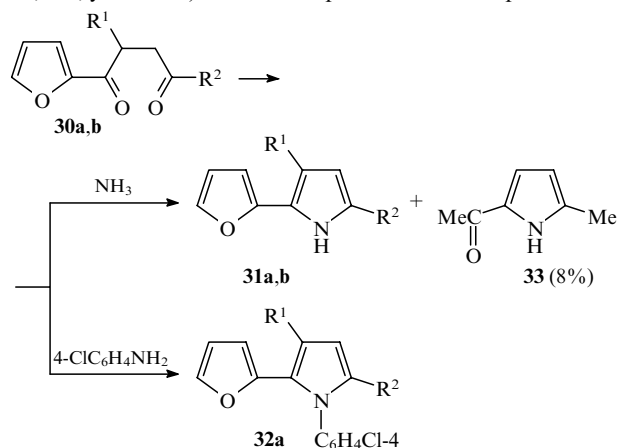
(a) NaH , PhSO_2Cl , DMF , 20 °C; (b) SO_2 , EtOH , Δ ; (c) AcONH_4 , Ac_2O , EtCO_2H , 140 °C; (d) NaOH , MeOH , 20 °C; (e) $(\text{Bu}^t\text{O}_2\text{C})_2$, Bu^tOK , THF , Δ ; (f) NBS , THF , –70 °C.

In a Japanese patent⁶³ it was proposed to prepare 1-(2-thienyl)pyrroles **29** (yields up to 80%) by the reaction of 2-aminothiophenes **27** with 1,4-diketones **28** on boiling for 20 min in benzene in the presence of *p*-toluenesulfonic acid.



R ¹	R ²	R ³	R ⁴	R ⁵
2-Cl	Me	Me	Me	Me
2-Cl	Me	Me	Me	H
H	H	Me	Me	H
H	H	Et	Me	H
H	Me	Me	Me	Me

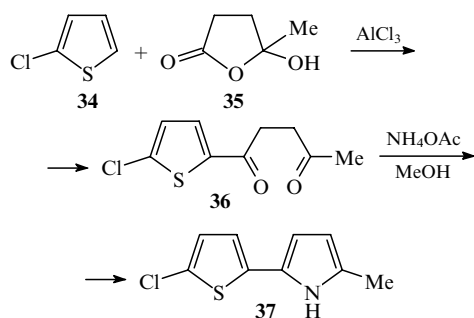
Furylpyrroles (**31a,b** and **32a**) were prepared from 1-(2-furyl)pentane-1,4-dione (**30a**) or 1-(2-furyl)-2,4-diphenylbutane-1,4-dione (**30b**) and ammonia (NH₄Cl, 180 °C, 20 h, yields of 40% and 50%, respectively) or 4-chlorophenylamine (AcOH, EtOH, 7 h, yield 85%) under atmospheric or elevated pressure.⁶⁴



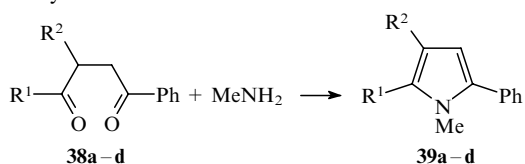
R¹ = H, R² = Me (a); R¹ = R² = Ph (b).

If ammonia is replaced by ammonium carbonate and the reaction is carried out in ethanol in the presence of acetic acid, a twofold increase in the yield of pyrrole **31a** is achieved.⁶⁴ It should be noted that the reaction of diketone **30a** with ammonia is accompanied by the formation of pyrrole **33** (yield 8%), while 2,4,5-tri(2-furyl)imidazole and 2,3,5,6-tetra(2-furyl)pyrazine (5% yield of each) are formed from diketone **30b**.⁶⁴

1-(5-Chloro-2-thienyl)pentane-1,4-dione (**36**) obtained from 5-chlorothiophene (**34**) and 5-methyl-5-hydroxytetrahydrofuran-2-one (**35**) reacts with ammonium acetate in methanol at 25 °C for 3 h to give 2-(5-chloro-2-thienyl)-5-methylpyrrole **37** in 65% yield.⁶⁵

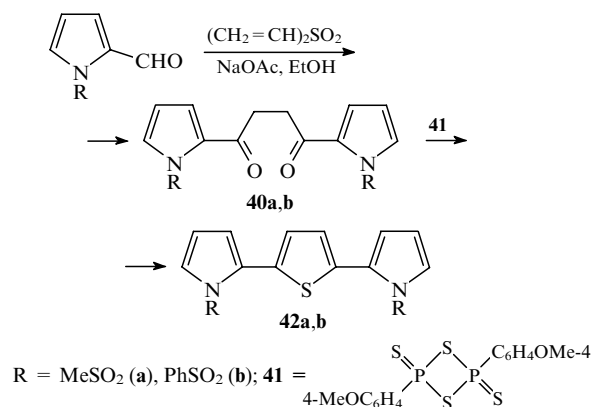


Pyrroles **39a–d** containing two thienyl substituents in the ring were obtained in high yields from the corresponding diketones **38a–d** and methylamine in boiling propanol containing methylamine hydrochloride.^{66, 67}



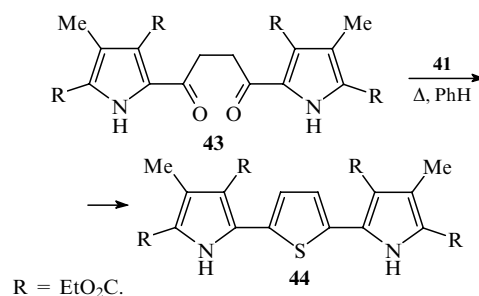
Compound 39	R ¹	R ²	Yield (%)
a	2-thienyl	2-thienyl	85
b	3-thienyl	2-thienyl	97
c	2-thienyl	3-thienyl	90
d	3-thienyl	3-thienyl	99

Synthesis of 2,5-bis(2-pyrrolyl)thiophenes **42** (yield 65%) was brought about^{62, 68} by cyclisation of symmetrical 1,4-diketones **40a,b** with Lawesson's reagent (**41**) upon boiling in toluene.



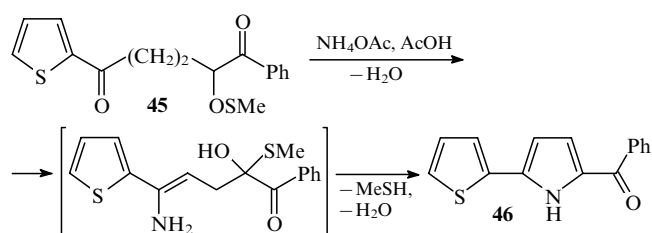
Diketones **40a,b** are obtained from pyrrole-2-carboxaldehydes in ethanol in the presence of NaOAc, divinyl sulfone and a thiazolium salt as the catalyst (yields 70% and 74%, respectively).

2,5-Bis[3,5-di(ethoxycarbonyl)-4-methyl-2-pyrrolyl]thiophene (**44**) was prepared in 76% yield from diketone **43** [synthesised by the reaction of 3,5-bis(ethoxycarbonyl)-4-methyl-2-formylpyrrole with divinyl sulfone in dioxane at 80 °C in the presence of triethylamine] and Lawesson's reagent **41**.⁶⁸

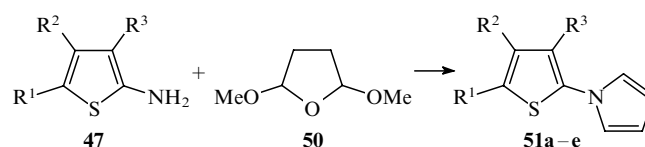


R = EtO₂C.

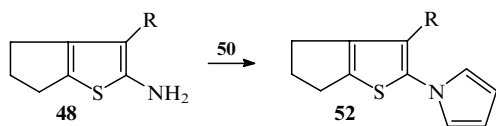
The reaction of 2-methylsulfinyl-1-phenyl-5-(2-thienyl)pentane-1,5-dione (**45**) with ammonium acetate in acetic acid (Δ, 10 min) leading to 2-(2-thienyl)pyrrole (**46**) with a yield of 19% may be regarded as a variant of the Paal–Knorr synthesis.⁶⁹



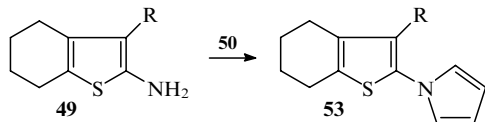
An elegant and efficient synthesis of 1-(2-thienyl)pyrroles **51–53** is based on the condensation of 2-aminothiophenes **47**, 2-amino-4,5-dihydrocyclopenta[*b*]thiophene **48** or 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophenes **49** with 2,5-dimethoxytetrahydrofuran (**50**) in acetic acid.^{70, 71}



Compound 51	R ¹	R ²	R ³	Yield (%)
a	Me	Me	H	86
b	Me	Et	CO ₂ H	96
c	Me	Me	CO ₂ H	97
d	H	H	CO ₂ Et	72
e	Me	Me	CO ₂ Et	70

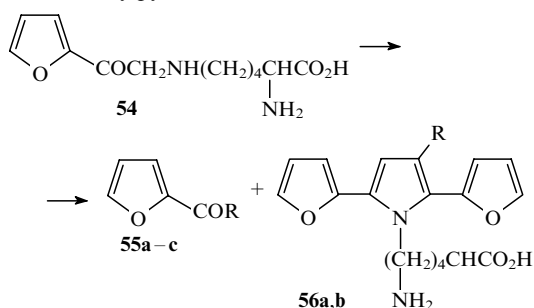


R = CO₂H (96%), CO₂Et (71%).



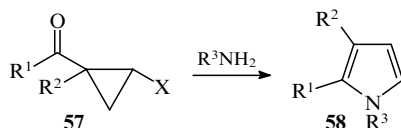
R = H (70%), CO₂H (97%), CN (86%), CO₂Et (59.5%).

The oxidation products of aminoacylfuran **54** are supposed to contain, along with the major compounds **55a–c**, insignificant amounts of furylpyrroles **56a,b**.⁷²



R = OH (**a**), NH(CH₂)₄CH(NH₂)CO₂H (**b**), CONH(CH₂)₄CH(NH₂)CO₂H (**c**).

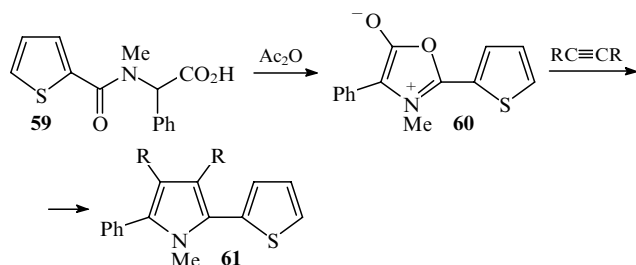
The reaction of cyclopropyl ketones **57** with amines leads to the formation of hetarylpyrroles **58** in high yields.^{73,74} The presence of an electron-acceptor substituent X (OMe, OEt, Cl) in the cyclopropane ring facilitates its isomerisation leading to the formation of a carbonyl group equivalent.



R¹ = 2-furyl, 2-thienyl; R² = H; R³ = H, Alk, Ar; X = OMe, OEt, Cl.

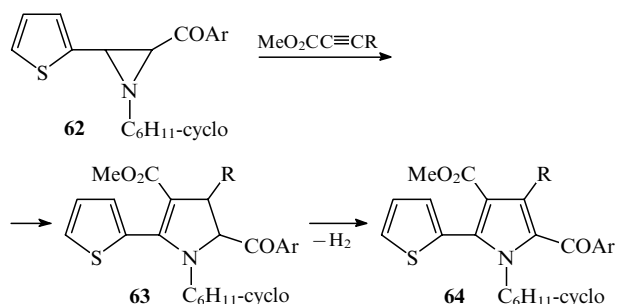
3. Syntheses involving activated acetylenes

Oxazolium oxide **60** formed from *N*-methyl-*N*-thenoylamino acid **59** and acetic anhydride is transformed into 2-(2-thienyl)pyrrole **61** upon boiling in benzene with dimethyl acetylenedicarboxylate (yield 89%).⁷⁵



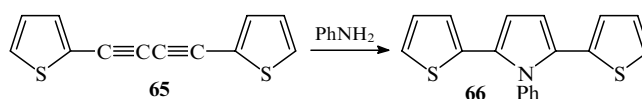
R = CO₂Me.

A general method for the synthesis of thienylpyrroles **64** has been developed, which is based on 1,3-dipolar cycloaddition of 2-(2-thienyl)aziridines **62** to activated acetylenes.^{76,77} The reaction proceeds on heating of the reagents in benzene with the formation of intermediate thienylpyrrolines **63**, which are readily dehydrogenated under the action of tetrachloro-1,4-benzoquinone to give pyrroles **64**, as a rule, in moderate yields.

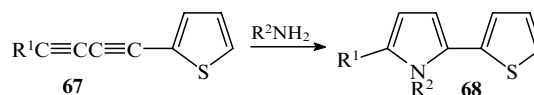


R	Ar	Yield of 64 (%)	R	Ar	Yield of 64 (%)
H	Ph	32	H	2-naphthyl	36
H	4-MeC ₆ H ₄	26	CO ₂ Me	4-MeC ₆ H ₄	53
H	4-MeOC ₆ H ₄	39	CO ₂ Me	4-MeOC ₆ H ₄	65
H	3-NO ₂ C ₆ H ₄	25	CO ₂ Me	3-NO ₂ C ₆ H ₄	32

Heating of 1,4-di(2-thienyl)butadiyne (**65**) with aniline at 140–160 °C in the presence of cuprous chloride leads to the formation of 2,5-di(2-thienyl)-1-phenylpyrrole (**66**) in 68% yield.⁷⁸

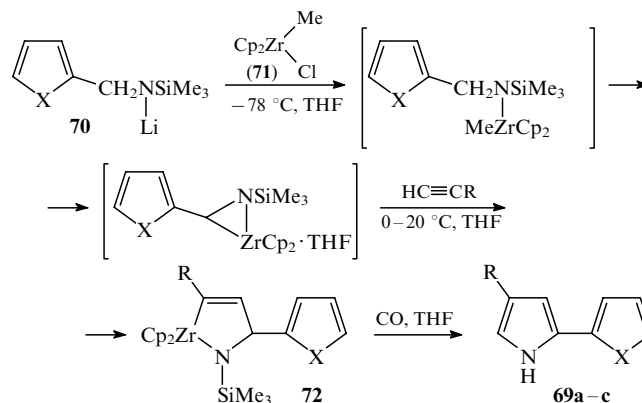


This reaction has a general character. Asymmetrically substituted butadiynes **67** react with amines, which allows preparation of various 2-(2-thienyl)pyrroles **68**.⁷⁸ Ethanol, dioxane and DMF are used as solvents.



R¹ = H, Me, Et, Ph; R² = H, Me, Et, Buⁿ, Ph.

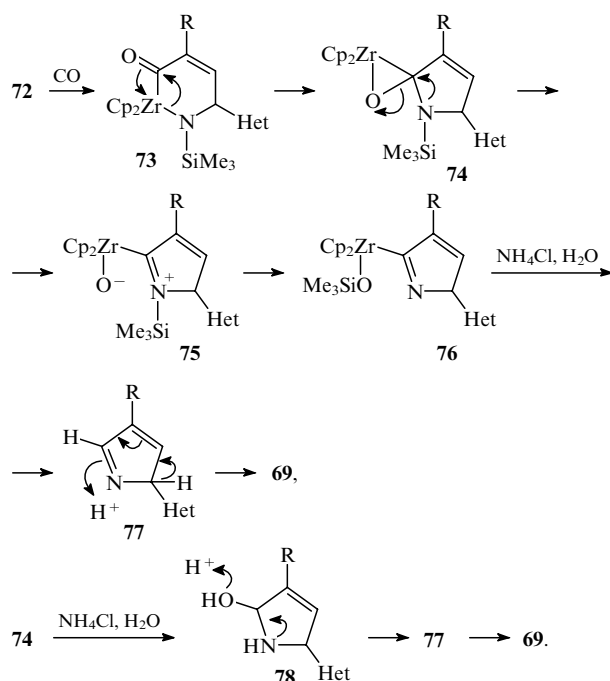
A new method has been developed for the synthesis of 2-(2-pyrrolyl)-, 2-(2-furyl)- and 2-(2-thienyl)pyrroles **69a–c** from the corresponding amines **70**, acetylenes **71** and carbon monoxide with the use of zirconium cyclopentadienyl complexes.⁷⁹



X = N, R = Prⁿ (**69a**, 68%); X = O, R = Ph (**69b**, 49%); X = S, R = Prⁿ (**69c**, 41%).

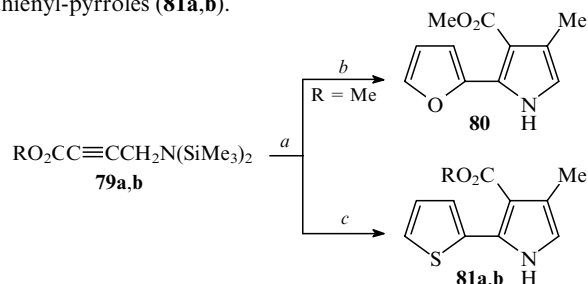
The reaction with CO leading to hetarylpyrroles may be realised both with and without isolation of metallocycles **72**. This reaction can be carried out in the presence of NH₄Cl, under CO pressure of ~ 100 atm, at ~ 20 °C, for 24 h (method A) or in the absence of NH₄Cl, at 80 °C, CO pressure of ~ 6 atm and for 36 h (method B). The former method is more efficient, though the role of NH₄Cl is still unclear.

The following mechanism of this reaction has been proposed:⁷⁹



Insertion of CO into the C–Zr bond gives metallocycle **73**. Migration of the nitrogen atom from zirconium to the acyl carbon (formally, reductive elimination) leads to the zirconium complex **74**. The intermediate **74** can undergo ring opening with the formation of a zwitter-ion **75**, which after migration of the trimethylsilyl group from nitrogen to zirconium gives compound **76**. Its hydrolysis yields intermediate **77**, which undergoes prototropic rearrangement into pyrrole **69**. An alternative pathway is possible: hydrolysis of the complex **74** to the alcohol **78**, which is dehydrated to give the intermediate **77** with subsequent formation of pyrrole **69**.⁷⁹

Synthesis of pyrroles⁸⁰ through carbocupration of *N,N*-bis(trimethylsilyl) derivatives of alkyl 4-aminobut-2-ynoates with subsequent treatment with acyl chlorides has opened a route to new polyheterocyclic compounds, including furyl- and thienylpyrroles and tetrapyrrole macrocycles. Thus, the reaction of lithium methyl(hexynyl)cuprate with methyl (**79a**) or ethyl 4-aminobut-2-ynoates (**79b**) with subsequent treatment with 2-furyl or 2-thienoyl chlorides leads to 2-furyl- (**80**) and 2-thienyl-pyrroles (**81a,b**).



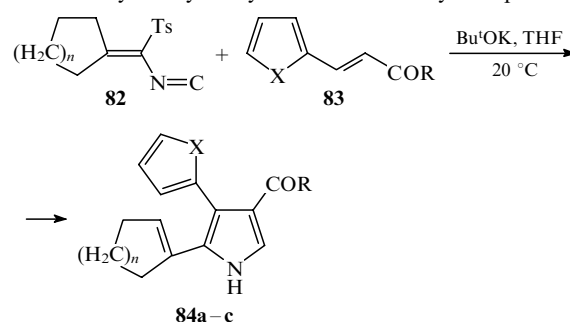
R = Me (**81a**, 30%), Et (**81b**, 58%); (a) $(\text{Bu}^n\text{C}\equiv\text{C})\text{MeCuLi}$,

Et_2O , -40°C ; (b) ; (c) .

4. Synthesis involving isocyanides

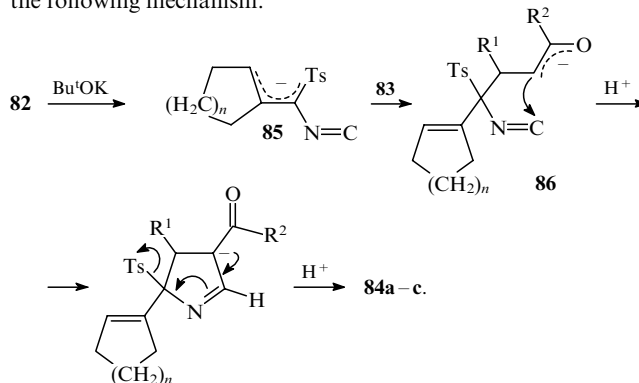
Isocyanides are rather common components in the synthesis of hetarylpyrroles.^{81–87} 3-(2-Furyl)- (**84a,b**) and 3-(2-thienyl)pyrroles **84c** were synthesised by addition of 1-tosylalk-1-enyl isocyanides **82** to chalcone analogues **83** in the presence of

Bu^tOK .⁸¹ The initial isocyanides **82** can be easily obtained by the reaction of tosylmethyl isocyanide with carbonyl compounds.



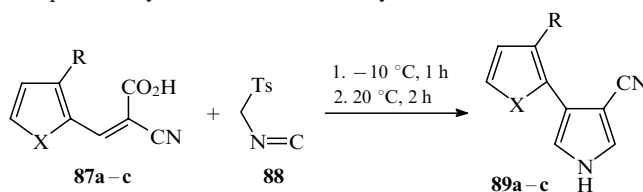
Compound 84	X	n	R	Yield (%)
a	O	1	2-furyl	93
b	O	3	Ph	89
c	S	2	2-thienyl	85

It is presumed⁸¹ that the formation of pyrroles **84** occurs by the following mechanism:



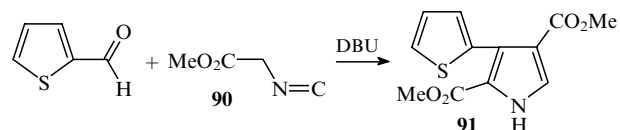
The Michael addition of the allylic anion **85**, formed under the action of a base, to the vinyl ketone **83** and subsequent cyclisation of the enolate anion **86** and elimination of the tosylate anion yield the final reaction product.

Pyrroles **89a–c** were obtained from 2-cyano-3-(2-furyl)- and -(2-thienyl)acrylic acids **87a–c** and tosylmethyl isocyanide (**88**) in a superbasic system KOH–dimethoxyethane.⁸²

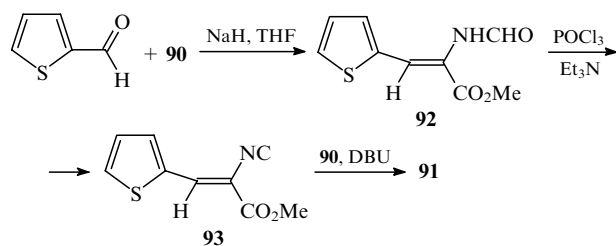


Compounds 87, 89	X	R	Yield of 89 (%)
a	O	H	92
b	S	H	97
c	S	Me	89

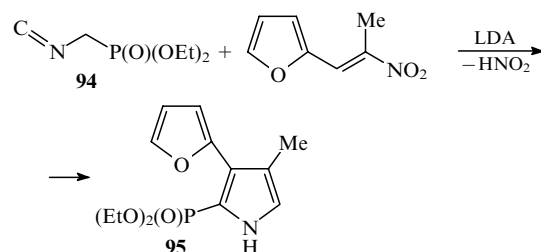
The addition of methyl isocyanoacetate (**90**) to thiophene-2-carbaldehyde in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF at $40–50^\circ\text{C}$ (15 h) leads to 3-(2-thienyl)-pyrrole (**91**) in 70% yield.^{85,87}



Sakai *et al.*⁸⁵ have obtained pyrrole **91** by a different scheme including intermediates **92** and **93**.

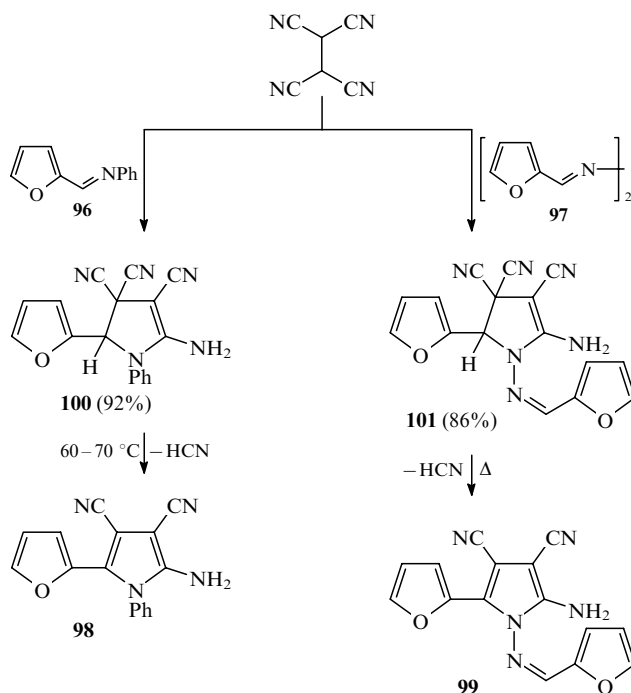


Phosphorylated 3-(2-furyl)pyrrole **95** was synthesised in 54% yield by the reaction of isocyanide **94** with 2-(2-nitroprop-1-enyl)furan in the presence of lithium diisopropylamide (LDA) (THF, -78°C , 3 h; $\sim 20^{\circ}\text{C}$, 72 h; reflux, 2 h) with subsequent treatment with ammonium chloride.⁸⁶



5. Syntheses from cyanides

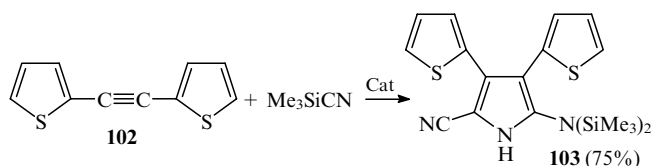
A simple and efficient method for the synthesis of 2-(2-furyl)pyrroles **98**, **99** is based on the reaction of tetracyanoethane with azomethine **96** or azine **97**.^{88–92}



Pyrrole **98** is synthesised either by heating ($90\text{--}100^{\circ}\text{C}$) of tetracyanoethane and azomethine **96** in aqueous dioxane (yield $60\% \text{--} 65\%$)⁸⁸ or with the intermediate isolation of pyrroline **100**, which is transformed into pyrrole **98** in 98% yield upon heating for 5–25 min at $60\text{--}70^{\circ}\text{C}$ in DMF.⁸⁹

Similarly, upon gentle heating in an aqueous-ethanolic or ethanolic medium pyrroline **101** loses one molecule of hydrocyanic acid and is transformed into pyrrole **99**.⁹¹

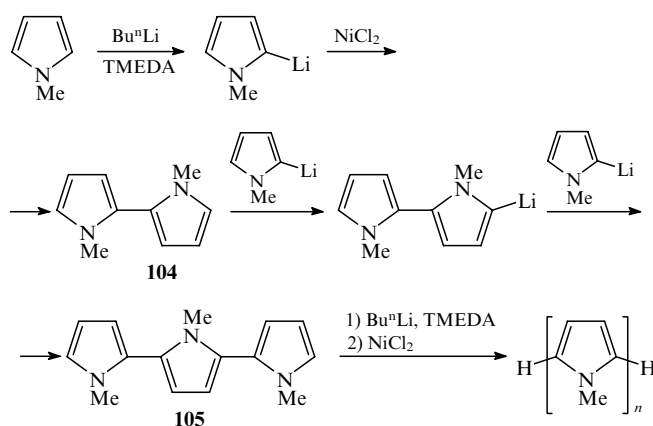
Condensation of bis(2-thienyl)acetylene **102** with an excess of trimethylsilyl cyanide catalysed by palladium or nickel chloride in pyridine yields 3,4-bis(2-thienyl)pyrrole (**103**).⁹³



The reaction involves such a profound rearrangement of trimethylsilyl cyanide that it is hardly possible to propose any reasonable mechanism of this reaction.

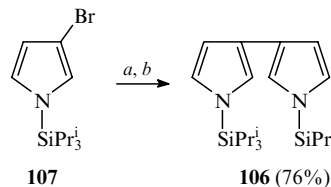
6. Organometallic synthesis

Kaufmann and Lexy⁹⁴ have synthesised bipyrrole **104** by α -lithiation of *N*-methylpyrrole with subsequent oxidative coupling of the intermediate obtained. Bipyrrole **105** was used for the preparation of terpyrrole and then oligopyrrole.



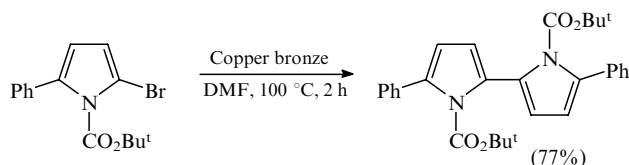
TMEDA is tetramethylethylenediamine; $n = 6$.

3,3-Bipyrrole **106** was obtained⁹⁵ by a Wurtz-type reaction from 3-bromo-1-(triisopropylsilyl)pyrrole (**107**) upon treatment of the latter with *tert*-butyllithium in the presence of CuI.

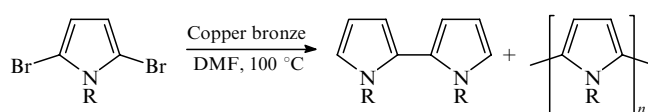


(a) Bu^tLi , CuI, $n\text{-C}_5\text{H}_{12}$ –THF, -78°C , 10 min; (b) 20°C , 2 h.

Groenendaal *et al.*⁹⁶ have described dimerisation of 5-bromo-1-*tert*-butoxycarbonyl-2-phenylpyrrole according to Ullmann.



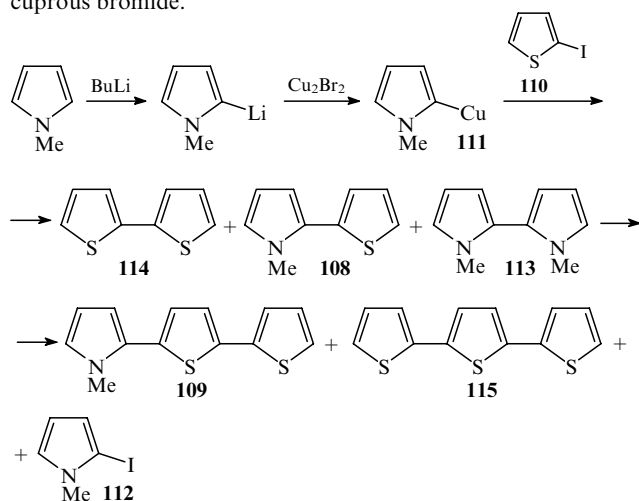
Under the same conditions,⁹⁶ 2,5-dibromo-1-*tert*-butoxycarbonylpyrrole afforded a dimer and other oligomers containing up to 24 pyrrole rings, which were isolated as individual products by preparative HPLC.



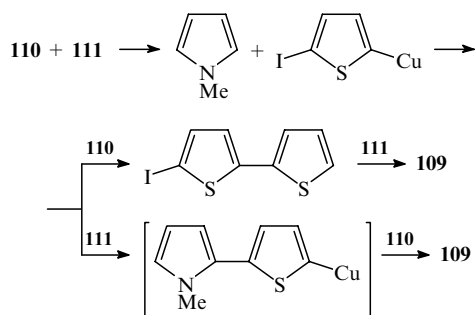
$\text{R} = \text{CO}_2\text{Bu}^t$; $n = 3\text{--}24$.

Gjøs and Gronowitz⁹⁷ have developed a method for the synthesis of thienylpyrroles **108** and **109** by reaction of 2-iodo-

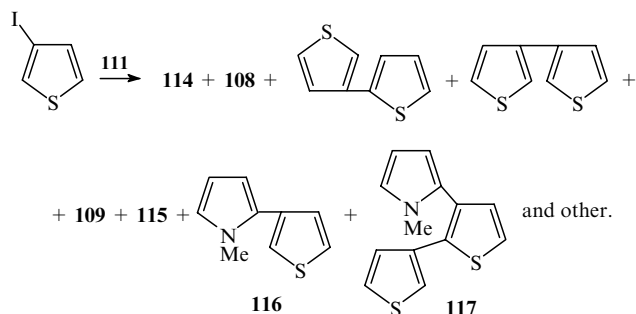
thiophene **110** with 1-methyl-2-pyrrolylcopper (**111**) prepared by metallation of 1-methylpyrrole with butyllithium in a mixture of ether and tetramethylethylenediamine followed by treatment with cuprous bromide.



The course of the reaction and the ratio of the products formed are substantially influenced by its duration: when the reaction was conducted for 1 h, a mixture was obtained that contained, along with thiopyrrole **108**, the initial iodothiophene (**110**), iodopyrrole **112**, bipyrrrole **113** and bithiophene **114**; when the mixture was allowed to react for 4 h, a decrease in the concentration of bithiophene **114** and an increase in the content of thiopyrrole **108** and bipyrrrole **113** were observed. Trace amounts of 1-methyl-2-[5-(2,2'-bithienyl)]pyrrole **109** and terthiophene **115** were also formed. According to GLC data, the ratio of products **108**:**109**:**113**:**114**:**115** was 53:14:24:7:<1. The major product, viz., thiopyrrole **108**, was isolated in 40% yield, while the yield of compound **109** was 15%.⁹⁷ The formation of the latter product is explained by the following scheme:

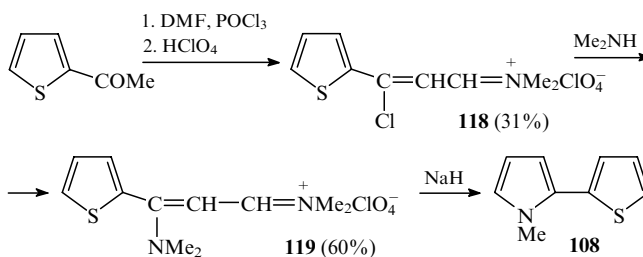


The reaction of the copper intermediate **111** with 3-iodothiophene leads to a more complex mixture of products.⁹⁷



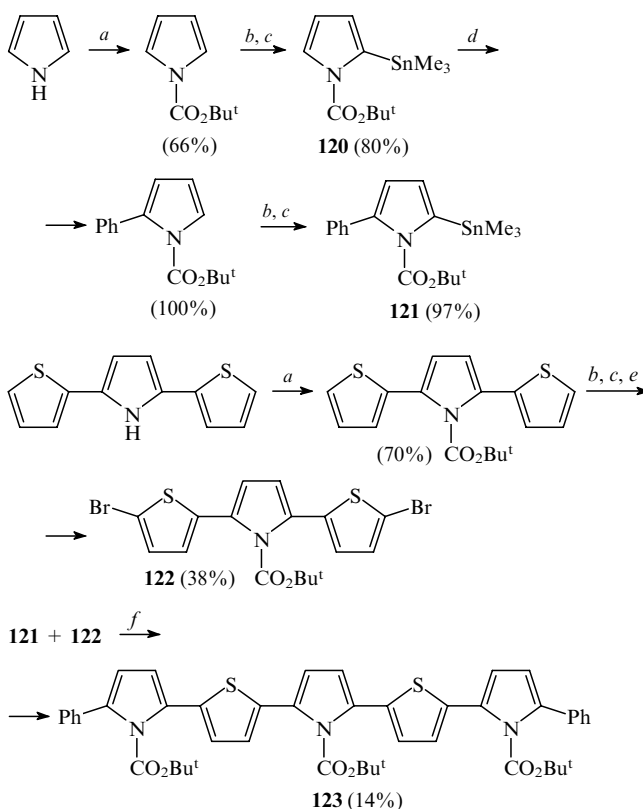
According to GLC data, bicyclic and tricyclic compounds constitute 7% and 30% of this mixture, respectively. Column chromatography with subsequent distillation and recrystallisation gave 1-methyl-2-(3-thienyl)pyrrole (**116**) (yield 72%), thiopyrrole **108** (yield 6%) and tricyclic compound **117** (yield 9%).

Thienylpyrrole **108** was obtained by the same authors⁹⁷ in three steps:



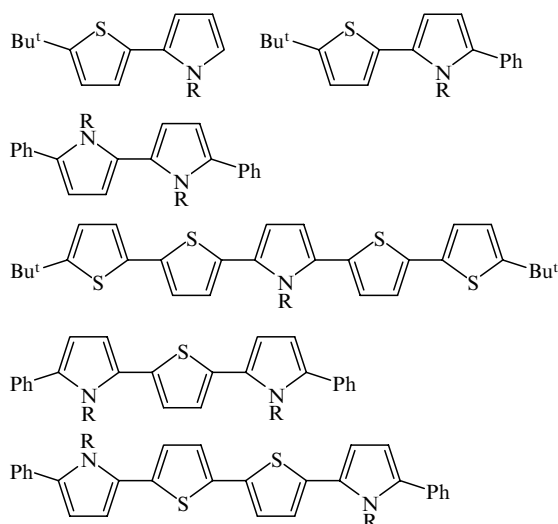
The reaction of 2-acetylthiophene with dimethylformamide and phosphorus oxychloride followed by treatment of the reaction mixture with HClO₄ yields perchlorate **118**. The reaction of salt **118** with dimethylamine gives perchlorate **119**; its heterocyclisation leads to thiopyrrole **108**, although in a low yield.⁹⁷

The use of the Stille reaction allowed one to synthesise oligoheterocyclic compounds containing pyrrole and thiophene units, e.g., *N-tert*-butoxycarbonyl-di-2-(5-*tert*-butoxycarbonyl-5-phenyl-2-pyrrolyl)thienylpyrrole (**123**).⁹⁸ Organotin derivative **120** is prepared by stannylation of a substituted pyrrole. Cross-coupling of compound **120** with bromobenzene according to Stille in the presence of palladium[tetrakis(triphenylphosphine)] followed by stannylation of the reaction product yields compound **121**. Pyrrole **122** is obtained by distannylation of *tert*-butyl 2,5-bis(2-thienyl)pyrrole-*N*-carboxylate with subsequent bromination of the reaction product with *N*-bromosuccinimide. Cross-coupling of compounds **121** and **122** according to the Stille method leads to the oligoheterocycle **123**.



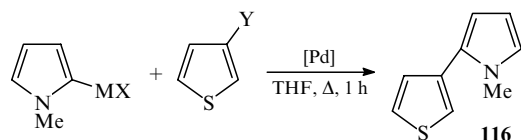
(a) (Bu^tO₂C)₂, Bu^tOK, THF, Δ; (b) tetramethylpiperidine, BuⁿLi, THF, −70 °C; (c) Me₃SnCl, THF, Pd(PPh₃)₄, −70 °C; (d) PhBr, Pd(PPh₃)₄, PhMe, H₂O, Na₂CO₃; (e) NBS, THF; (f) Pd(PPh₃)₄, PhMe, Na₂CO₃, H₂O, Δ.

Cross-coupling according to Stille was also used to prepare the following compounds:⁹⁸



R = Bu^tO₂C.

Cross-coupling of *N*-methylpyrrolylmagnesium(zinc) halides with 3-halogenothiophenes in the presence of a palladium catalyst leads to 1-methyl-2-(3-thienyl)pyrrole (**116**) in high yield.^{99, 100}

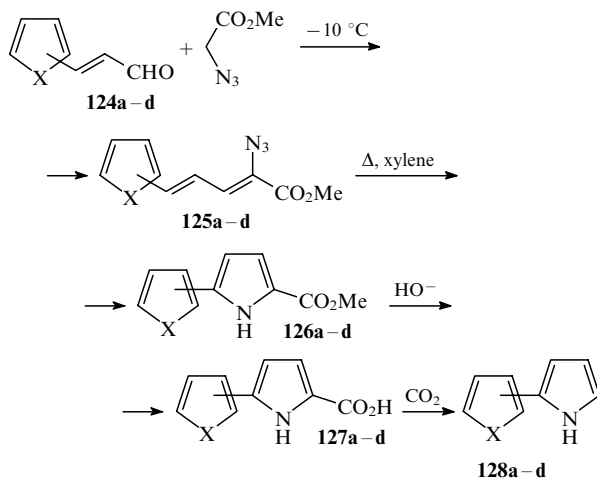


M = Mg, Zn; X = Cl, Br, I; Y = Cl, Br;

[Pd] = PdCl₂, Ph₂P(CH₂)₄PPh₂ (2.5 mol %).

7. Synthesis from azides

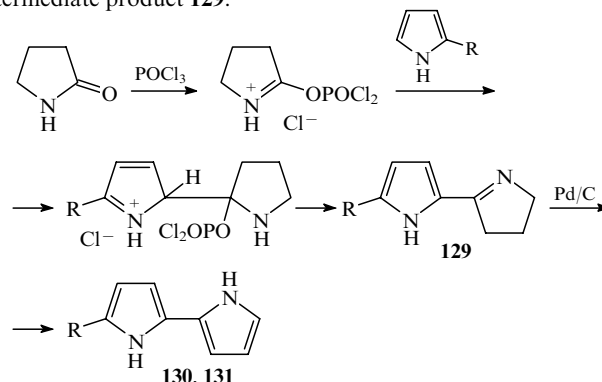
Thermolysis of azidobutadienes **125a–d** containing a hetaryl substituent yields the corresponding 2-hetarylpyrroles **126a–d**. The starting compounds for the preparation of azides **125a–d** were β-2(3)furyl- and β-2(3)-thienylacroleins **124a–d** and methyl azidoacetate. Alkaline hydrolysis of compounds **126a–d** and subsequent decarboxylation of acids **127a–d** in quinoline (with barium-promoted copper chromite as a catalyst) lead to the corresponding 2-(2-furyl)- and 2-(2-thienyl)pyrroles (**128a,b**) or 2-(3-furyl)- and 2-(3-thienyl)pyrroles **128c,d**.¹⁰¹



Compound	Substituent position	X	Yield (%)		
			126	127	128
a	2	O	90	79	68
b	2	S	90	75	46
c	3	O	92	79	43
d	3	S	87	89	57

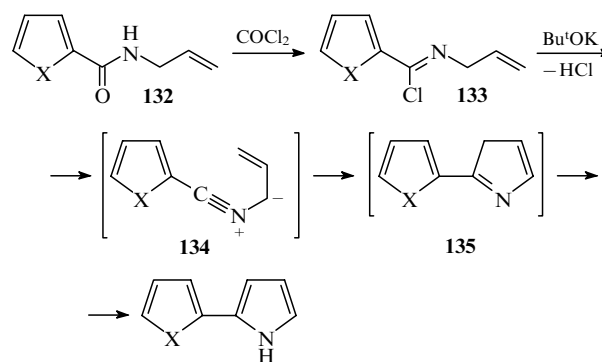
8. Synthesis from unsaturated aminocarbonyl compounds

Rapoport *et al.*^{102–106} have synthesised 2,2-bipyrrole (**130**) and 2,2':5',2''-terpyrrole (**131**) by the reaction of 2-pyrrolidone with phosphorus oxychloride and subsequent dehydrogenation of the intermediate product **129**.



R = H (**130**), 2-pyrrolyl (**131**).

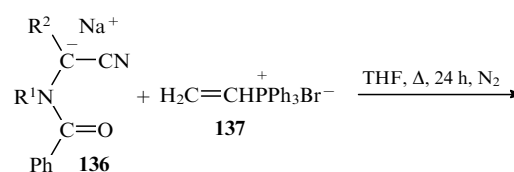
2-(2-Furyl)- and 2-(2-thienyl)pyrroles have been synthesised in 86% yields by the reaction of *N*-allyl carboxamides **132** with phosgene followed by the elimination of HCl from the chloroimines **133**.¹⁰⁷

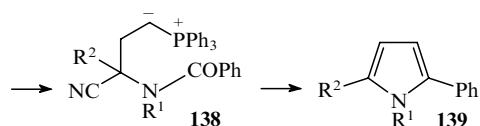


X = O, S.

The construction of the pyrrole ring is presumed¹⁰⁷ to result from the intramolecular 1,5-dipolar cyclisation of the intermediate nitrile ylides **134** to 3*H*-pyrroles **135**, which are further isomerised to 1*H*-pyrroles.

1-(2-Thienyl)pyrroles **139** were obtained in good yields in the reaction of sodium derivatives of cyanoamides **136** with vinyltriphenylphosphonium bromide (**137**) followed by the intramolecular cyclisation of the intermediate **138** under the action of a base with elimination of HCN and Ph₃PO.¹⁰⁸

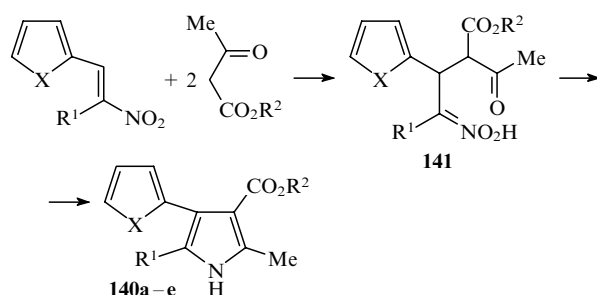




$R^1 = 2\text{-thienyl}$; $R^2 = \text{Ph}, 4\text{-ClC}_6\text{H}_4$.

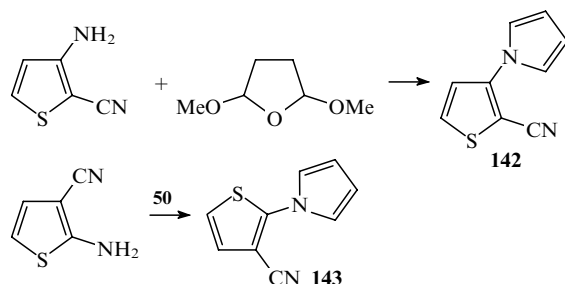
9. Miscellaneous methods

Boberg *et al.*¹⁰⁹ have proposed to obtain 3-(2-furyl)- (**140a**) and 3-(2-thienyl)pyrroles (**140b–e**) from nitronic acids **141** formed upon reaction of nitrovinylfurans or -thiophenes with alkyl acetoacetates. Heterocyclisation of compound **141** takes place at 60 °C in the presence of reducing agents, such as a mixture of sodium sulfide with ammonium chloride, aqueous ammonia with ammonium sulfide or Zn in HCl. This method does not have any preparative value because of low yields of pyrroles.

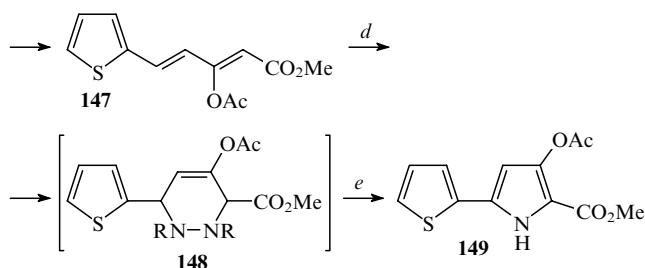
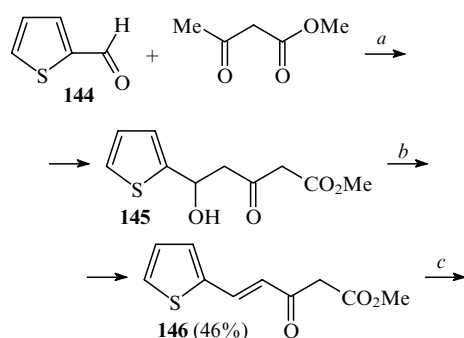


Compound 140	X	R^1	R^2	Yield (%)
a	O	Et	Et	1
b	S	Me	Et	17
c	S	Et	Et	14
d	S	Me	Bu ^t	10
e	S	Ph	Et	8

Synthesis of 1-(2-cyano-3-thienyl)pyrrole (**142**) and 1-(3-cyano-2-thienyl)pyrrole (**143**) by the reaction of 2,5-dimethoxytetrahydrofuran (**50**) with 3-amino-2-cyano- and 2-amino-3-cyanothiophenes, respectively, has been described.^{110–113}



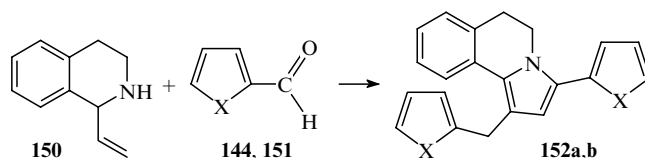
Kresze *et al.*¹¹⁴ have carried out a multistep synthesis of 4-acetoxy-5-(methoxycarbonyl)-2-(2-thienyl)pyrrole (**149**) in which the key compound is a tetrahydropyridazine derivative **148**.



(a) NaH, THF, BuⁿLi, 0 °C, 3 h; (b) 1. *p*-TsCl, Py, 20 °C, 12 h; 2. 80 °C, 0.5 h; (c) MeCOCl, Py, 0 °C, 5 h; (d) RN=NR (R = Cl₃CCH₂OCO), Δ, PhH; (e) Zn, AcOH, MeOH, 55 °C, 3 h.

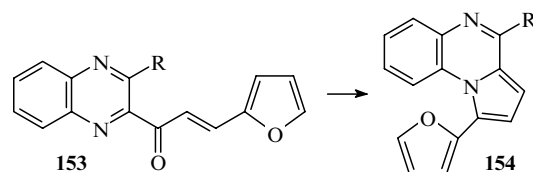
Condensation of 2-formylthiophene **144** with ethyl acetoacetate leads to hydroxy ketone **145** (yield of a crude product 93%) dehydration of which yields *E*-olefin **146**.¹¹⁴ Its *O*-acetylation affords a mixture of *E*- and *Z*-isomers of diene **147** from which the *Z*-isomer was isolated by crystallisation from ether (yield 31%). The Diels–Alder reaction of the *Z*-diene with trichloroethyl azo-*N,N'*-dicarboxylate results in a tetrahydropyridazine derivative **148** as an intermediate; its treatment with Zn powder in acetic acid yields thienylpyrrole **149**.¹¹⁴

1-Vinyltetrahydroisoquinoline (**150**) (obtained from 3,4-dihydroisoquinoline and vinylmagnesium bromide) reacts with 2-formylfuran (**151**) or 2-formylthiophene (**144**) to form polycyclic systems (**152a,b**) with 2-furyl or 2-thienyl substituents.¹¹⁵



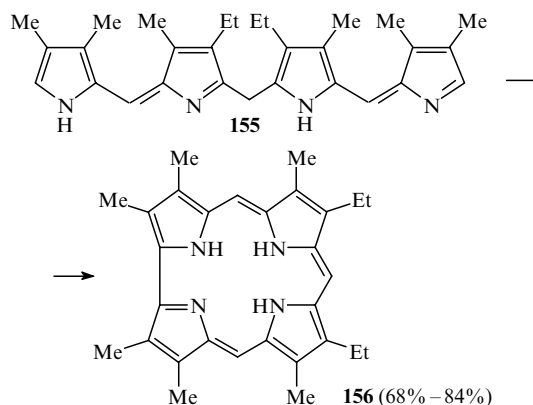
X = O (**a**, 40%), S (**b**, 53%).

Pyrrolo[1,2-*a*]quinoxalines **154** containing a 2-(2-furyl)pyrrole fragment have been synthesised by the cyclisation of 2-(2-furfurylideneacetyl)quinoxalines **153** under the action of HCl or HClO₄.¹¹⁶



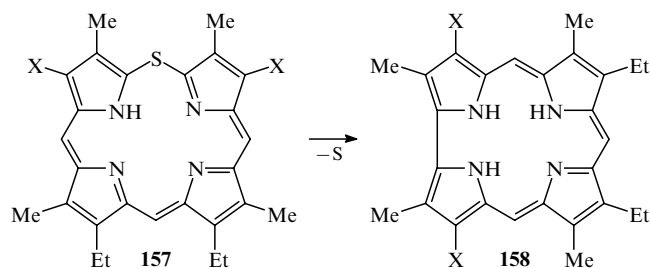
R = H, Me.

Corrole **156** is prepared by the oxidative cyclisation of a linear tetrapyrrole **155** in an alkaline medium.¹¹⁷



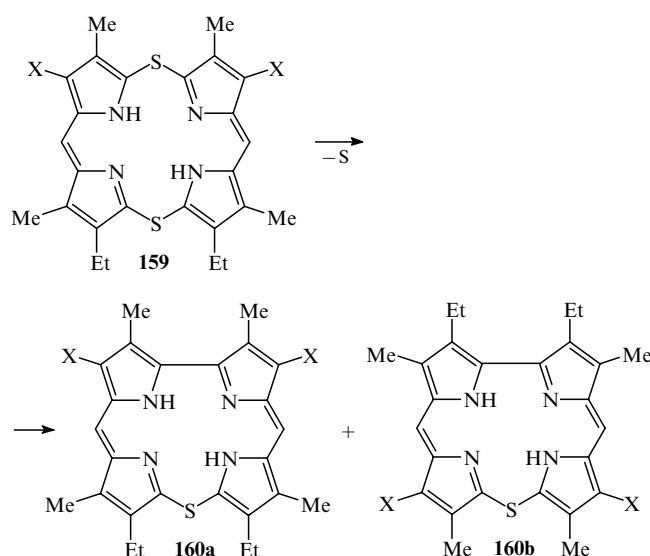
As expected, boiling of *meso*-thiaphlorin **157** in *o*-dichlorobenzene resulted in elimination of sulfur with the formation of

corrole **158** in 35%–40% yield.¹¹⁸ In the presence of triphenylphosphine, the yield of corrole **158** reaches 60%.



X = CO₂Et.

In the case of *meso*-dithia macrocycle **159**, the extrusion of sulfur occurs less readily (213 °C, 10 h, triphenylphosphine) and leads to two isomers of *meso*-thiacorrole **160a,b** in a total yield of 42% (ratio 1 : 1).¹¹⁸



X = CO₂Et.

III. Reactivity

Until recently, chemical properties of pyrroles bound to five-membered aromatic heterocycles have been very little studied because of the absence of reliable general methods for their synthesis. There were only fragmentary data on some reactions that included mostly interactions of their functional substituents (with the exception of formylation of the pyrrole fragment). The development of methods for the synthesis of hetaryl-substituted pyrroles in the last two decades has led to a considerable expansion of the array of preparatively accessible representatives of this group of compounds and to the appearance of real conditions for systematic studies of their reactivity and other properties.

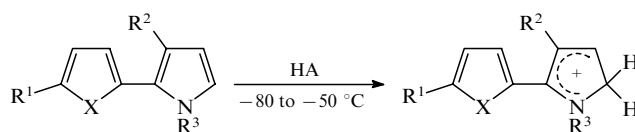
1. Electrophilic substitution

a. Protonation

It is known^{1–3, 119–125} that the most characteristic reaction of the pyrrole ring is electrophilic substitution, which is also typical of substituted furans and thiophenes.^{121–125} The simplest reaction of this type is reversible protonation (degenerate electrophilic substitution of hydrogen).

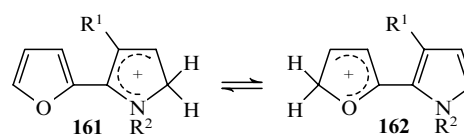
Over the last decade, the ¹H NMR method was used for the systematic studies of protonation of the series of 2-(2-furyl)- and 2-(2-thienyl)pyrroles and their 1-vinyl derivatives.

Numerous studies^{21, 25, 27, 126–133} have shown that at –80 to –50 °C all pyrroles, regardless of the nature of the second heterocycle and the acid (except for the ‘magic’ acid HSO₃F–SbF₅), are protonated at the C(5) atom of the pyrrole ring; in the case of vinyl derivatives (R³ = CH=CH₂), the double bond is retained.



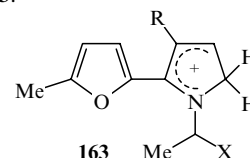
X = O, S; R¹ = H, Me; R² = H, Me, Prⁱ; R³ = H, CH=CH₂, Et;
A = Cl[–], Br[–], CF₃COO[–], FSO₃[–].

The reaction of furylpyrroles with hydrogen halides (HCl, HBr) at –30 °C yields a mixture of pyrrolium **161** and furanium **162** cations.^{21, 25, 128} An analogous mixture is also formed on gradual elevation of temperature from –80 to –30 °C.^{21, 25, 128}



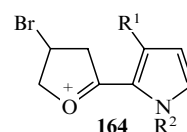
Protonation of vinyl derivatives (–30 °C) is accompanied by the addition of HX to the 1-vinyl group.^{21, 25, 27, 126–131}

On warming from –80 to –30 °C, the cation in which both α -positions in the furan ring are occupied adds HX only to the double bond with the formation of the pyrrolium ion **163**.^{21, 25, 27, 128}



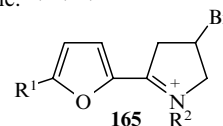
R = H, Me; X = Cl, Br.

As the temperature is increased to 0 °C, the reaction of furylpyrroles with HBr leads to 4-bromo-4,5-dihydro-2-(2-pyrrolyl)furanium bromides **164** as the result of addition of HBr to the protonated furan ring.^{21, 25, 27, 128}



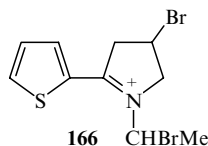
R¹ = H; R² = H, CHBrMe, Et; R¹ = Me; R² = H, CHBrMe.

At 20 °C, dihydrofuranium cations **164** are completely transformed into 4-bromo-4,5-dihydro-2-(2-furyl)pyrrololium bromide **165** with the rearomatization of the furan moiety of the molecule.^{21, 25, 27, 128}

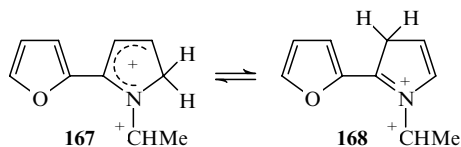


R¹ = H, Me; R² = CHBrMe.

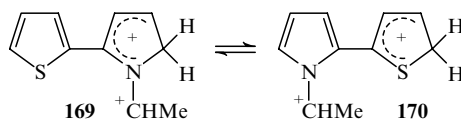
In contrast to the furan ring, the thiophene ring is not involved in the reaction with HBr. In this case, the formation of only 4-bromo-4,5-dihydro-2-(2-thienyl)pyrrololium bromide (**166**) is observed.^{21, 25, 130, 131}



Unlike ordinary acids, the superacidic system $\text{HSO}_3\text{F} - \text{SbF}_5$ reacts with 2-(2-furyl)-1-vinylpyrrole at -70°C to give an equilibrium mixture of dications: 1-(1-ethanio)-2-(2-furyl)-5H-pyrrolium (**167**) and 1-(1-ethanio)-2-(2-furyl)-3H-pyrrolium (**168**) in the ratio 3 : 1.^{21,25}

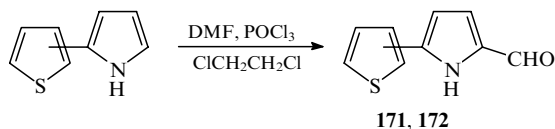


In the reaction with the superacidic system $\text{HSO}_3\text{F} - \text{SbF}_5 - \text{SO}_2$, 2-(2-thienyl)-1-vinylpyrrole forms two cations: 1-(1-ethanio)-2-(2-thienyl)-5H-pyrrolium (**169**) and 2-[1-(1-ethanio)-2-pyrrolyl]-5H-thiophenium (**170**) in the ratio 2 : 1. Heating of the reaction mixture up to 10°C changes the ratio **169** : **170** to 1 : 2.^{21,25,130,131}

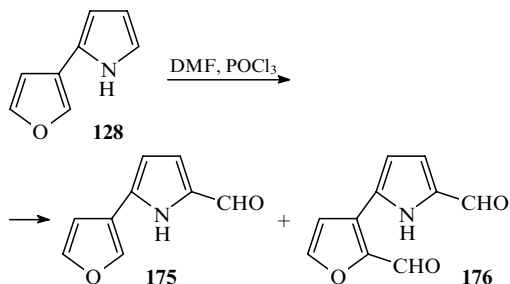
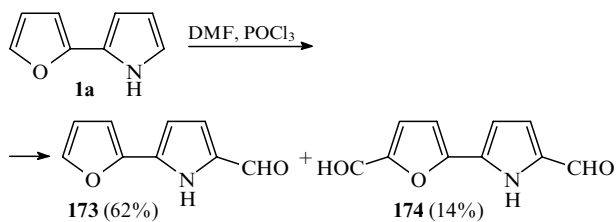


b. Formylation

Formylation of 2-(2-furyl)-, 2-(2-thienyl)-, 2-(3-furyl)- and 2-(3-thienyl)pyrroles and their α -methoxycarbonyl derivatives under conditions of the Vilsmeier reaction has been studied.^{101,134} Thienylpyrroles are formylated only at the α -position of the pyrrole ring with the formation of 2-thienyl- (**171**) (yield 75%) and 3-thienyl-2-formylpyrrole (**172**).

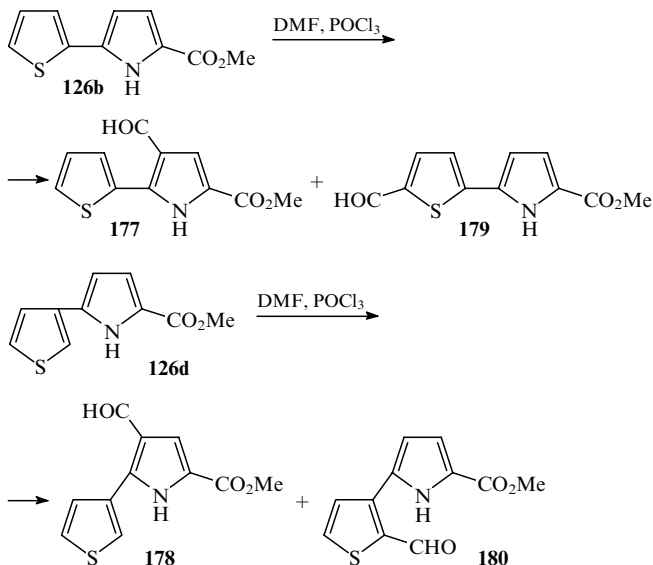


Formylation of furylpyrroles results in a mixture of mono- (**173, 175**) and diformyl derivatives (**174, 176**), the former being predominant.^{101,134}



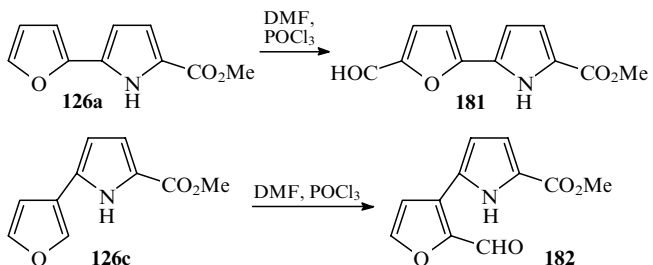
In 2-(3-furyl)pyrrole (**128**), both α -positions of the furan ring are free. However, the formyl group enters the position 2 of the furan ring, which is in accord with the standard orientation rule.

5-Methoxycarbonyl-2-(2-thienyl)- (**126b**) and -2-(3-thienyl)pyrrole (**126d**) give a mixture of 3-formyl-substituted pyrroles (**177, 178**) and 2-(5-formyl-2-thienyl)- (**179**) and 2-(2-formyl-3-thienyl)-derivatives **180**, respectively.¹³⁴

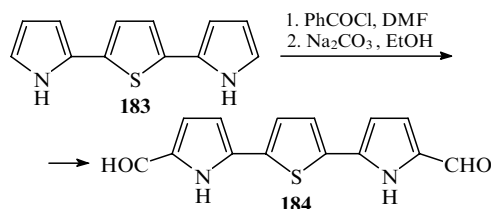


Because of the orienting effect of the α -methoxycarbonyl group, formylation in pyrroles **126b,d** occurs mostly in the β -position of the pyrrole ring (95%); the formylation product in the α -position of the thiophene ring is formed in the yield not exceeding 5%.

Unlike its thienyl analogues, 2-(2-furyl)- (**126a**) and 2-(3-furyl)-5-methoxycarbonylpyrrole (**126c**) form in this case virtually only the products of formylation at positions 5 and 2 of the furan ring, viz., pyrroles **181, 182**.¹³⁴



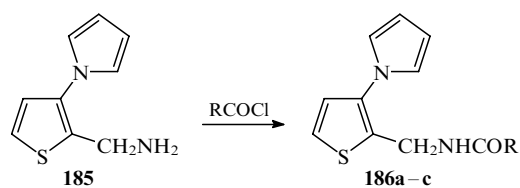
Heating of 2,5-di(2-pyrrolyl)thiophene **183** with benzoyl chloride in DMF leads to the formation of 2,2-di(5-formyl-2-pyrrolyl)thiophene **184** in 47% yield.⁶²



c. Acylation

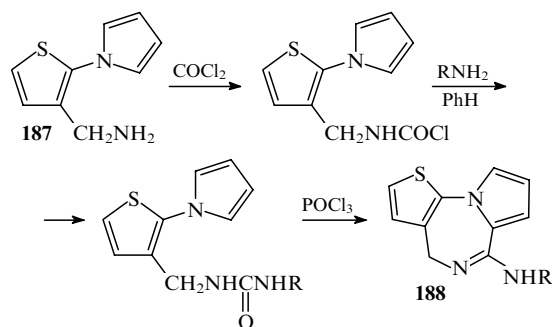
Acylation of bipyrroles, furyl- and thienylpyrroles devoid of functional substituents with carboxylic acid anhydrides and halides has not been studied, except for trifluoroacetylation.

Acylation of 1-(2-aminomethyl-3-thienyl)pyrrole **185** occurs exclusively at the amino group with the formation of 1-(2-aroyleamidomethyl-3-thienyl)pyrroles **186a-c**.¹¹¹



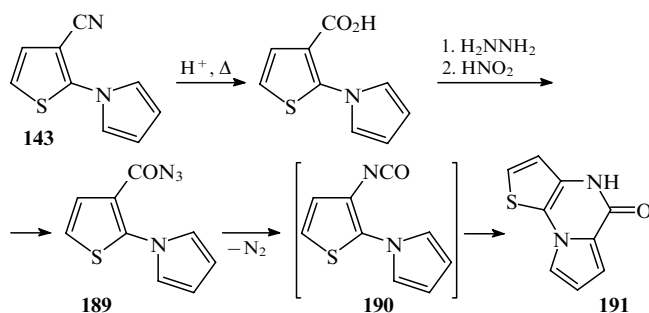
R = Ph (**a**, 82%), 4-ClC₆H₄ (**b**, 89%), 4-NO₂C₆H₄ (**c**, 74%).

Starting from an isomeric aminomethylthienylpyrrole **187**, thienylpyrrolodiazepines **188** were obtained.^{111, 113}

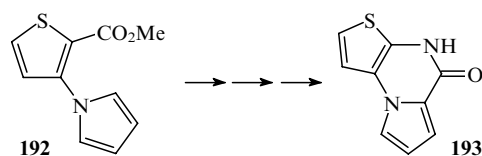


R = H, Me, Et, Ph, MeC₆H₄, 2-thienyl, NHPh.

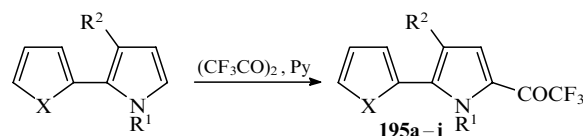
Tricyclic compound **191** was obtained from 1-(3-cyano-2-thienyl)pyrrole (**143**) by a series of consecutive reactions, including the rearrangement of the azide **189** into an intermediate **190**.¹¹²



Similarly, isomeric tricyclic compound **193** was synthesised from thienylpyrrole **192**.¹¹²



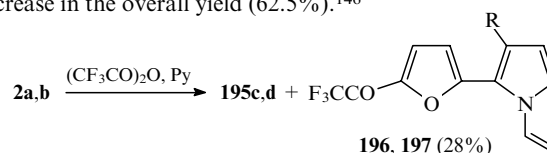
Trifluoroacetyl derivatives of various pyrrole systems have been attracting attention of researchers since the 1960–1970s.^{135–145} Trifluoroacetylation was often used on many occasions for comparing reactivities of various pyrrole, furan and thiophene derivatives in electrophilic substitution reactions.^{121, 124, 135–137} The relative trifluoroacetylation rates of pyrrole, furan and thiophene with trifluoroacetic anhydride are 5.3×10^4 , 1.4×10^2 and 1, respectively.^{121, 124} This ratio of rates illustrates the well known fact that pyrrole, owing to the higher, compared to other five-membered aromatic heterocycles, ability of its nitrogen atom to delocalise the positive charge in cationic σ -complexes, is appreciably more reactive than furan and the more so thiophene in reactions of electrophilic substitution.¹²² It was thus believed¹⁴⁶ that 2-(2-furyl)- (**1a**) and 2-(2-thienyl)pyrroles (**7a**), as well as their 1-vinyl (**2a, b**, **8a–c**), 1-ethyl (**194a**) and 1-triethylsilylmethyl derivatives (**194b**), would be acylated with trifluoroacetic anhydride only at position 5 of the pyrrole ring.



Initial compound	X	R ¹	R ²	Reaction product	Yield of 195 (%)
1a	O	H	H	195a	41
7a	S	H	H	195b	75
2a	O	CH ₂ =CH	H	195c	18
2b	O	CH ₂ =CH	Me	195d	34
8a	S	CH ₂ =CH	H	195e	78
8b	S	CH ₂ =CH	Me	195f	76
8c	S	CH ₂ =CH	Et	195g	63
194a	S	Et	H	195h	54
194b	S	CH ₂ SiEt ₃	H	195i	75

It was shown^{146, 147} that it is compounds **195** that are formed upon trifluoroacetylation of furyl- and thienylpyrroles. In the case of 2-(2-furyl)pyrrole **1a**, the reaction mixture contains, in addition to the initial pyrrole and the final 2-(2-furyl)-5-trifluoroacetylpyrrole **195a**, an admixture of a third compound, presumably the product of trifluoroacetylation in the α -position of the furan ring or the β -position of the pyrrole ring. The latter is possible for activated pyrroles.¹²² In contrast to 2-phenylpyrrole,¹⁴⁵ under comparable conditions the trifluoroacetylation of 2-(2-furyl)- (**1a**) and 2-(2-thienyl)pyrroles (**7a**) is not complete: the degree of conversion is 50%–60%, and the yields of the corresponding 5-trifluoroacetylpyrroles **195a, b** are 40%–50% with respect to the initial pyrrole. The use of a twofold excess of anhydride relative to pyrrole and the increase in the reaction temperature to 50 °C do not change its direction, though the yield of compound **195b** increases to 75%.

2-(2-Thienyl)-1-vinylpyrrole **8a** is acylated with both the equimolar amount and the twofold excess of trifluoroacetic anhydride to give virtually only one compound **195e**, whereas the major route of trifluoroacetylation of 2-(2-furyl)-1-vinylpyrrole **2a** is the attack at the α -position of the furan ring with the formation of compound **196**. With the twofold excess of anhydride, the content of isomer **195c** increases to 40% along with the increase in the overall yield (62.5%).¹⁴⁶

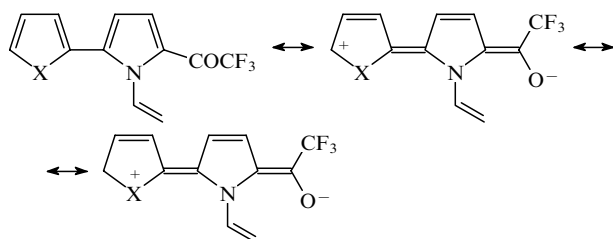


R = H (**196**, 28%); Me (**197**, 27%).

Substitution of α -hydrogen in the pyrrole ring by the trifluoroacetyl group is facilitated with the increase in its basicity, as is the case with 2-(2-furyl)- and 2-(2-thienyl)-1-vinylpyrroles with alkyl substituents at position 3. In contrast to compound **2a**, the attack of 2-(2-furyl)-3-methyl-1-vinylpyrrole (**2b**) by the trifluoroacetyl cation is directed mostly not at the furan but at the pyrrole ring. Structurally isomeric trifluoroacetylpyrroles **195d** and **197** are formed in 34% and 27% yields, respectively.¹⁴⁸ 3-Alkyl-2-(2-thienyl)-1-vinylpyrroles **8b, c** form only α -trifluoroacetylpyrroles **195f, g**. Substitution of the vinyl group by the ethyl group at the nitrogen atom (compound **194a**) does not change the direction of trifluoroacetylation. It also occurs in the pyrrole ring of compound **194b** in which there is a rather bulky triethylsilylmethyl substituent.¹⁴⁸

In order to interpret the results obtained, Trofimov *et al.*¹⁴⁶ considered the following factors; (a) an appreciably larger nucleophilicity of the furan ring compared to that of thiophene; (b) a decrease in the electron density in the pyrrole ring due to competitive conjugation of the vinyl group with the unshared electron pair on nitrogen and also owing to its negative inductive effect; (c) possible steric hindrance due to the vinyl group for the

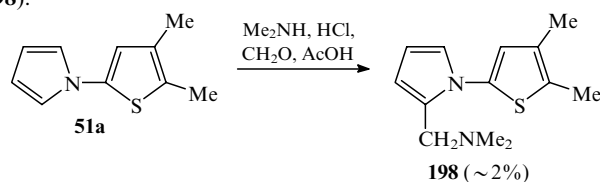
attack at the α -position of the pyrrole ring. The reactivity of the thiophene ring is so low compared to the furan ring, and the more so, the pyrrole ring, that the factors (a) and (b) seem to be insufficiently strong for changing the direction of trifluoroacetylation of 2-(2-thienyl)-1-vinylpyrrole. The absence of double acetylation products points to a very strong influence of the electron-acceptor trifluoroacetyl substituent that is transferred to the thiophene ring. The mechanism of such a transfer cannot be reduced solely to the inductive effect but should include formation of a common conjugation system.¹⁴⁶



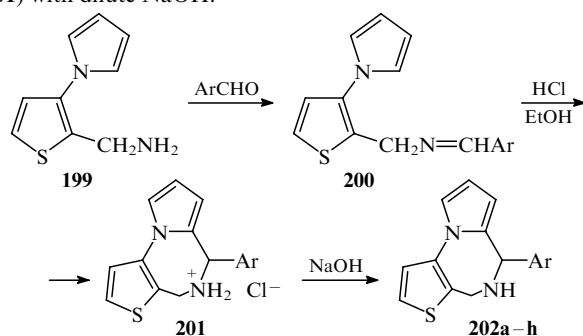
It is known that trifluoroacetylation of 1-vinylamides,¹⁴⁹ ethyl iminoacetoacetate¹⁵⁰ and 9-alkenylcarbazoles¹⁵¹ can result in electrophilic substitution of hydrogen in the 1-vinyl group. This reaction route was not observed for 2-(2-furyl)- and 2-(2-thienyl)-1-vinylpyrroles.

d. Aminomethylation

The reaction 1-(4,5-dimethyl-2-thienyl)pyrrole (**51a**) with the aminomethylation system $\text{Me}_2\text{NH} - \text{HCl} - \text{CH}_2\text{O}$ in acetic acid results in a 2-dimethylaminomethyl derivative of this pyrrole (**198**).¹⁰⁹



4-Aryl-5,6-dihydro-4H-pyrrolo[1,2-a]thieno[2,3-f]-1,4-diazepines **202a–h** were synthesised by the reaction of 1-(2-benzylideneaminomethyl-3-thienyl)pyrroles **200**, obtained from 1-(2-aminomethyl-3-thienyl)pyrrole (**199**) and the corresponding aromatic aldehydes, with hydrogen chloride in dry ethanol (Δ , 45 min) with subsequent treatment of the hydrochlorides formed (**201**) with dilute NaOH.¹¹⁰

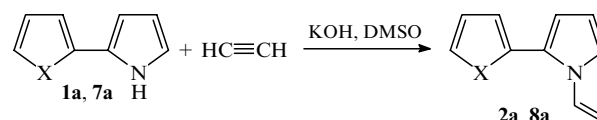


Compound 202	Ar	Yield (%)
a	Ph	48
b	2-ClC ₆ H ₄	62
c	3-ClC ₆ H ₄	56
d	4-ClC ₆ H ₄	53
e	3-MeOC ₆ H ₄	65
f	4-MeOC ₆ H ₄	63
g	3,4-(MeO) ₂ C ₆ H ₃	52
h		62

2. Nucleophilic addition to the triple bond

Vinylation of NH-heterocycles with acetylene is usually carried out under a pressure of 20–40 atm at 160–200 °C. This process has limited laboratory uses because of its explosion hazard and the need for special equipment, though several such technologies have been realised on the industrial scale.²²

The use of superbasic catalytic systems of the KOH–DMSO type allows vinylation of alkyl- and arylpyrroles at 100–200 °C and atmospheric pressure.¹⁵² Under these conditions, 2-(2-furyl)- (**1a**) and 2-(2-thienyl)pyrroles (**7a**) are successfully vinyated.¹⁵³ The results of vinylation of compounds **1a**, **7a** and 2-phenylpyrrole are presented in Table 2.



X = O (**1a**, **2a**), S (**7a**, **8a**).

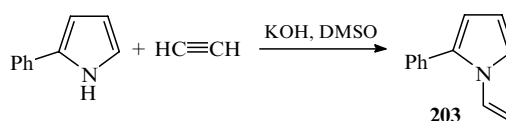


Table 2. Effect of vinylation conditions on the yield of 2-(2-furyl)- (**2a**), 2-(2-thienyl)- (**8a**) and 2-phenyl-1-vinylpyrroles (**203**).¹⁵³

Temperature / °C	Time / h	Yield of the vinylation product ^{a, b}		
		2a	8a	203
110	4	(2:98)	(15:85)	—
110	4.5	98	(3:97)	(12:78)
110	5	—	98.5	(5:95)
110	5.5	—	—	(2:98)
110	6	—	—	(~0.1:99.9)
120	3	86	(5:95)	(7:93)
120	4	—	(~0.1:99.9)	87

^a The yield was calculated after distillation. ^b The ratio of the initial compound to the reaction product (according to GLC) is indicated in parentheses.

Acetylene was passed through the reaction mixture under atmospheric pressure. Vinylation was carried out at a fivefold molar excess of KOH. Virtually quantitative yields (96%–98.5%) of 1-vinylpyrroles were attained at 110 °C within 4.5–6 h (see Table 2). With increase in the temperature to 120 °C the duration of vinylation is reduced, although the yield of 1-vinylpyrroles drops by 9%–16% because of side processes.

When vinylation was conducted in an autoclave (initial acetylene pressure 10–14 atm, maximal pressure 20–30 atm, DMSO, threefold molar excess of KOH, 120 °C), the yield of vinylpyrroles did not exceed 80% due to resinification. Thus, vinylation of aryl- and hetarylpyrroles under atmospheric pressure is not only safe but also more efficient.

The vinylation rate of pyrroles increases in the sequence 2-phenylpyrrole < 2-(2-thienyl)pyrrole < 2-(2-furyl)pyrrole (see Table 2). Their NH acidity increases in the same order. (Jackson³ did not give the value of 2-(2-furyl)pyrrole acidity, but it can be estimated from the cited dependence of pK_a on induction constants of substituents in the pyrrole ring). The observed order of reactivity of pyrroles fully confirms the previously established general regularity^{153–157} that the rate of base-catalysed addition of structurally similar azoles to acetylene, including 2-furyl- and 2-thienylpyrroles, increases with their acidity. However, it was reported¹⁵³ that the yield of 1-vinyl derivatives of tetrahydro- γ -carbolines increases with the introduction into their molecule of a methyl group, which decreases the NH-acidity. Thus, the infor-

mation available at that time did not give any clear idea about the influence of NH-acidity (nucleophilicity) of azoles on the rate of their addition to acetylene.

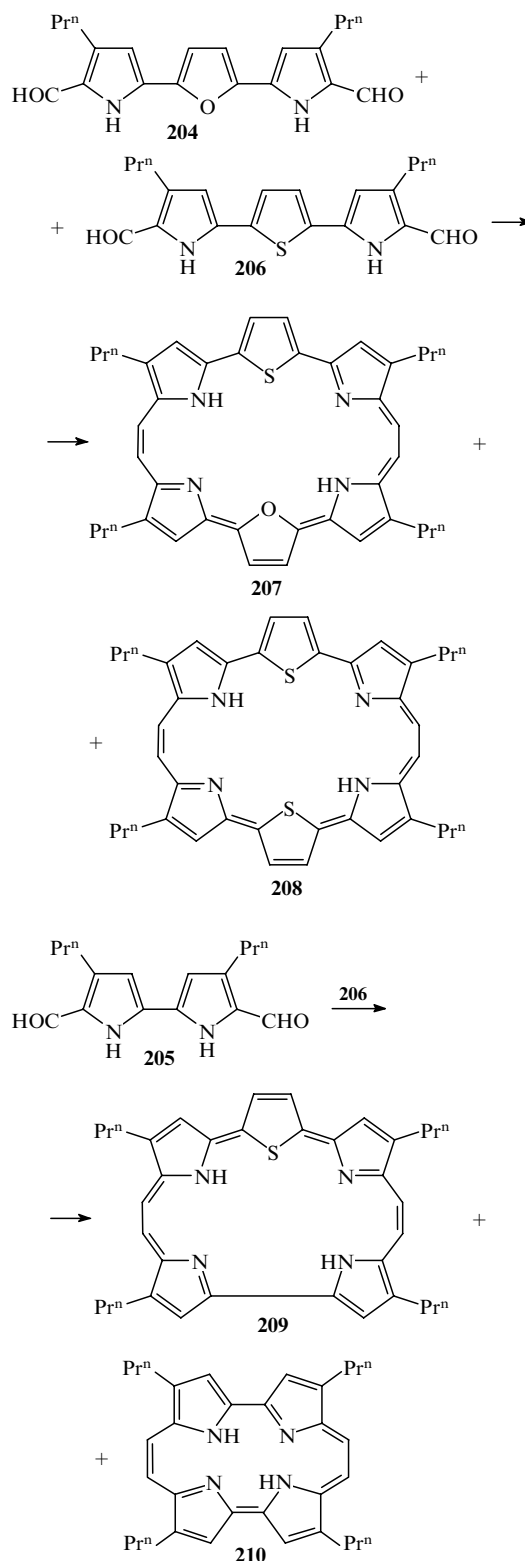
In order to assess the influence of substituents on the vinylation rate of pyrroles, the kinetic curves of vinylation of the series of NH-pyrroles for which precise values of pK_a of relative acidity are known have been compared quantitatively¹⁵⁶ with the correlation equations relating these parameters to the substituent constants.^{4, 157, 158} Vinylation was carried out in a KOH–DMSO system at 100 °C under atmospheric pressure. The course of the process was monitored using GLC. It was found¹⁵⁶ that the vinylation rates of 2-benzyl-3-phenyl-, 3-hexyl-2-phenyl-, 2,3-diphenyl-, 2-(4-ethylphenyl)- and 2-(4-methoxyphenyl)pyrroles increase with the decrease in their acidity (increase in pK_a values¹⁵⁹). However, 2-(2-furyl)- and 2-(2-thienyl)pyrroles are vinylated more readily than expected from consideration only of the values of their acidity, *i.e.*, possessing a stronger acidity than that of 2-phenylpyrroles, they have higher vinylation rates. The observed deviation may be explained by the fact that the nucleophilicity of anions is determined not only by their basicity (pK_a values of conjugated acids) but also by their polarisability and ionisation potential. Therefore, furyl- and thienylpyrroles, which are more easily polarised and possess lower ionisation potentials (owing to the heteroatoms conjugated with the pyrrole moiety of the molecule), should form anions of increased nucleophilicity with concomitantly decreased basicity. Despite the fact that the acidity of pyrroles increases and the basicity of the corresponding anions decreases in the order: 2-phenylpyrrole < 2-(2-thienyl)pyrrole < 2-(2-furyl)pyrrole, the reaction rate increases in the same order since the ionisation potentials^{160, 161} decrease in the following order (eV): 2-phenylpyrrole (7.61) > 2-(2-thienyl)pyrrole (7.41) > 2-(2-furyl)pyrrole (7.29). Thus, the 2-(2-furyl)- and 2-(2-thienyl)pyrrole anions, while being less basic than the 2-phenylpyrrole anion, are superior to it in their nucleophilicity.

Yet another peculiarity of the vinylation reaction of pyrroles has been revealed:¹⁵⁶ all kinetic curves are clearly S-shaped, which is characteristic of autocatalytic reactions. In principle, autocatalysis should be characteristic of vinylation reactions in aprotic and especially superbasic media. Indeed, with the consumption of protogenic substrate (the NH group of pyrrole in this case) one observes an increase in both nucleophilicity of the remaining anions (due to lower solvation) and the degree of ionisation of the remaining substrate molecules (owing to increased medium basicity). At the same time, the chemical activity of acetylene molecules is enhanced owing to complexation with partially dehydrated molecules of the base serving as the catalyst (KOH). The presence of a one-electron route of nucleophilic addition to the triple bond can also contribute to the manifestation of this effect.¹⁵⁶ This reaction can occur by a chain mechanism and be inhibited by admixtures that quench radical and non-radical intermediates. Such a mechanism is highly probable for superbasic systems in which highly reactive, dehydrated anions are especially prone to electron transfer. This is also consistent with the reported¹⁵⁶ approximate correlation between the reaction rate and the ionisation potentials of the initial pyrroles. The presumed existence of a one-electron route in the vinylation reaction of pyrroles has been confirmed in later studies.^{162–164}

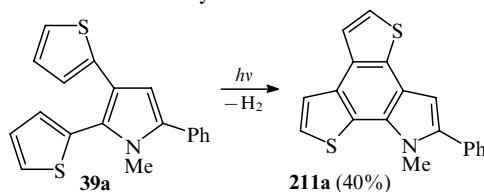
3. Cyclisation

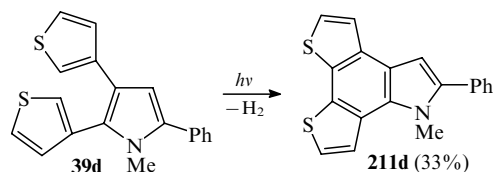
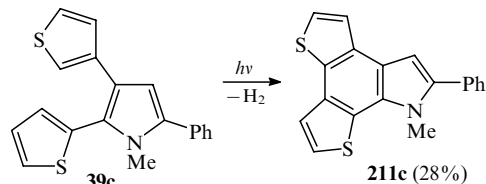
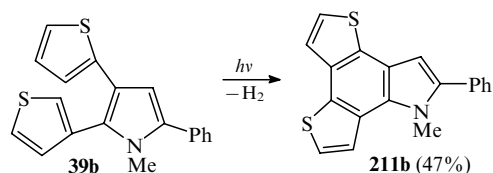
Cyclisation of pyrroles linked to aromatic five-membered heterocycles leads to difficultly accessible polycyclic systems.

Porphyrin-like macrocycles **207–210** have been obtained by the reaction of 2,5-bis(5-formyl-4-n-propyl-2-pyrrolyl)furan **204** or dipyrroledicarbaldehyde **205** with 2,5-bis(5-formyl-4-n-propyl-2-pyrrolyl)thiophene **206**.¹⁶⁵

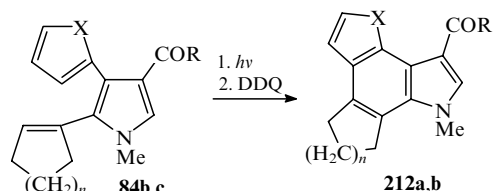


Oxidative photocyclisation of isomeric 2,3-dithienyl-5-phenylpyrroles **39a–d** resulted in a series of isomeric dithienoindoles **211a–d** in 28%–47% yields.⁶⁶



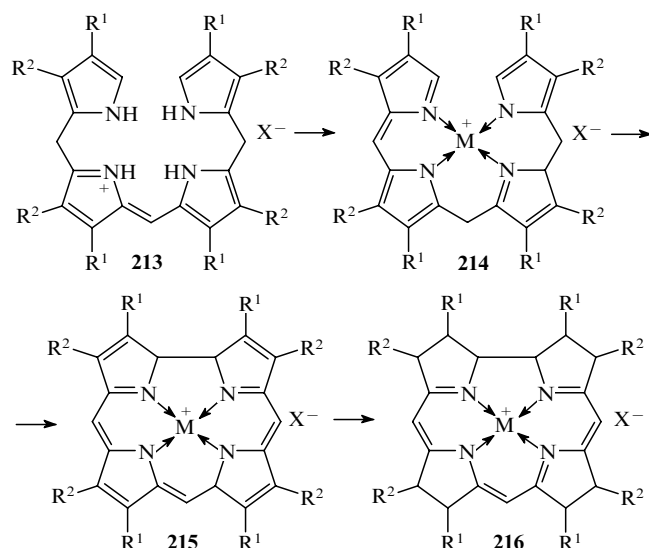


Photochemical electrocycloisalisation of 3-(2-furyl)- and 3-(2-thienyl)pyrroles **84b,c** with subsequent dehydrogenation with 2,3-dichloro-5,6-dicyanoquinone (DDQ) leads to indole derivatives **212a,b**.⁸¹ Irradiation was carried out with a high-pressure mercury lamp at room temperature for 12 h in cyclohexane.



Compound 212	X	n	R	Yield of 212 (%)
a	O	3	Ph	73
b	S	2	2-thienyl	78

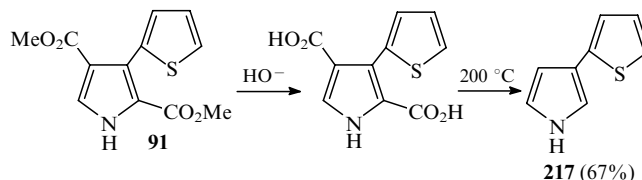
Linear tetrapyrrole intermediates (**213**) form complexes (**214**) with transition metal salts ($M = Ni, Co$; $X = Cl, Br, ClO_4$) upon heating in *o*-dichlorobenzene (100 °C, 14 h). These complexes are oxidised by atmospheric oxygen to corrole-like macrocycles **215** containing the bipyrrrole fragment. Subsequent reduction of the latter under drastic conditions (100 °C, 100 atm) leads to corrins. Their structural element forms the basis of numerous vitally important compounds, including vitamin B₁₂.^{166, 167}



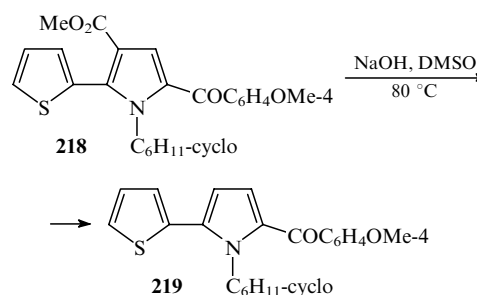
$R^1, R^2 = Me, Et$; $M = Ni, Co$; $X = Cl, Br, ClO_4$.

4. Hydrolysis, decarboxylation, oxidation and other reactions of substituents

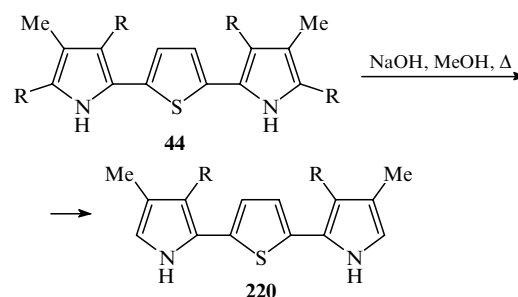
Hetaryl-substituted pyrroles often contain alkoxy-carbonyl groups. These can be eliminated by hydrolysis and decarboxylation (200 °C) (see Section II.7, synthesis of compounds **1a**, **7a**, **128**, **129**).¹⁰¹ 3-(2-Thienyl)pyrrole (**217**) was obtained in this way from the diester **91**.⁸⁵



Alkaline hydrolysis of the ester **218** leading to thienylpyrrole **219** has been described.⁷⁶

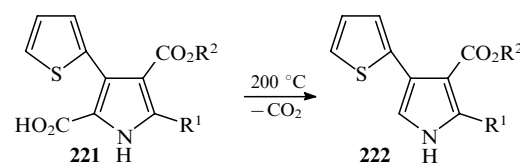


When di(pyrrolyl)thiophene **44** with four ethoxycarbonyl groups in the α - and β -positions of the pyrrole rings was boiled in methanolic NaOH, only the α -positions were selectively liberated with the formation of di(pyrrolyl)thiophene **220**.⁶⁸



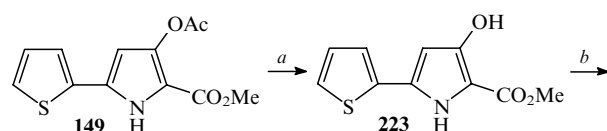
$R = CO_2Et$.

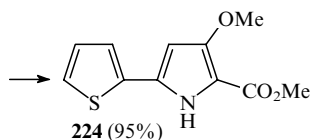
Esters of 4-(2-thienyl)pyrrole-3-carboxylic acids **222** were synthesised by decarboxylation of 3-(2-thienyl)-2,4-pyrroledicarboxylic acid derivatives **221**.¹⁶⁸



$R^1 = H, Alk$; $R^2 = Alk$.

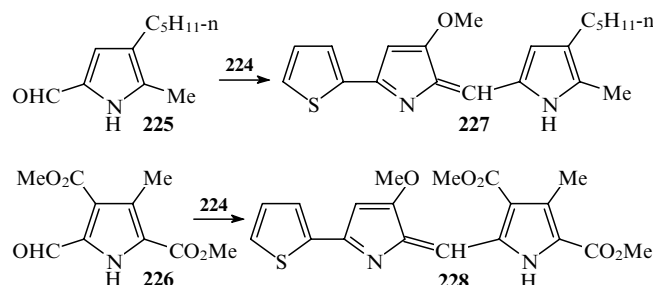
Solvolysis of thienylpyrrole **149** results in its deacetylation and formation of 4-hydroxy-5-methoxycarbonyl-2-(2-thienyl)pyrrole (**223**).¹¹⁴ Its methylation with dimethyl sulfate gives pyrrole **224**.¹¹⁴



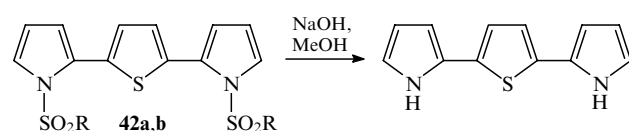


(a) 5N NaOMe, MeOH, 3 h; (b) Me₂SO₄, NaH, THF.

Pyrrole-2-carbaldehydes **225**, **226** form prodigiosin analogues **227**, **228** upon reaction with the pyrrole **224** (yields up to 95%).¹¹⁴

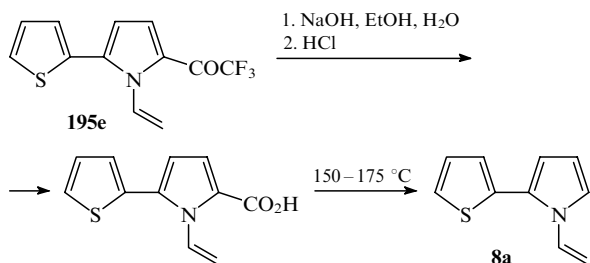


The *N*-sulfonyl protective groups in dipyrrolylthiophenes **42a,b** are removed by boiling with methanolic NaOH.⁶⁸

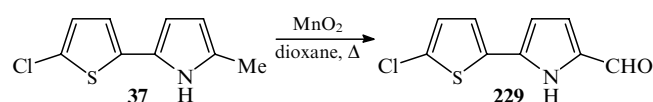


R = Me (a), Ph (b).

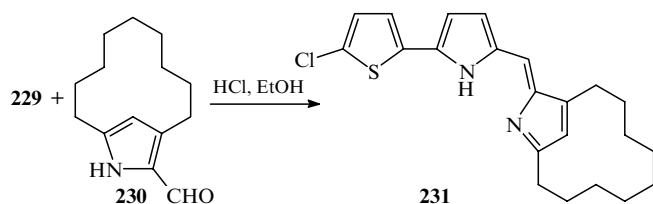
Treatment of 2-(2-thienyl)-5-trifluoroacetyl-1-vinylpyrrole **195e** with boiling ethanolic NaOH gave 2-(2-thienyl)pyrrole-carboxylic acid (yield 88%), which is decarboxylated to vinylpyrrole **8a** upon heating (150–175 °C).¹⁶⁹



α -Formyl derivative of 2-(5-chloro-2-thienyl)pyrrole **229** was synthesised in 45% yield by the oxidation of pyrrole **37** with MnO₂ in dioxane.⁶⁵



The aldehyde **229** reacts with 2,4-pyrrolophane **230** in ethanol in the presence of concentrated HCl (8 °C, 15 min; 0 °C, 24 h) to give pyrrolophane **231**.⁶⁵



5. Reactions of the *N*-vinyl group

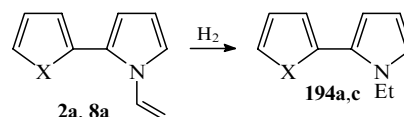
Systematic studies of the reactivity of 2-(2-furyl)- and 2-(thienyl)-1-vinylpyrroles became possible after the development of a

convenient and efficient method for their synthesis.⁴ Before that, there were virtually no data on the *N*-vinylpyrroles linked to five-membered aromatic heterocycles. Studies of reactions involving the *N*-vinyl groups of furyl- and thienylpyrroles open wide possibilities for the synthesis of new hetaryl-substituted pyrroles.

a. Hydrogenation

Hydrogenation of substituted pyrroles is a rather well-studied reaction,^{1,2} which allows one to synthesise pyrrolines and pyrrolidines in high yields. Platinum, ruthenium and nickel catalysts are most often used for catalytic hydrogenation of pyrroles.^{1,2,170} Depending on the nature of the substituent and its position in the ring, it is possible to bring about selective hydrogenation of either the pyrrole ring or the side chain.^{1,2} Electron-acceptor substituents in the α - and β -positions of the ring impede its reduction, whereas substituents at the nitrogen atom facilitate this process.^{1,2}

Hydrogenation of 2-(2-furyl)-1-vinyl- and 2-(2-thienyl)-1-vinylpyrroles in the presence of catalysts such as Raney nickel, platinum black, palladium chloride was first studied by Korostova *et al.*¹⁴⁸ It was shown that hydrogenation on Raney nickel (80 °C, 60 atm) results in the reduction of the vinyl group in 2-(2-furyl)-1-vinylpyrrole (**2a**) to the ethyl group which occurs as easily and selectively as in 2-alkyl(aryl)-1-vinylpyrroles,¹⁷¹ giving 1-ethyl-2-(2-furyl)pyrrole **194c** in 94% yield.¹⁴⁸

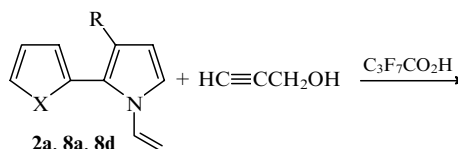


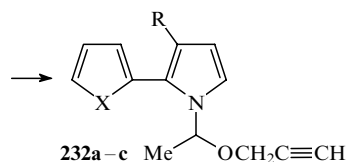
X = O (**2a**, **194c**); S (**8a**, **194a**).

In the hydrogenation over Raney nickel, a decrease in the hydrogen pressure to 10–12 atm (all other conditions remaining the same) leads to a sharp deceleration of the reaction and a decrease in the yield of ethylpyrrole **194c** to 65%. In the hydrogenation over palladium chloride (15 mass. % with respect to vinylpyrrole, 80 °C, 40 atm) the yield of ethylpyrrole **194c** amounts to 75%. In contrast with the data reported by Lunn,¹⁷² who succeeded in reducing pyrrole to pyrrolidine in the presence of a nickel–aluminium alloy, the pyrrole and furan rings of compound **2a** remain intact under the described conditions.¹⁴⁸ The presence of the thiophene ring complicates hydrogenation of 2-(2-thienyl)-1-vinylpyrrole (**8a**) over nickel catalyst (50 °C, 48 atm) due to poisoning of the catalyst. Only the use of a very large amount of the catalyst (50 mass. % with respect to vinylpyrrole) has allowed preparation of ethylpyrrole **194a** in 46% yield; in this case, hydrogenolysis resulted in the formation of low-boiling products. When PdCl₂ was used at room temperature, the yield of ethylpyrrole **194a** was as low as 7%. In the presence of palladium black (80 °C, 40 atm), 2-(2-thienyl)-1-vinylpyrrole is not hydrogenated.

b. Addition of alcohols

Electrophilic addition of alcohols to 2-(2-furyl)- and 2-(2-thienyl)-1-vinylpyrroles was studied in the example of reaction with propargyl alcohol in the presence of perfluorobutyric acid (PFBA).^{148,173,174} This reaction is conducted at 96 °C. Higher temperature and longer reaction time enhance resinification. The yield of adducts **232a–c** depends on the catalyst's concentration and the ratio of reagents: the optimum conditions are 1.5-fold excess of propargyl alcohol and 1.5%–2% of PFBA relative to the substrate.

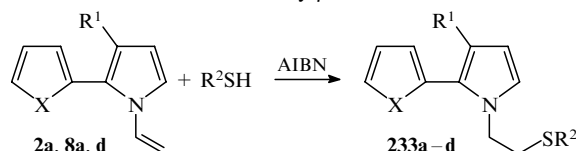




R = H: X = O (**232a**, 55%), S (**232b**, 71%); R = Me, X = S (**232c**, 56%).

c. Addition of thiols

Free-radical thiylation of 2-(2-furyl)- and 2-(2-thienyl)-1-vinylpyrroles initiated by azobis(isobutyronitrile) (AIBN) gives *anti*-Markovnikov formation of solely β -adducts **233**.¹⁴⁸



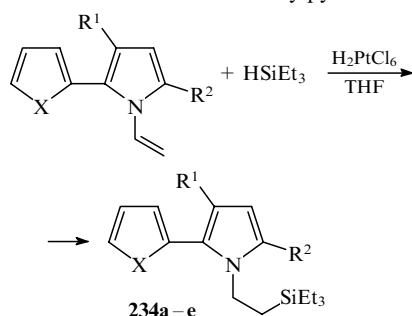
Substrate	X	R ¹	R ²	Product	Yield (%)
2a	O	H	Et	233a	84
8a	S	H	Et	233b	78
8d	S	Pr ⁿ	Et	233c	95
8d	S	Pr ⁿ	Pr ⁿ	233d	80

At 70–80 °C, the reaction is completed within 18–25 h (the yield of adducts **233a–d** is 80%–95%). Under comparable conditions without initiator, the yield drops to 15%–20%.¹⁴⁸ This reaction has been successfully used for purification of 2-(2-thienyl)pyrroles from their 1-vinyl derivatives.⁴³

d. Hydrosilylation

Kopylova *et al.*¹⁷⁵ performed hydrosilylation of 2-(2-furyl)- and 2-(2-thienyl)-1-vinylpyrroles in the presence of different catalysts; they also used various hydrosilylation agents.

The highest yields of silyl derivatives were reached upon hydrosilylation with triethylsilane at an equimolar ratio of reagents in the presence of 0.05 M solution of $\text{H}_2\text{PtCl}_6 \cdot 6\text{H}_2\text{O}$ in THF (140 °C, 5 h). The reaction proceeded regiospecifically with the formation of β -adducts **234a–e**. (The yields were calculated relative to the consumed vinylpyrrole).¹⁷⁵



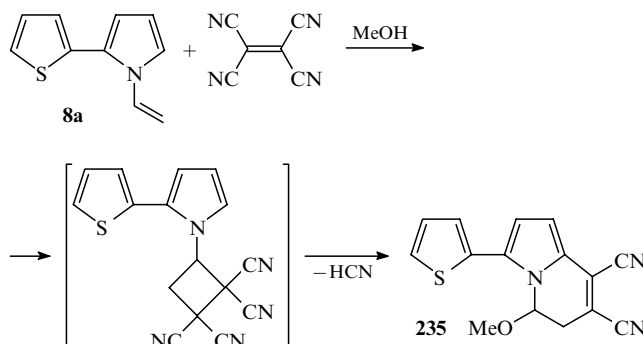
Compound 234	X	R ¹	R ²	Yield (%)
a	O	H	H	40
b	S	H	H	70
c	S	Me	H	65
d	S	Et	H	44
e	S	H	COCF_3	10

The Wilkinson complex $[(\text{Ph}_3\text{P})_3\text{RhCl}]$ also catalyses this reaction. Longer reaction time and the use of polar solvents (THF, dioxane) favour an increase in yields of the adducts. No positive results have been reported for the reactions involving trichloro-, triethoxy- and alkylchlorosilanes. Only upon reaction of methylchlorosilane with 2-(2-thienyl)-1-vinylpyrrole, the

formation of the corresponding adduct in ~7% yield was observed. In the absence of catalysts, the reaction does not take place under UV-initiation. The yield of adducts depends not only on the nature of the silane but also on the substituents in the pyrrole ring. Thus the yield of the pyrrole **234b** was 70%; upon introduction of an electron-acceptor substituent ($\text{R}^2 = \text{COCF}_3$) into the pyrrole ring, the yield of the corresponding pyrrole **234e** drops to 10%.¹⁷⁵

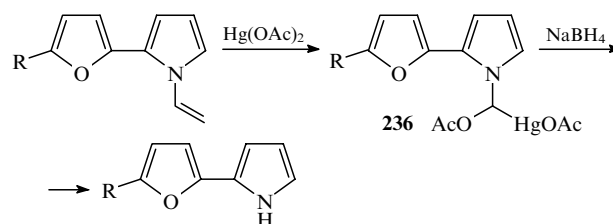
e. Cyclisation

7,8-Dicyano-5-methoxy-3-(2-thienyl)-5,6-dihydroindolizine (**235**) was synthesised from 2-(2-thienyl)-1-vinylpyrrole (**8a**), tetracyanoethylene and methanol.¹⁷⁶



f. 2-(2-Furyl)-1-vinylpyrroles as protected pyrroles

Protection of the NH group of the pyrrole fragment is often the key stage in the synthesis of complex pyrrole derivatives. In this case, not only the acidity of the NH group is temporarily blocked, but the reactivity of different positions of the pyrrole ring is substantially changed due to steric and electronic effects of the protective groups. The role of protective group is played by, *e.g.*, trialkylsilyl, tosyl, pyridylethyl, phenylsulfonyl or *N*- β -alkylthioethyl groups. The *N*-vinyl group may also be rather successfully used for the protection of the NH group.^{51, 95, 177–180} In this case, deprotection can be effected by acid hydrolysis in the presence of hydroxylamine hydrochloride¹⁸¹ or by mercuration with mercuric acetate followed by treatment with sodium borohydride.⁵¹ 2-(2-Furyl)- and 2-(5-methyl-2-furyl)-1-vinylpyrroles have thus been transformed into the corresponding 1*H*-pyrroles in 93% and 83% yields, respectively (relative to the consumed vinylpyrrole).¹⁸²



R = H, Me.

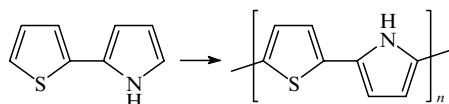
Mercuration is carried out at room temperature until disappearance of the initial 1-vinylpyrrole with subsequent *in situ* reduction of the intermediate mercuric acetate **236** with sodium borohydride.

Despite complete disappearance of the starting vinylpyrrole in the mercuration stage, it appears again in small amount after the reduction with sodium borohydride. It is presumed that the intermediate **236** is preceded by a complex of vinylpyrrole with the mercury cation, the reduction of which leads to regeneration of 1-vinylpyrrole.¹⁸²

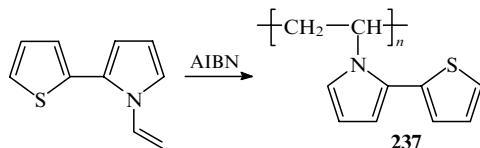
g. Polymerisation

Polymerisation of furyl- and thienylpyrroles and their vinyl derivatives has been little studied so far. Electrochemical polymer-

isation of 2-(2-thienyl)pyrrole yielded poly(thienylpyrrole), apparently with alternating thienyl and pyrrole rings.¹⁸³

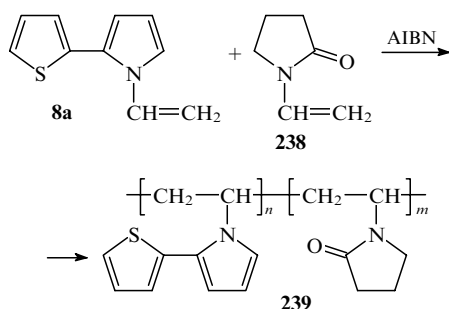


Under the conditions of radical initiation, *i.e.*, under the action of azobis(isobutyronitrile), 2-(2-thienyl)-1-vinylpyrrole forms homopolymers **237** with a molecular mass of 3700 Da.¹⁸⁴



The formation of polymers with involvement of only the *N*-vinyl group was proved by spectral data (IR, ¹H NMR) and turbidimetric titration data in different solvent–precipitant systems. It was suggested¹⁸⁴ that poly(1-vinylpyrroles) **237** form complexes upon contact with atmospheric oxygen; this suggestion is supported by intense EPR signals in polymers following their prolonged exposure in air.

Free-radical copolymerisation of 2-(2-thienyl)-1-vinylpyrrole **8a** with vinylpyrrolidone **238** yielded a copolymer **239** enriched in the vinylpyrrolidone units.^{185, 186} The molecular mass and the yield of the copolymer depend directly on the concentration of vinylpyrrolidone.



IV. Prospects for the use

The chemistry of pyrroles linked to five-membered aromatic heterocycles is still in its infancy. Nonetheless, the currently available data on their properties allow one to consider them and their derivatives as promising compounds for medicine, agriculture and some industrial fields.

This concerns primarily the 1-vinyl derivatives of furyl- and thienylpyrroles. Reactions of electrophilic substitution in the pyrrole ring and addition reactions to the vinyl group occur highly selectively making it possible to use these compounds as building blocks for the synthesis of various derivatives.

The potentialities of furyl- and thienylpyrroles are still far from being fully disclosed. Poly(furylpyrroles) and poly(thienylpyrroles) with regularly alternating rings can differ appreciably in their electrophysical properties¹⁸⁴ from polypyrroles — organic metals, which are already applied in novel technologies.^{187–190} Indolizines with thienyl substituents have been recommended as efficient photosensitisers.¹⁷⁶

The antiviral activity of a series of 2-(2-furyl)- and 2-(2-thienyl)-1-vinylpyrroles has been investigated. 2-(2-Thienyl)-1-vinylpyrrole was found to be moderately active against the herpes virus, whereas 3-ethyl-2-(2-thienyl)-1-vinylpyrrole proved to be active against the pox virus.²⁶ It should be pointed out that furylvinyl- and thienylvinylpyrroles are as a rule moderately or weakly toxic compounds^{23, 24, 26} (Table 3).

Table 3. Toxicity of 1-vinyl-2-(2-hetaryl)pyrroles, some of their precursors and derivatives.

Compound	LD ₅₀ /mg kg ^{−1} (see ^a)
3-Ethyl-2-(2-furyl)-1-vinylpyrrole	760
2-(2-Furyl)-3-isopropyl-1-vinylpyrrole	1300
3-Butyl-2-(2-furyl)-1-vinylpyrrole	270
2-(2-Thienyl)pyrrole	260
2-(2-Thienyl)-1-vinylpyrrole	630
3-Methyl-2-(2-thienyl)-1-vinylpyrrole	30
3-Ethyl-2-(2-thienyl)-1-vinylpyrrole	830
3-Propyl-2-(2-thienyl)-1-vinylpyrrole	1370
3-Butyl-2-(2-thienyl)-1-vinylpyrrole	620
3-Hexyl-2-(2-thienyl)-1-vinylpyrrole	1500
2-(2-Thienyl)-5-trifluoroacetylpyrrole	3900
2-(2-Thienyl)-5-trifluoroacetyl-1-vinylpyrrole	1870
2-(2-Thienyl)-1-vinyl-5-pyrrolecarboxylic acid	270

^a Approximate values.

The activity of a series of 2-(2-furyl)- and 2-(2-thienyl)pyrroles towards 11 strains of different bacterial and fungal species has been assayed. 2-(2-Thienyl)-1-vinylpyrrole proved to be the most active against staphylococci and candidas as well as against the anthracoid bacilli.²⁶

Investigation into the repellent and insecticidal activity of furylvinyl- and thienylvinylpyrroles has revealed that 2-(2-furyl)-1-vinylpyrrole is a highly active and selective repellent for forest pests (black coniferous longhorn beetle) and is non-toxic for warm-blooded animals and the ichthiofauna of rivers; 3-ethyl-2-(2-thienyl)-1-vinylpyrrole was also found to manifest weak repellent activity.^{4, 24, 26} The same vinylpyrroles proved to be moderately toxic for the larvae of the coniferous longhorn beetle.^{4, 26}

The assay of insecticidal activity of a series of 2-(2-furyl)- and 2-(2-thienyl)pyrroles has revealed moderate activity of 3-propyl-2-(2-thienyl)-1-vinylpyrrole against sugar-beet root aphid and high activity of 2-(2-thienyl)-, 3-ethyl- and 3-propyl-1-vinylpyrroles against larvae of the domestic fly.²⁶ 3-Propyl-2-(2-thienyl)-1-vinylpyrrole possesses high herbicidal activity, while 2-(2-thienyl)-1-vinylpyrrole and its copolymer with *N*-vinylpyrrolidone exhibit the growth-regulating activity.^{26, 186, 191}

A number of 4-cyano-3-furyl- and 3-thienylpyrroles were recommended as starting compounds for the synthesis of medicinal substances and pesticides,⁸² while esters of 4-(2-thienyl)-3-pyrrolecarboxylic acids seem to be appropriate drugs for the therapy of cardiac insufficiency.¹⁶⁸

V. Conclusion

The data discussed in this review demonstrate appreciable progress in the field of the synthesis of pyrroles linked to other heterocycles, *viz.*, bipyrroles, furyl-, thienyl- and selenienylpyrroles and their derivatives.

Broad synthetic potential of hetarylpyrroles and especially of their *N*-vinyl derivatives in various reactions, such as electrophilic substitution, nucleophilic addition to the triple bond, cyclisation, hydrogenation, thiylation, hydrosilylation, polymerisation, as well as useful properties inherent in certain compounds of this series open up broad prospects for their use in fine organic synthesis, medicine, agriculture and some technological fields.

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^g — *Russ. J. Gen. Chem. (Engl. Transl.)*

C-Alkenylation of pyrimidine nucleosides and their analogues

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Abstract. Methods for C-alkenylation of heterocycle moieties of pyrimidine nucleosides and their analogues are generalised. The methods employing both organoelement nucleoside derivatives (organomercury, -tin, -boron and -lithium) and organoelement alkene derivatives (organomagnesium, -boron, -aluminium, -tin and -silicon) as well as palladium-catalysed oxidative coupling and photochemical reactions are considered. The reaction conditions (the role of solvents, catalysts and co-catalysts, temperature and time modes) are discussed. The advantages and the drawbacks of different approaches for introduction of alkenyl groups are discussed. Examples of practical applications of alkenylated nucleoside derivatives and their analogues are given. The bibliography includes 92 references.

I. Introduction

Derivatives of pyrimidine nucleosides with substituents at positions 5 and 6 have been the permanent focus of attention of investigators. The number of papers devoted to the synthesis and application of these compounds is rapidly increasing. This interest is largely associated with antiviral and antitumour properties of these nucleosides and the possibility of using them as probes for studying the interactions between biomolecules^{1,2} or as fluorescent probes for DNA sequencing.

Very often these properties are exhibited by nucleosides containing a C—C bond with various substituents at positions 5 and 6 (alkyl, alkenyl, alkynyl, aryl, hydroxyalkyl, acyl, *etc.*). In this context, systematisation of methods used for the synthesis of such compounds is especially important. A review³ on C-alkylation of nucleosides which is devoted to problems of synthesis of the majority of derivatives with the above substituents was published in 1990. A detailed study⁴ describing the synthesis of alkynyl derivatives of nucleosides and their analogues has appeared more recently.

Alkenyl-substituted nucleosides seem to play the most crucial role among other nucleosides under consideration; these are extensively used in practically all the fields mentioned above. Thus 5-(*E*)-bromovinyluridine and its carbocyclic analogues, 5-(*E*)-(propen-1-yl)uridine and 5-(*E*)-(3,3,3-trifluoropropen-1-yl)uridine, are known as efficient antiviral agents. Many alkenyl derivatives, particularly those containing a porphyrin fragment,⁵ manifest an antitumour activity. The extensively investigated reactions between certain alkenes and nucleosides are used to prepare probes to study biomolecules. These reactions allow both direct incorporation of a label into a biomolecule and its addition through an alkenyl linker. As an illustration, we can refer to biotin-containing probes,⁶ photoactivated labels^{7,8} and fluorescent probes⁹ used in DNA sequencing. Evidently, alkenyl linkers can also be used for other purposes. An interesting example is the addition of carborane-containing fragments¹⁰ used in anticancer boron neutron capture therapy (BNCT).

It can be mentioned that the synthesis of alkenyl derivatives of pyrimidine nucleosides and their analogues has a number of special features and often presents a more complicated task than the alkenylation of classical aromatic compounds, *e.g.*, benzene. Such complications can be associated with both the preparation of the starting activated nucleosides and the conducting of the alkenylation reaction. They result from the presence of several reactive functional groups in the nucleoside molecule and the complex behaviour of the quasi-aromatic system of pyrimidine nucleic bases. For example, alkenylation of mercury derivatives of nucleosides with non-activated alkenes in methanol yields predominantly α -methoxyalkyl derivatives, which are not typical of the analogous reactions for the benzene series.

One can say that generalised information on these reactions has not been adequately addressed in the literature, especially when one takes into consideration that all the presently known methods of C-alkenylation of pyrimidine nucleosides are extremely diverse. The reviews^{11,12} describing the synthesis of alkenyl-substituted nucleosides point to the exclusive use of 5-mercurionucleoside derivatives. It is of note that the first of them¹¹ was published as long ago as in 1982, while the second one¹² is rather a summary of results obtained by the authors in the preceding period. Even since the publication of the review by Krečmerová,³ several novel alkenyl nucleoside analogues and methods of their synthesis have appeared, which necessitates generalisation and critical evaluation of the vast body of experimental data concerning the methods of synthesis of pyrimidine nucleosides with C-alkenylated heterocycles.

All the currently known methods used for the synthesis of alkenylated pyrimidine nucleosides can be conventionally divided

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into two groups. The most efficient (Group 1) methods consist in the direct formation of the C—C bond of a nucleoside with an alkenyl substituent. In contrast, Group 2 methods in which the pyrimidine ring is formed in the first step with subsequent glycosylation, have serious drawbacks. These include the necessity for preliminary preparation of reagents for cyclisation and the formation of a mixture of α - and β -anomers in the glycosylation step. The present review deals with the description of Group 1 methods, *viz.*, direct alkenylation of the pyrimidine ring of nucleosides and their analogues at position 5 or 6.

From our standpoint, the methods of direct alkenylation should best be classified according to the structural features of nucleosides and alkenylating agents involved in the reaction. The choice of compounds to be introduced in the reaction is determined, among other factors, by the ease of their synthesis. In many respects, this factor is crucial for a synthesis-oriented chemist. Thus 5-chloromercury derivatives of nucleosides formed under mild conditions are widely employed in the coupling with alkenes; examples of 'reversed' coupling of nucleosides by this reaction are unknown. The readers who are interested in the mechanisms of the reactions discussed below can be referred to the monograph.¹³ According to the structure of reagents (alkenylating reagents) and substrates (nucleosides), the methods used for alkenylation of pyrimidine nucleosides can be classified as follows:

1. *Alkenylation of nucleosides containing a C—E bond (E is the electropositive element, viz., Hg, B, Sn and Li).* Coupling of organomercury nucleoside derivatives with alkenes and cross-coupling of organoboron and organotin nucleoside derivatives with alkenyl halides are catalysed by palladium compounds. Nucleoside organolithium derivatives and their analogues as nucleophiles substitute the fluorine atom in perfluoro- or fluoro-chloroalkenes.

2. *Alkenylation of nucleosides with a C—Hal or a C—OTf bond.* The methods referred to this group can be additionally divided into four subgroups:

- a. Reactions of halogeno derivatives of nucleosides with alkenes in which carbon atoms at the double bond are not linked to heteroelements.

- b. Reactions of halogeno derivatives of nucleosides with vinyl acetate.

- c. Reactions of halogeno derivatives or triflates of nucleosides with organoelement derivatives of alkenes [Group III (B, Al) or Group IV elements (Si, Sn, Zr)].

- d. Photochemical introduction of alkenyl groups into nucleosides.

The reactions related to the first three groups are catalysed by palladium compounds.

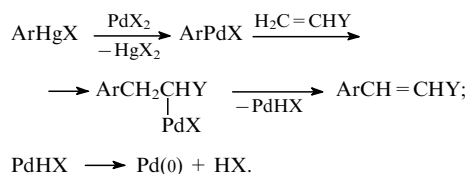
3. *Coupling of non-substituted nucleosides with alkenes.* These include addition of nucleosides to activated alkenes, cross-coupling with triflate derivatives of alkenes and addition to alkenyl organomagnesium compounds. The first two reactions are catalysed by palladium complexes.

II. Alkenylation of organoelement nucleoside derivatives and their analogues

1. Coupling of organomercury derivatives of pyrimidine nucleosides and their analogues with alkenes

Coupling of 5-mercury derivatives of pyrimidine nucleosides with alkenes was the first reaction¹⁴ used in the synthesis of alkenylated nucleosides by direct formation of the C—C bond between the substituent being introduced and the heterocycle. It is also the first reaction which has a versatile preparative significance for C-alkylation of nucleosides in general, since the alkenyl group being introduced can be further (or directly, in the course of the reaction) subjected to easy modification. Reduction of vinyl groups with hydrogen over a platinum catalyst and decarboxylation of carboxyvinyl groups are typical examples of such modifications. The regio- and stereoselectivity of addition of certain substituents is an important feature of the alkenylation reaction.

As a matter of fact, this coupling represents the Heck reaction,^{15, 16} although its application to nucleosides has a number of specific features (see below). Its mechanism^{13, 15, 16} can be presented as a sequence of transmetallation reactions (Hg is replaced by Pd), insertion of an alkene and reductive elimination, and for the sake of simplicity can be represented as follows:



This reaction occurs easily for all types of nucleic acid components (nucleic bases, nucleosides and nucleotides). 5-Chloromercurio-, 5-acetoxymmercurio- and 5-trifluoroacetoxymmercurio-pyrimidine nucleosides are normally used.^{17, 18} Depending on the solubility of the starting compounds and reaction products, the reaction is carried out in methanol, dimethylformamide, acetonitrile or aqueous-organic media. Li_2PdCl_4 , Na_2PdCl_4 , K_2PdCl_4 and $\text{Li}_2\text{Pd}(\text{OAc})_2\text{Cl}_2$ are most commonly used as catalysts (Table 1).

In the alkenylation of 5-mercurionucleoside derivatives, Pd(II) is irreversibly reduced to Pd(0); therefore, the catalyst has to be used in at least equimolar amounts. To avoid this, an agent which oxidises Pd(0) to Pd(II) (as a rule, CuCl_2) is added to the reaction mixture. This allows the use of palladium in catalytic quantities (~ 0.2 mol. %), but the yield of the target product is slightly lower (Table 1, entries 12, 27 and 30). The mechanism of such coupling has been described in the original study by Heck¹⁵ as well as in the review¹¹ devoted to the behaviour of nucleosides and their analogues in this reaction. As can be seen from Table 1 (entries 1 and 5), significant differences from the classical Heck reaction are observed when the reaction is carried out in methanol: with ethylene and propylene devoid of M-effects, methoxyalkyl nucleoside derivatives are formed predominantly. Moreover, the reaction with propylene gives all types of alkenyl isomers, *viz.*, *cis*-, *trans*- and isopropenyl isomers. These regularities are observed with all simple vinyl compounds of the type $\text{H}_2\text{C}=\text{CHR}$ ($\text{R} = \text{Me, OMe, OAc, Hal}$). In principle, the formation of α -methoxyalkyl derivatives in the reaction of nucleoside 5-mercury derivatives with ethylene and certain alkenes that react regioselectively (Table 1, entries 2–4, 8 and 9) is not important, since methoxy derivatives, as alkenes, are reduced with hydrogen over 10% Pd/C to the corresponding saturated derivatives in overall yields of about 60%–80%. The double bond C(5)=C(6) in the pyrimidine ring is unaffected by this process. Much better results are achieved in reactions with activated alkenes, particularly with styrene derivatives, esters, amides and nitriles of acrylic, metacrylic and crotonic acids. Here, the reaction usually proceeds regio- and stereoselectively (the β -carbon atom of the double bond is linked to the heterocycle, exclusively *E*-isomers are formed). The product yields vary from 10% to 80%, being, on the average, $\sim 40\%$ – 60% .

A typical synthetic procedure consists in the following. An appropriate mercurionucleoside (mercury derivatives of nucleosides are insoluble in any known solvent, although a recent report³⁸ describes the synthesis of water-soluble mercury derivatives) is suspended in an excess of an alkene (1.2–11.0 moles per mole of nucleoside) or the substrate is stirred under the pressure of the corresponding gaseous alkene in the presence of 1 equiv. of a palladium catalyst or of 0.1–0.2 equiv. of a Pd catalyst and 2–4 equiv. of CuCl_2 at room temperature or with heating to 50–60 °C. After termination of the reaction, Pd is separated by filtration and mercury salts are precipitated by passing hydrogen sulfide through the reaction mixture or by reduction with sodium borohydride. The latter is used, in particular, for subsequent hydrogenation over Pd/C. In some cases, after removal of

Table 1. Alkenylation of 5-mercuriopyrimidine nucleosides.

Entry	Substrate ^a	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
1		H ₂ C=CH ₂	1) 0.1 M Na ₂ PdCl ₄ , MeOH, 9 h; 2) H ₂ S		6 (without isolation) + 39	19
2	1	H ₂ C=CH ₂	1) 0.1 M Li ₂ PdCl ₄ , MeOH, 3 h; 2) NaBH ₄ , ice; 3) H ₂ , 10% Pd/C, MeOH, 16 h		86	19
3	1	H ₂ C=CH ₂	1) 0.1 M Li ₂ PdCl ₄ , CuCl ₂ , MeOH, 3 h; 2) H ₂ S; 3) H ₂ , 10% Pd/C, MeOH, 18 h	3	48	19
4		H ₂ C=CH ₂	1) 0.1 M Li ₂ PdCl ₄ , MeOH, 12 h; 2) NaBH ₄ , 0 °C; 3) H ₂ , 10% Pd/C, MeOH–H ₂ O, 24 h		57	19
5	4	MeCH=CH ₂	1) 0.1 M Li ₂ PdCl ₄ , MeOH, 2 h; 2) H ₂ S		11 ^b (6 : 9 : 10 = 2.3:1.4:1.0; the yield of products 7 and 8 is low)	19
6	1	PhCH=CH ₂	1) 0.1 M Li ₂ PdCl ₄ , MeOH, Ar, 3 h; 2) NaBH ₄ –EtOH		39	19
7	1	H ₂ C=CHCO ₂ Me	1) 0.1 M Li ₂ PdCl ₄ , MeOH, Ar, 10 h; 2) H ₂ S		48	19
8	1	H ₂ C=CHCH ₂ – –CH(OH)Me	1) 0.1 M Li ₂ PdCl ₄ , MeOH, Ar, 2 h; 2) NaBH ₄ –Pr ⁱ OH; 3) H ₂ , MeOH, 14 h		55 + 12	19
9	4	H ₂ C=CHCH ₂ – –CH(OH)CH ₂ OBn	1) 0.1 M Li ₂ PdCl ₄ , MeOH, 3 h; 2) NaBH ₄ –MeOH; 3) H ₂ , 10% Pd/C, MeOH, 20 h		57	19

Table 1 (continued).

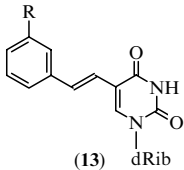
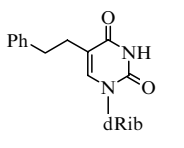
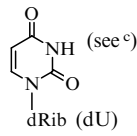
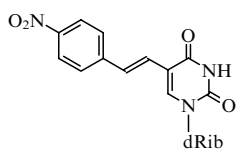
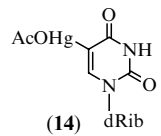
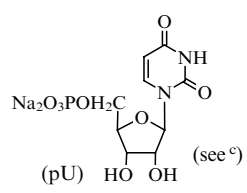
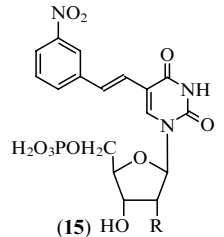
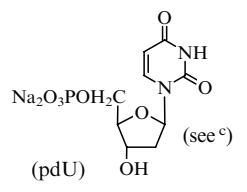
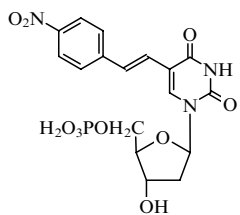
Entry	Substrate ^a	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
10	4	PhCH=CH ₂	1) 0.1 M Li ₂ PdCl ₄ , MeOH, 12 h; 2) H ₂ S	 (13) R		
				13 , R = H	57	18
11	4	<i>m</i> -O ₂ NC ₆ H ₄ CH=CH ₂	the same but <i>t</i> = 18 h	13 , R = NO ₂	50	18
12	4	<i>m</i> -O ₂ NC ₆ H ₄ CH=CH ₂	the same but with the addition of CuCl ₂	13 , R = NO ₂	47	18
13	4	PhCH=CH ₂	1) 0.1 M Li ₂ PdCl ₄ , MeOH, 18 h; 2) NaBH ₄ -MeOH; 3) H ₂ , 10% Pd/C, MeOH, 20 h	 Ph	58	18
14	 (see ^c)	PhCH=CH ₂	1) 0.1 M Li ₂ PdCl ₄ , MeOH, 12 h; 2) H ₂ S	13 , R = H	45	18
15	dU (see ^c)	<i>m</i> -O ₂ NC ₆ H ₄ CH=CH ₂	the same	13 , R = NO ₂	62	18
16	dU (see ^d)	<i>m</i> -O ₂ NC ₆ H ₄ CH=CH ₂	1) 0.1 M Li ₂ PdCl ₄ , MeOH, -30 °C, 18 h; 2) H ₂ S	13 , R = NO ₂	52	18
17	dU (see ^c)	<i>p</i> -O ₂ NC ₆ H ₄ CH=CH ₂	the same but at 60 °C	 O ₂ N	11	18
18	 (14) AcOHg	<i>m</i> -O ₂ NC ₆ H ₄ CH=CH ₂	1) 0.1 M Li ₂ PdCl ₄ , MeOH, THF, 6 h; 2) H ₂ S	13 , R = NO ₂	80	18
19	14	<i>m</i> -H ₂ NC ₆ H ₄ CH=CH ₂	the same but under reflux, 9 h	13 , R = NH ₂	30	18
20	 (pU) Na ₂ O ₃ POH ₂ C	<i>m</i> -O ₂ NC ₆ H ₄ CH=CH ₂	1) 0.14 M Li ₂ PdCl ₄ , MeOH-H ₂ O, 50 °C, 0.5 h; 2) H ₂ S	 (15) R		
				15 , R = OH	82	18
21	 (pdU) Na ₂ O ₃ POH ₂ C	<i>m</i> -O ₂ NC ₆ H ₄ CH=CH ₂	the same	15 , R = H	66	18
22	pdU	<i>p</i> -O ₂ NC ₆ H ₄ CH=CH ₂	1) 0.1 M Li ₂ PdCl ₄ , MeOH-Et ₂ O-H ₂ O, 60 °C, 6 h; 2) H ₂ S	 O ₂ N	59	18

Table 1 (continued).

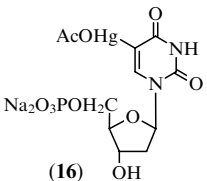
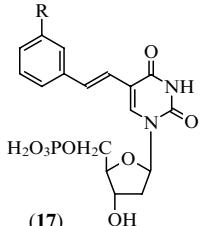
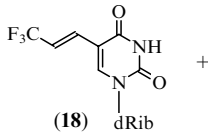
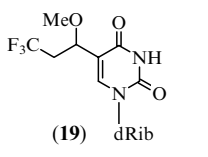
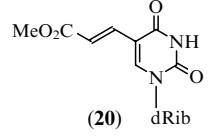
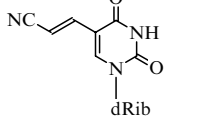
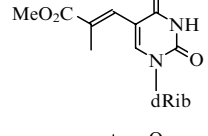
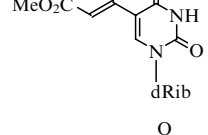
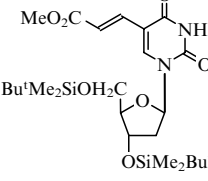
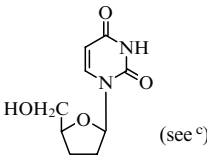
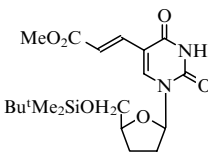
Entry	Substrate ^a	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
23	 (16)	PhCH=CH ₂	1) 0.1 M Li ₂ PdCl ₄ , MeOH–THF–H ₂ O, 50 °C, 5 h; 2) H ₂ S	 (17) 17, R = H	50	18
24	16	<i>m</i> -N ₃ C ₆ H ₄ CH=CH ₂	1) 0.274 M Li ₂ PdCl ₄ , MeOH–H ₂ O, 50 °C, 2.5 h 2) H ₂ S	17, R = N ₃	25	18
25	4	F ₃ CCH=CH ₂	1) Li ₂ PdCl ₄ , MeOH, 20 °C, 3.5 h; 2) H ₂ S	 (18) +  (19)	17 + 36	20
26	4	F ₃ CCH=CH ₂	1) 0.1 M Li ₂ PdCl ₄ , MeOH, 20 °C, 6.5 h; 2) H ₂ S	18 + 19	26 + 59	21
27	4	H ₂ C=CHCO ₂ Me	1) 0.1 M Li ₂ PdCl ₄ , CuCl ₂ , MeOH, 20 °C, 3 h; 2) H ₂ S	 (20)	60	22
28	4	H ₂ C=CHCN	1) 0.1 M Li ₂ PdCl ₄ , MeOH, 20 °C, 12 h; 2) H ₂ S		16	22
29	4	H ₂ C=C(Me)CO ₂ Me	1) 0.1 M Li ₂ PdCl ₄ , MeOH, 20 °C, 16 h; 2) H ₂ S		63	22
30	4	MeCH=CHCO ₂ Me	1) 0.1 M Li ₂ PdCl ₄ , CuCl ₂ , MeOH, 20 °C, 96 h; 2) H ₂ S		21	22
31	dU (see ^c)	H ₂ C=CHCO ₂ Me	1) 0.1 M Li ₂ PdCl ₄ , Et ₃ N, MeOH, 20 °C, 12–16 h; 2) H ₂ S 3) Bu ^t Me ₂ SiCl, imidazole, DMF, 20 °C, 18 h		76	23
32	 (see ^c)	H ₂ C=CHCO ₂ Me	the same		65	23

Table 1 (continued).

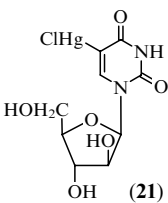
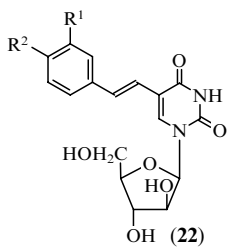
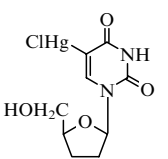
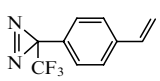
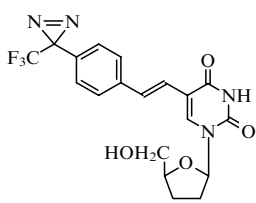
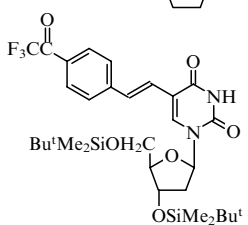
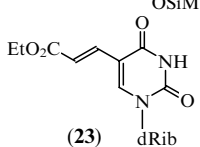
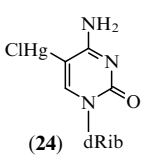
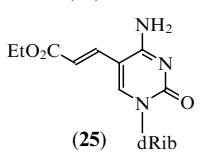
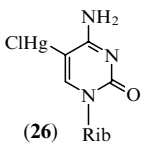
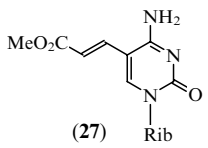
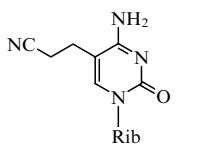
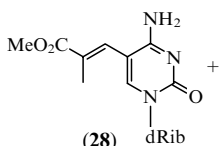
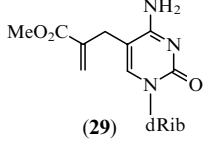
Entry	Substrate ^a	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
33	 (21)	PhCH=CH ₂	1) 0.1 M Li ₂ PdCl ₄ , MeOH, 24 h; 2) H ₂ S	 (22)		
				22 , R ¹ = R ² = H	49	24
34	21	<i>p</i> -O ₂ NC ₆ H ₄ CH=CH ₂	the same	22 , R ¹ = H, R ² = NO ₂	19	24
35	21	<i>m</i> -O ₂ NC ₆ H ₄ CH=CH ₂	"	22 , R ¹ = NO ₂ , R ² = H	22	24
36	 (21)		0.1 M Li ₂ PdCl ₄ , MeOH, 20 °C, 5 h		10	8
37	4	<i>p</i> -CF ₃ COC ₆ H ₄ CH=CH ₂	1) 0.1 M Li ₂ PdCl ₄ , MeOH, 20 °C, 2 h; 2) Bu ^t Me ₂ SiCl, imidazole, DMF, 20 °C, 4 h		21	25
38	4	H ₂ C=CHCO ₂ Et	Li ₂ PdCl ₄	 (23)	—	26
39	 (24)	H ₂ C=CHCO ₂ Et	the same	 (25)	—	26
40	 (26)	H ₂ C=CHCO ₂ Me	1) 0.1 M Li ₂ PdCl ₄ , MeOH, 20 °C, 8 h; 2) H ₂ S	 (27)	42	27
41	26	H ₂ C=CHCN	1) 0.1 M Li ₂ PdCl ₄ , DMF, 20 °C, 6 days; 2) NaBH ₄ –H ₂ O		32	27
42	24	H ₂ C=C(Me)CO ₂ Me	the same	 (28) +  (29)	12 ^b (28 : 29 = 1:2)	27

Table 1 (continued).

Entry	Substrate ^a	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
43	26	$\text{H}_2\text{C}=\text{CHCONHR}$ ($\text{R} = (\text{CH}_2)_5\text{CO}_2\text{Me}$)	1) 0.1 M Li_2PdCl_4 , MeOH, 24 h; 2) H_2S		34	28
44		$\text{H}_2\text{C}=\text{CH}_2$	1) 0.095 M Li_2PdCl_4 , DMF, 20 °C, 7 h; 2) H_2S , MeOH, 0 °C		57	29
45	30	$\text{H}_2\text{C}=\text{CHCO}_2\text{Et}$	1) 0.105 M Li_2PdCl_4 , MeOH, 20 °C, 7 h; 2) H_2S		23	29
46			1) $\text{Pd}(\text{OAc})_2$, LiCl, MeCN, 25 °C, 12 h; 2) H_2S		66 + 24	30, 31
47	31		the same		20 + 32	31
48	31		"		20 + 73	31
49		$\text{H}_2\text{C}=\text{CHCO}_2\text{Et}$	1) 0.1 M Li_2PdCl_4 , MeOH, N_2 , 20 h; 2) H_2S		57	32
50		$\text{ClCH}_2\text{CH}=\text{CH}_2$	1) 0.1 M Li_2PdCl_4 , MeOH, 3 h; 2) H_2S ; 3) EtOH, $\text{RhCl}(\text{PPh}_3)_3$, N_2 , 16–36 h		19	33

enes in $\text{H}_2\text{O}-\text{MeOH}-\text{Et}_2\text{O}$ are comparable (59% and 66%, respectively) (Table 1, entries 21 and 22).

Reactions of nucleotides with alkenes in aqueous-organic media give rise to several valuable compounds. Thus the reaction of 5-acetoxymercuro-2'-deoxyuridine 5'-phosphate with 3-azidostyrene gave a photoactivated uridine derivative which inhibits thymidylate synthase (Table 1, entry 24). Coupling of 5-chloromercuriuridine 5'-triphosphate with allylamine (Table 1, entries 52 and 53) results in the formation of a linker useful for labelling studies.

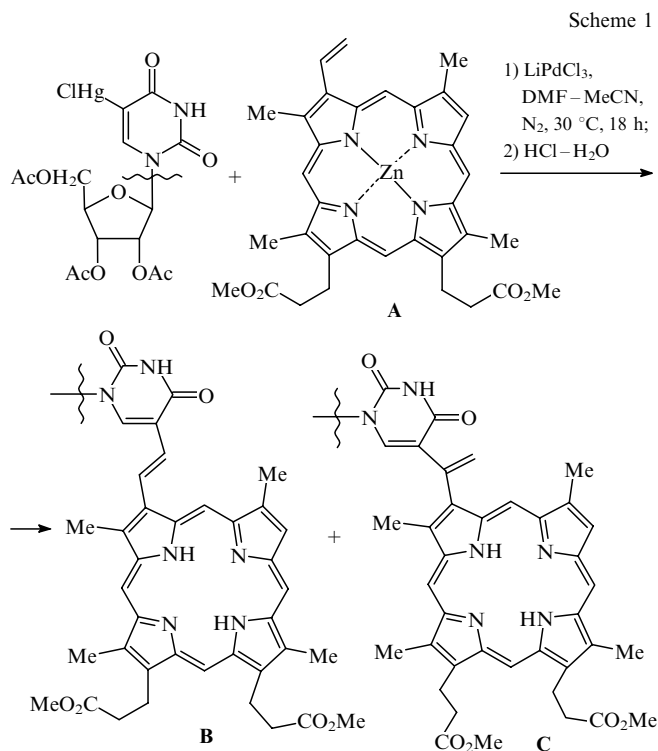
Organomercury derivatives of nucleic bases can also react with alkenes. For example, two 5-substituted 1,3-dimethyluracils are formed from 5-acetoxymercuro-1,3-dimethyluracil and 3,4-dihydro-2*H*-pyran (Table 1, entry 46). An attempt has been made to use this reaction in the synthesis of C-nucleosides;³¹ however, in this case cyclic derivatives are predominantly formed.

In addition to the above-mentioned compounds, allyl chlorides were introduced into the reaction with 5-mercuro-nucleosides and their derivatives (Table 1, entries 50 and 51).^{33,39} The allylation of mercury derivatives of aromatic compounds in the presence of a Pd catalyst was described for the first time by Heck.⁴⁰ Strictly speaking, this reaction is irrelevant to the material described in this Section, but 5-allylated nucleosides obtained by this method are easily isomerised into the corresponding 5-(alk-1-enyl)pyrimidine nucleosides to give exclusively *trans*-isomers in the presence of rhodium complexes.

It should be remembered that direct coupling of non-activated alkenes with mercury derivatives of nucleosides normally gives complex mixtures of products.

This method (*i.e.*, coupling with alkenes) was used to obtain a series of substituted nucleosides that were further used as antiviral agents. An example is 5-(*E*)-bromovinyluridine and its carbocyclic analogues, 5-(*E*)-(prop-1-enyl)uridine¹⁹ and 5-(*E*)-(3,3,3-trifluoroprop-1-enyl)uridine.²¹

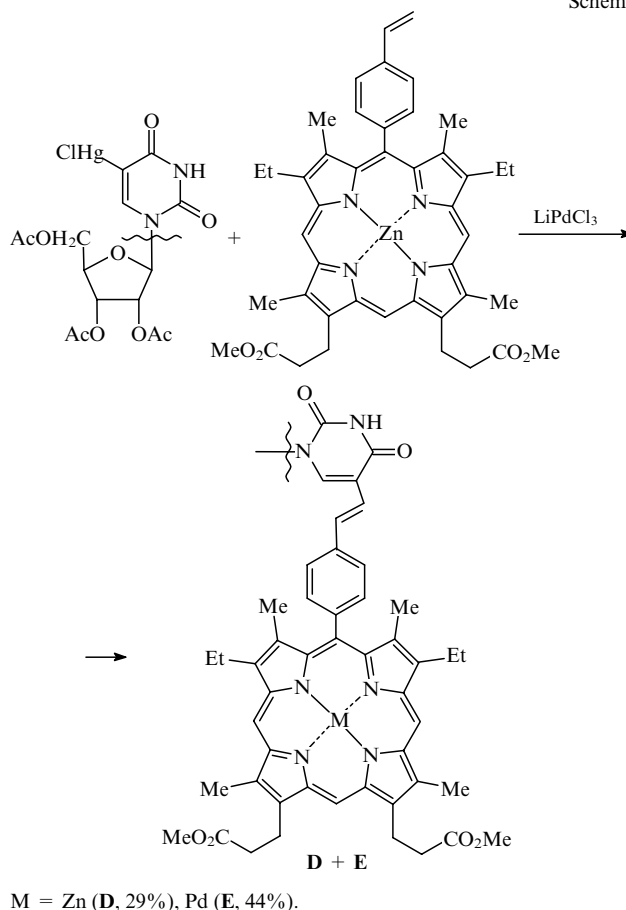
Of definite interest are the attempts to use nucleoside derivatives containing a porphyrin fragment as antitumour agents.^{33,39} A covalent binding of vinylporphyrins at position 5 of uridine has been carried out recently.⁵ Thus porphyrin **A** (Scheme 1) was



introduced into the reaction with an excess (3.3 equiv.) of acetylated 5-chloromercuriuridine in the presence of 1 equiv. (with respect to uridine) of a Pd catalyst. This reaction gave a mixture of *trans*- (**B**, 16.5%) and *gem*-isomers (**C**, 19.6%) irrespective of the fact that the vinyl group of porphyrin was conjugated with an aromatic system.

However, in the presence of a styryl group in the porphyrin fragment, this coupling occurs regio- and stereoselectively. It is noteworthy that this reaction is accompanied by partial substitution of Pd for Zn in the porphyrin fragment of the reaction product (Scheme 2).⁵

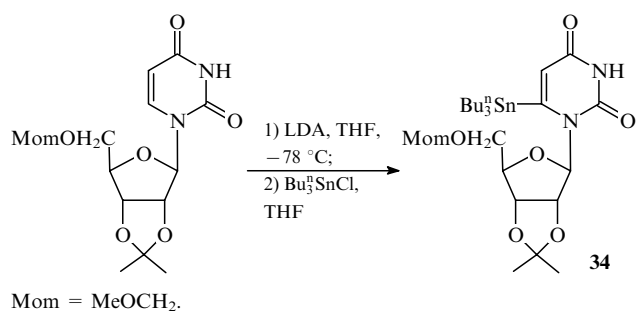
Scheme 2



Yet another rapidly developing field of the application of alkenylated nucleosides is their use for probing biological molecules in structural and functional studies. To this end, labels are introduced into nucleosides that are directly linked to the pyrimidine ring (Table 1, entries 36 and 37) or separated from it by a linker (Table 1, entry 54). Aminoallyl, aminoalkylacrylamide and acrylate groups at position 5 are the linkers of choice.

2. Cross-coupling of organotin pyrimidine derivatives of nucleosides with alkenyl halides

One of approaches to the synthesis of 6-alkenylated pyrimidine derivatives of nucleosides is based on the reaction of 6-tributylstannyl derivatives of nucleosides **34** with alkenyl halides (the Stille reaction).⁴¹ An alternative approach consists in the reaction of 6-iodo-substituted pyrimidine nucleosides and their analogues with organoelement derivatives of alkenes (see below). Organotin derivatives of pyrimidine nucleosides are prepared from the corresponding lithium derivatives (6-iodopyrimidine nucleosides and their analogues are synthesised in a similar way) according to the following scheme:



It should be noted that despite the data⁴² on the synthesis of the 5-trimethylstannyl derivative of a pyrimidine nucleoside and its arylation, we are not aware of its application for the incorporation of alkenyl groups. The mechanism of this conversion,¹³ similar to the mechanisms of other cross-coupling reactions of organometallic compounds with alkyl halides in the presence of transition metal complexes, represents a sequence of reactions of oxidative addition of a transition metal with a low oxidation number [most often, Pd(0) or Ni(0); complexes of low-valent metals can be formed *in situ*] to aryl or vinyl halides with subsequent transmetalation (substitution of R' for the halogen atom) and reductive elimination.



Alkenylation of 6-tributylstannyl nucleosides has made it possible to obtain the corresponding alkenyl derivatives the yields of which vary from moderate to high (Table 2).⁴³ Depending on the reagent's structure, one can synthesise *cis*-, *trans*- and *gem*-isomers. As can be seen from the reaction scheme, transition metal complexes are required exclusively in catalytic amounts in

Table 2. Alkenylation of the organotin nucleoside derivative **34**.⁴³

Entry	Reagent	<i>t</i> /min	Product	Yield (%)
1	H ₂ C=CHBr	100		80
2	H ₂ C=CBrCO ₂ Et	75	R = CO ₂ Et	56
3	Br-CH=CH-CO ₂ Me	10	 (35) + (36)	81 ^a (35:36 = 3:1)
4	Br-CH=CH-C(OH)(Me) ₂	60		70

Note: The reaction was carried out in DMF at 80 °C in the presence of 0.1 equiv. of Pd(PPh₃)₄ as a catalyst and with 0.2 equiv. of CuI;

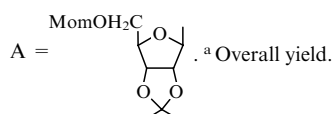


Table 3. Alkenylation of organolithium derivatives of nucleosides and their analogues.⁴⁶

Entry	Substrate ^a	Reagent	Solvent	<i>t</i> /h	Product	Yield (%)
1	 (37)	Cl ₂ C=CF ₂	Et ₂ O	1.5		55
2	37	CF ₃ CF=CF ₂	Et ₂ O	1.0	 +	42 ^b
3	 (38) dRib (see °)	ClFC=CF ₂	n-C ₆ H ₁₄	1.0	 +	6 ^b
4	38 (see °)	CF ₃ CF=CF ₂	n-C ₆ H ₁₄	1.0	 +	24 ^b
5	38 (see °)	CF ₃ CF=CF ₂	n-C ₆ H ₁₄	1.0	 <i>n</i> = 3 <i>n</i> = 4	7 9

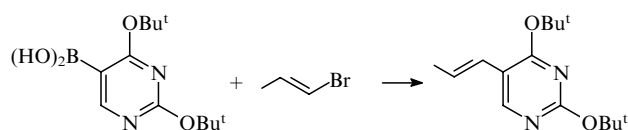
^a The corresponding organolithium derivatives are prepared by treatment of the substrate with BuⁿLi. ^b Overall yield. ^c Prior to coupling, the hydroxy groups of the substrate were protected by the action of (Me₃Si)₂NH–Me₃SiCl–Py.

this case. It should be noted that in some syntheses the presence of copper(I) iodide permits one to increase the product yields more than twofold. Presumably, the role of CuI is connected with the formation of an organocopper intermediate in the transmetallation of Pd for Sn.

3. Cross-coupling of organoboron derivatives of nucleoside analogues with alkenyl halides

Only one example of such a coupling is known (Scheme 3). Transmetallation of organoboron compounds was extensively studied by Suzuki⁴⁴ who was the first to establish that this reaction requires the presence of a base. Organoboron compounds are prepared from the corresponding organolithium derivatives. In the above example, the target product is formed in 72% yield (Scheme 3).⁴⁵

Scheme 3



Reagents and conditions: Pd(PPh₃)₄, 1 M NaHCO₃, MeO(CH₂)₂OMe, N₂, 4 h.

It should be remembered that this type of product cannot be obtained by coupling of organomercury derivatives with alkenes.

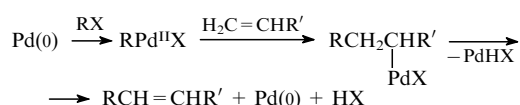
4. Reactions of organolithium derivatives of pyrimidine nucleosides and their analogues with fluoroalkenes

Alkenyl derivatives of pyrimidine bases and nucleosides can also be obtained by nucleophilic substitution of polyfluoroalkenes with the corresponding organolithium derivatives. The reaction of 5-bromo-2,4-dimethoxypyrimidine (37) and 5-iodo-3',5'-di-*O*-trimethylsilyl-2'-deoxyuridine with butyllithium was carried out in an atmosphere of nitrogen at -70 °C. After addition of an excess (5 equiv.) of the fluorinated alkene, the reaction mixture was kept at a temperature of solid carbon dioxide for 4 days (Table 3). The product yields were small, as a rule, but higher with nucleic bases (42%–55%) than with nucleosides (6%–24%). In addition, the reaction is not stereoselective (*Z*- and *E*-isomers are formed). Perfluorocycloalkenes could be added at position 5 of deoxyuridine, but the yields of the products were as low as a few per cent.⁴⁶

III. Alkenylation of C-halogeno derivatives and triflates of nucleosides and their analogues

1. The Heck-type coupling of idonucleosides with alkenes

Yet another example of the Heck-type coupling⁴⁷ is the reaction of idonucleosides and their analogues with alkenes in the presence of palladium compounds, which has found wide use in nucleoside chemistry. Its application in organic synthesis has been described in several reviews.^{48,49} This reaction was discovered independently by Heck⁴⁷ and a group of Japanese investigators.⁵⁰ Its mechanism consists in oxidative addition of vinyl or aryl halides to Pd(0) with subsequent insertion of an alkene at the aryl(vinyl)–palladium bond and elimination of PdHX with regeneration of Pd(0).



The reaction of alkenes with both nucleosides and nucleic bases has been described. Depending on the position of the iodine in the pyrimidine ring, one can obtain 5- and 6-substituted derivatives. Most often, activated alkenes of the acrylic ester type are introduced into the reaction; arylvinyl ketones and

terminal aliphatic alkenes are also used. Of special interest is the synthesis of 5- and 6-vinyl derivatives of pyrimidine nucleosides from the corresponding idonucleosides and 1-arylpropynols in the presence of CuI as the co-catalyst and the synthesis of 5-vinyl derivatives of nucleosides and nucleic bases from the corresponding iodo derivatives and vinyl acetate.

The coupling is carried out in dioxane, DMF, acetonitrile or aqueous-organic mixtures. Pd(OAc)₂ in the presence of Et₃N and PPh₃ or Pd(PPh₃)₂Cl₂/Et₃N are used as catalysts. In the latter case, small amounts of CuI are added. In contrast with the reaction of mercurionucleosides with alkenes, this type of the Heck reaction requires catalytic (but not equimolar) amounts of palladium (most often, as small as 0.05–0.15 equiv.). Depending on the reaction conditions and the nature of nucleosides and reagents used, the yields of the products vary from 8% to 90%. In general, the yields are higher than those in analogous reactions of mercurionucleosides with alkenes. The literature data concerning the synthesis of alkenylated nucleosides by the Heck reaction are summarised in Table 4.

These examples demonstrate that pretreatment of the catalyst significantly increases the yield of the product (Table 4, entries 1 and 2). When contemplating the influence of reaction conditions, one cannot but note the recently established increase in the product yield in the coupling of 5-iodo-2,4-dimethoxypyrimidine with methyl acrylate in water (Table 4, entry 29) rather than in organic solvents (the heterogenous Heck reaction⁶⁴). It is interesting to note that under these conditions the coupling occurs at room temperature, while the classical Heck reaction requires heating to 70–90 °C, which slightly restricts its application. An increase in temperature to 50 °C in the heterogenous reaction results in deiodination of the original pyrimidine and decreases the yield from 90% to 79%. It should be noted that deiodination of nucleosides and their analogues is also the main side reaction in other types of the Heck coupling reaction.⁶⁵ Presumably, milder conditions of the heterogenous reaction favour the inhibition of side reactions and increase the yields of the target products.

High yields of the target compounds in this particular reaction are achieved with alkyl acrylates and arylvinyl ketones as alkenylating reagents. In contrast, the use of terminal alkenes with alkyl substituents results in low yields (Table 4, entries 5–7). Low yields are also characteristic of coupling of vinyl acetate with uridine (the yield of 5-vinyluridine is 37%) and cytidine (8%), although vinyl acetate reacts readily with derivatives of nucleic bases under different conditions in ~60% yields (Table 4, entries 27 and 28). Alkynylation of the corresponding 6-iodo-substituted uracils with 1-arylpropynols occurs through intermediate formation of allenic alcohols, which are further isomerised into aroylalkenyl derivatives of nucleic bases (Table 4, entries 20–26).⁶⁰ Obviously, a mixture of *cis*- and *trans*-isomers is formed in this case, although this aspect has not been specially discussed.⁶⁰

The first alkynylation of aryl iodides was described simultaneously by Heck⁶⁶ and Cassar.⁶⁷ The Sonogashira reaction⁶⁸ (addition of CuI) in the Robins and Barr⁶⁹ modification (Et₃N as the base) is used in the synthesis of the corresponding nucleosides. A detailed description of this reaction is given in the review.⁴

Of note is a recently published paper⁷⁰ devoted to the synthesis of a porphyrin derivative of deoxyuridine (reaction of acrylamidoporphyrin with 5-iodo-2'-deoxyuridine, 5-IdU) (Scheme 4) used to investigate the reactions of porphyrins with the DNA double helix.

Coupling of a 5-iodo-substituted nucleoside or its analogue with methyl or ethyl acrylates followed by decarboxylation–bromination of the resulting product with *N*-bromosuccinimide is used in the synthesis of antiviral analogues of nucleosides containing the *E*-bromovinyl group at position 5 of the pyrimidine ring more often (due to higher yields) than other alkenylation reactions.

Table 4. Heck alkenylation of iodo derivatives of nucleosides and their analogues.

Entry	Substrate	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
1		$\text{H}_2\text{C}=\text{CHCO}_2\text{Me}$	$\text{Pd}(\text{OAc})_2$, PPh_3 , Et_3N , Δ , 12 h	12	53	19
2	39	$\text{H}_2\text{C}=\text{CHCO}_2\text{Me}$	$\text{Pd}(\text{OAc})_2$, PPh_3 , Et_3N –dioxane (1 : 8), 70 °C, 1 h	12	86 ^a	51
3	39	$\text{H}_2\text{C}=\text{CHCO}_2\text{Et}$	$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, Et_3N , MeCN, 80 °C, 24 h		79	52
4	38	$\text{H}_2\text{C}=\text{CHCO}_2\text{Me}$	$\text{Pd}(\text{OAc})_2$, PPh_3 , Et_3N –dioxane, Δ , 40 min	20	70 ^a	53
5	38	$\text{Pr}^n\text{CH}=\text{CH}_2$	$\text{Pd}(\text{OAc})_2$, Et_3N , 100 °C, 12 h		25	22
6	38	$\text{Bu}^n\text{CH}=\text{CH}_2$	the same but $t = 2$ h	40 , $\text{R} = \text{Bu}^n$	15	22
7	38	$\text{Bu}^t\text{CH}=\text{CH}_2$	the same but $t = 48$ h	40 , $\text{R} = \text{Bu}^t$	16	22
8		$\text{H}_2\text{C}=\text{CHCO}_2\text{Et}$	$\text{Pd}(\text{OAc})_2$, PPh_3 , Et_3N , DMF, Ar, 85 °C, 24 h		37	29
9		$\text{H}_2\text{C}=\text{CHCO}_2\text{Me}$	$\text{Pd}(\text{OAc})_2$, PPh_3 , Et_3N , dioxane, 85 °C, 3 h		80 ^a	54
10		$\text{H}_2\text{C}=\text{CHCO}_2\text{Me}$	the same		64	55
11		$\text{H}_2\text{C}=\text{CHCO}_2\text{Me}$	$\text{Pd}(\text{OAc})_2$, PPh_3 , Et_3N , dioxane, Ar, 70 °C, 2.5 h		66 ^a	56
12		$\text{H}_2\text{C}=\text{CHCO}_2\text{Me}$	the same but $t = 4$ h		75 ^a	56

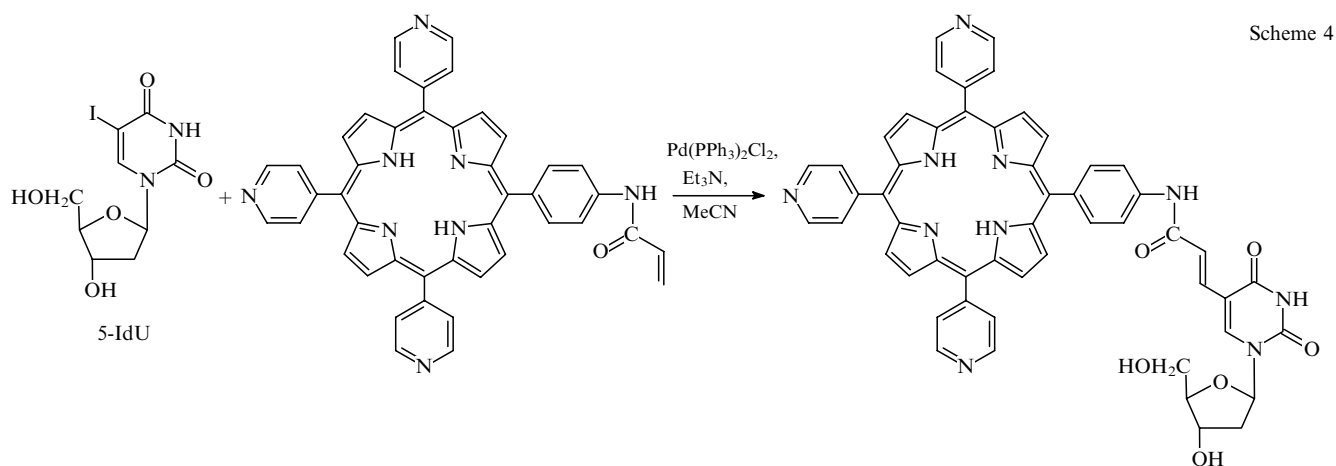
Table 4 (continued).

Entry	Substrate	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
13	41 (homochiral)	$\text{H}_2\text{C}=\text{CHCO}_2\text{Me}$	$\text{Pd}(\text{OAc})_2$, PPh_3 , Et_3N , dioxane, Ar, 70 °C, 4 h	42 (homochiral)	69 ^a	56
14		$\text{H}_2\text{C}=\text{CHCO}_2\text{Me}$	$\text{Pd}(\text{OAc})_2$, PPh_3 , Et_3N , DMF, Ar, 75 °C, 10 h		56 ^a	57
15		$\text{H}_2\text{C}=\text{CHCO}_2\text{H}$	$\text{Pd}(\text{OAc})_2$, PPh_3 , Et_3N , dioxane, 1 N NaOH, 95 °C, 3 h		49	58
16		$\text{PhC}(\text{O})\text{CH}=\text{CH}_2$	$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, CuI , Et_3N , DMF, N_2 , 80 °C, 24 h			
	(43)			(44)		
				44 , $\text{R}^1 = \text{R}^2 = \text{H}$	62	59
17	43	$p\text{-MeC}_6\text{H}_4\text{C}(\text{O})\text{CH}=\text{CH}_2$	the same	44 , $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$	78	59
18	43	$p\text{-MeOC}_6\text{H}_4\text{C}(\text{O})\text{CH}=\text{CH}_2$	"	44 , $\text{R}^1 = \text{OMe}$, $\text{R}^2 = \text{H}$	62	59
19	43	$m\text{-MeC}_6\text{H}_4\text{C}(\text{O})\text{CH}=\text{CH}_2$	"	44 , $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$	62	59
20		$\text{PhCH}(\text{OH})\text{C}\equiv\text{CH}$	$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, CuI , Et_3N , DMF, N_2 , 55 °C, 6 h			
	(45)			(46)		
				46 , $\text{R}^1 = \text{R}^2 = \text{H}$	39	60
21	45	$p\text{-MeC}_6\text{H}_4\text{CH}(\text{OH})\text{C}\equiv\text{CH}$	the same	46 , $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$	60	60
22	45	$p\text{-MeOC}_6\text{H}_4\text{CH}(\text{OH})\text{C}\equiv\text{CH}$	"	46 , $\text{R}^1 = \text{OMe}$, $\text{R}^2 = \text{H}$	57	60
23	45	$o\text{-MeOC}_6\text{H}_4\text{CH}(\text{OH})\text{C}\equiv\text{CH}$	"	46 , $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{OMe}$	35	60
24		$\text{PhCH}(\text{OH})\text{C}\equiv\text{CH}$	"			
	(47)			(48)		
				48 , $\text{R} = \text{H}$	76	60
25	47	$p\text{-MeC}_6\text{H}_4\text{CH}(\text{OH})\text{C}\equiv\text{CH}$	"	48 , $\text{R} = \text{Me}$	80	60
26	47	$p\text{-MeOC}_6\text{H}_4\text{CH}(\text{OH})\text{C}\equiv\text{CH}$	"	48 , $\text{R} = \text{OMe}$	58	60
27		$\text{H}_2\text{C}=\text{CHOAc}$	$\text{Pd}(\text{PPh}_3)_2(\text{OAc})_2$, Et_3N , 100 °C, 5 h		60	61
	(49)					
28		$\text{H}_2\text{C}=\text{CHOAc}$	the same		58	61
	(50)					

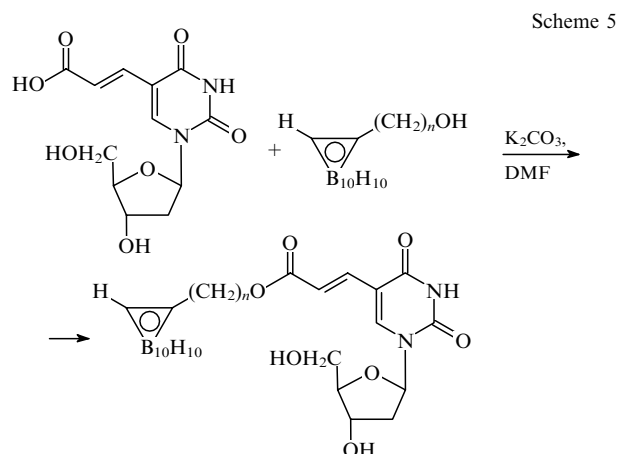
Table 4 (continued).

Entry	Substrate	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
29	50	$\text{H}_2\text{C}=\text{CHCO}_2\text{Me}$	$\text{Pd}(\text{OAc})_2$, PPh_3 , K_2CO_3 , Bu_4NHSO_4 , H_2O , 20 °C, 90 h		90	62
30	49		$\text{Pd}(\text{PPh}_3)_2(\text{OAc})_2$, Et_3N , 100 °C, 5 h		64	30
31	38	$\text{H}_2\text{C}=\text{CHOAc}$	$\text{Pd}(\text{OAc})_2$, PPh_3 , Et_3N , DMF, 70 °C, 5.5 h		37 ^a	63
32		$\text{H}_2\text{C}=\text{CHOAc}$	$\text{Pd}(\text{OAc})_2$, PPh_3 , Et_3N , DMF, 90 °C, 2 h		8 ^a	63

^a The catalyst was prepared beforehand by heating $\text{Pd}(\text{OAc})_2$, PPh_3 and Et_3N in dioxane or DMF up to the appearance of deep red colouring (10–20 min) at 70–75 °C.



The addition of carborane-containing fragments¹⁰ to 5-alkenyl nucleosides (Scheme 5) is an illustrative example of the application of alkenyl fragments as linkers; this reaction is used in cancer boron neutron capture therapy (for a review, see Ref. 71).



2. Cross-coupling of nucleoside halogeno derivatives and triflates with organoelement derivatives of alkenes

Recently, coupling of 5-halogeno derivatives and 5-triflates of nucleosides with organoelement derivatives of alkenes has acquired growing popularity for the synthesis of the corresponding 5-alkenyl derivatives of nucleosides.^{72–84} As mentioned above, in this case alkene derivatives with Group III (boron and aluminium) and Group IV elements (silicon, tin, zirconium) of the Periodic system are used as the starting compounds. The literature data on alkenylation of 5-halogeno derivatives and 5-triflates of nucleosides are summarised in Table 5. The mechanisms of the corresponding reactions are considered in Section II.2 exemplified in the cross-coupling of organotin nucleoside derivatives with alkenyl halides.

An essential advantage of this method is the possibility of performing the reaction with non-activated alkenes to obtain the corresponding 5-alkenyl-substituted nucleosides (particularly, 5-vinyl-substituted ones) (Table 5, entries 3, 13, 18, 26, 29–31, 33 and 35) in good yields.

It should be remembered that of all 5-mercurionucleosides only the 5-mercuriuridine derivative reacts with ethylene in DMF under conditions of the Heck reaction (Table 1, entry 44); 5-vinyluridine undergoes polymerisation under these condi-

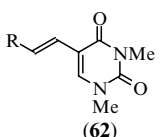
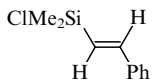
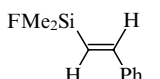
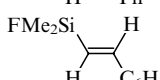
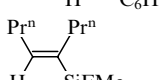
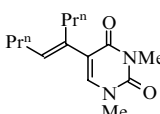
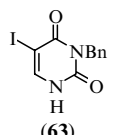
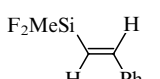
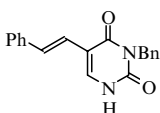
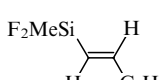
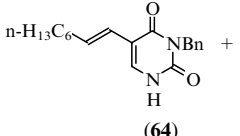
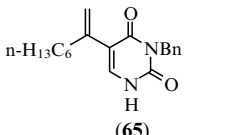
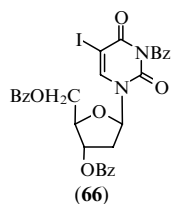
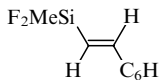
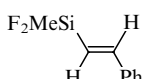
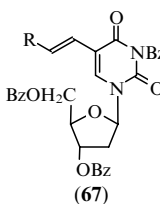
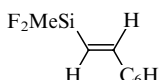
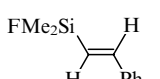
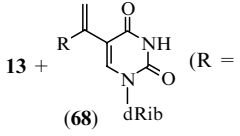
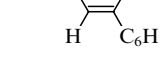
Table 5. Alkenylation of halogeno derivatives and triflates of nucleosides and their analogues with organoelement derivatives of alkenes.

Entry	Substrate	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
1	38		$\text{Pd}(m\text{-Ph}_2\text{PC}_6\text{H}_4\text{SO}_3\text{M})_3$ (M = Na, K), $\text{H}_2\text{O}-\text{MeOH}$, N_2 , 80°C , 3 h	13 , R = H	47	72
2		$\text{Me}_2\text{Al}-\text{CH}=\text{CH}-\text{C}_6\text{H}_{13-n}$	1) HMDS- $(\text{NH}_4)_2\text{SO}_4$; 2) PdCl_2 , PPh_3 , THF, Ar, 24 h; 3) $\text{NH}_4\text{Cl}-\text{H}_2\text{O}-\text{MeOH}$, 2.5–24 h	 (53)	27 ^a	73
3		$\text{R}-\text{CH}=\text{CH}-\text{ZrCp}_2$	1) $\text{Pd}(\text{PhCN})_2\text{Cl}_2$, 20°C , 15 h; 2) $\text{H}_2\text{O}-\text{MeOH}$	 (51)		
	(54)	R = H		51 , R = H	83	74, 75
4	54	R = Bu ⁿ	the same	51 , R = Bu ⁿ	95	74
5	54	R = C ₈ H _{17-n}	"	51 , R = C ₈ H _{17-n}	96	74
6	54	R = Ph	"	51 , R = Ph	85	74
7	54	R = <i>p</i> -MeOC ₆ H ₄	"	51 , R = <i>p</i> -MeOC ₆ H ₄	39	74
8	54	R = HC≡C(CH ₂) ₂	"	51 , R = HC≡C(CH ₂) ₂	80	74
9	54	R = MeCHCl(CH ₂) ₂	"	51 , R = MeCHCl(CH ₂) ₂	89	74
10	54	R = MeCHCN(CH ₂) ₂	"	51 , R = MeCHCN(CH ₂) ₂	76	74
11	54	R = EtO	"	51 , R = EtO	49	74
12	54	R = H ₂ C=CMe	"	51 , R = H ₂ C=CMe	30	74
13	43		$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, MeCN, N ₂	 (55)		
		R = H	20°C , 6 h	55 , R = H	86	76
14	43	R = SiMe ₃	60°C , 16 h	55 , R = SiMe ₃	82	76
15	43	R = Ph	50°C , 16 h	55 , R = Ph	81	76
16	43	R = CO ₂ Et	50°C , 20 h	55 , R = CO ₂ Et	57	76
17	43	R = CH ₂ OTHP	60°C , 16 h	55 , R = CH ₂ OTHP	82	76
18			$\text{Pd}(\text{PPh}_3)_4$, LiCl, dioxane, N ₂ , Δ	 (57)		
	(56)	R = H	4 h	57 , R = H	87	77, 78
19	56	R = SiMe ₃	4 h	57 , R = SiMe ₃	73	77, 78
20	56	R = Ph	8 h	57 , R = Ph	75	77, 78
21	56	R = Pr ⁱ Me ₂ CSiMe ₂ OCH ₂	5 h	57 , R = Pr ⁱ Me ₂ CSiMe ₂ OCH ₂	92	77, 78
22	56	R = CO ₂ Et	1 h	57 , R = CO ₂ Et	92	77, 78
23	56		$\text{Pd}(\text{PPh}_3)_4$, LiCl, dioxane, N ₂ , Δ 15 h	 (57)	46	77, 78

Table 5 (continued).

Entry	Substrate	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
24	56		the same but $t = 5$ h		86	77, 78
25			$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, THF, Ar, 50 °C, 16 h		50	79
26			$\text{Pd}_2(\text{dba})_3$, TFurP, NMP, 20 °C, 16 h			
		R = H		59 , R = H	89	80
27	58	R = Ph	the same	59 , R = Ph	92	80
28	58		$\text{Pd}_2(\text{dba})_3$, TFurP, NMP, 16 h at 20 °C and 5 h at 50 °C		70	80
29		$\text{H}_2\text{C}=\text{CHSnBu}_3^n$	$\text{Pd}_2(\text{dba})_3$, TFurP, NMP, 20 °C, 72 h		76	80
30	60	$\text{H}_2\text{C}=\text{CHSnBu}_3^n$	$\text{Pd}_2(\text{dba})_3$, TFurP, THF, 50 °C, 40 h	61	98	80
31		$\text{H}_2\text{C}=\text{CHSnBu}_3^n$	$\text{Pd}_2(\text{dba})_3$, TFurP, NMP, 20 °C, 72 h		91	80
32	38		$\text{Pd}(\text{PPh}_3)_4$, DMF, Ar, 100 °C, 4 h		28	81
33		$(\text{H}_2\text{C}=\text{CH})_4\text{Sn}$	1) $\text{Pd}(\text{PPh}_3)_4$, HMPA, N_2 , 60 °C, 18 h; 2) MeONa – MeOH	51	80	82
34		$\text{H}_2\text{C}=\text{CHSnBu}_3^n$	$\text{Pd}(\text{PPh}_3)_4$, DMF, Ar, 90 °C, 1.5 h		95	83

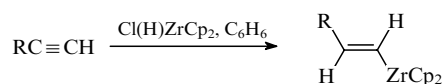
Table 5 (continued).

Entry	Substrate	Reagent	Conditions of synthesis	Product	Yield (%)	Ref.
35	49	$\text{H}_2\text{C}=\text{CHSiMe}_2\text{Cl}$	$[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}]_2$, Bu_4NF , THF, Ar, 60 °C, 14 h	 (62)		
36	49		the same	62 , R = H	82	84
37	49		"	62 , R = Ph	70	84
38	49		"	62 , R = $\text{C}_6\text{H}_{13}\text{-n}$	69	84
39	49		"		70	84
40	 (63)		"		63	84
41	63		"	 (64)	58	84
42	58		"	 (65)	53 ^a (64 : 65 = = 2:1)	84
43	 (66)		"	the reaction does not occur	—	84
44	66		"	 (67)		
45	38		"	67 , R = Ph	64	84
46	38		"	67 , R = $\text{C}_6\text{H}_{13}\text{-n}$	60	84
47	38		"	 (68)	79 ^a (13 : 68 = 5:1)	84
48	38		"	53 + 68 (R = $\text{C}_6\text{H}_{13}\text{-n}$)	74 ^a (53 : 68 = 2:1)	84

Note. The following abbreviations are used: TFurP, tris(2-furyl)phosphine; NMP, *N*-methylpyrrolidone; HMPA, hexamethylphosphorotriamide (hexametapoli); THP, tetrahydropyran; dba, dibenzylideneacetone. ^a Overall yield.

tions.²⁹ In the reaction of vinyl acetate with 5-iodouridine, the yield of the target product is as low as 37% (Table 4, entry 31), while the yield of vinylcytidine is even lower (8%) (Table 4, entry 32).⁶³

As can be seen from the results presented in Table 5, there are only a few examples of nucleoside alkenylation with organoboron and organoaluminium compounds and the yields of reaction products are low. Thus styrylboronic acid reacts with 5-iododeoxyuridine in the presence of $\text{Pd}(m\text{-Ph}_2\text{PC}_6\text{H}_4\text{SO}_3\text{M})_3$ ($\text{M} = \text{K}, \text{Na}$) even in aqueous-organic media, the yield of the target product is 47% (Table 5, entry 1).⁷² The possibility of carrying out the reaction in the presence of water is important, particularly for modification of oligonucleotides. In the coupling of organoaluminium alkene derivatives with nucleosides, the product yields are significantly lower (Table 5, entry 2).⁷³ However, the use of organozirconium alkene derivatives and $\text{Pd}(\text{PhCN})_2\text{Cl}_2$ as a catalyst makes it possible to obtain a broad spectrum of 5-alkenyl nucleoside derivatives, including vinyl (Table 5, entry 3), alkylvinyl (Table 5, entries 4 and 5), containing a second multiple bond in the chain introduced (Table 5, entries 8 and 12), styryl (Table 5, entries 6 and 7) and other derivatives. It is of note that the reaction (*e.g.*, with 5-iodo-2'-deoxy-3',5'-di-*O*-trimethylsilyluridine in THF) occurs even at room temperature.^{74,75} The zirconium-containing alkenyl reagent is synthesised from the corresponding alkyne and the Schwartz reagent.



Organotin compounds are most often used for C-alkenylation of nucleosides. Alkenyltributyltin is normally employed for this purpose; alkenyltrimethyltin (Table 5, entry 24) and tetraalkenyltin (Table 5, entry 33) are used less often. The amounts of the alkenylating reagent vary from 1 to 5 equiv. 5-Iodo-substituted nucleosides and nucleoside 5-triflates (as a rule, with protected

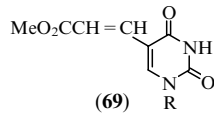
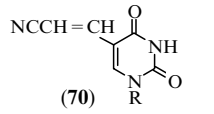
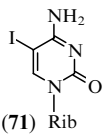
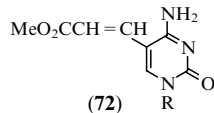
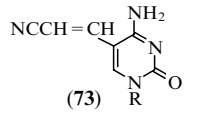
hydroxy groups) serve as substrates. The reactions are conducted in acetonitrile, dioxane, THF, *N*-methylpyrrolidone, hexametapoll and DMF. $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, $\text{Pd}(\text{PPh}_3)_4$, $\text{Pd}(\text{PPh}_3)_4$ in the presence of LiCl and $\text{Pd}_2(\text{dba})_3$ in the presence of TFurP serve as catalysts. The yields of the target compounds obtained by this method vary from 28% to 98%. Depending on the reagent's structure, one can obtain *trans*-, *cis*- (Table 5, entry 28) and *gem*-products (Table 5, entries 23 and 24).

The reaction of alkenylfluoro- and alkenylchlorosilanes with 5-iodouracil and 5-iodo-2'-deoxyuridine derivatives, which gives target products in high yields, has been studied recently.⁸⁴ To obvious merits of organosilicon reagents one can relate their low toxicity, moisture resistance and low cost. This reaction was carried out in the presence of 0.025 equiv. of $[(\eta^3\text{-C}_3\text{H}_5)\text{PdCl}]_2$ and 2 equiv. of Bu_4NF . This method allows the modification of the pyrimidine ring with alkenyl radicals of various structure, *e.g.*, vinyl (Table 5, entry 35), styryl (Table 5, entries 36, 37, 40, 43 and 45), alkylvinyl (Table 5, entries 38, 41, 44 and 46), *etc.* As a rule, protected substrates are used; non-protected halogeno derivatives of nucleosides react with organosilicon compounds less readily. Thus 5-iodouracil does not react with alkenylfluoro- and alkenylchlorosilanes and 5-iododeoxyuridine forms a mixture of *trans*- and *gem*-isomers.

3. Photochemical alkenylation of nucleosides

The advantages of the photochemical reaction of activated alkenes with 5-iodopyrimidine nucleosides are technologically simple and versatile procedures used for the synthesis and isolation. However, the yields of the target products are small, varying from low (12%) to moderate (41%) (the literature data on photochemical coupling of nucleosides with alkenes are presented in Table 6). In addition, alkenes are linked non-stereoselectively to give a mixture of *cis*- and *trans*-isomers. Therefore, it is reasonable to use this reaction exclusively for the synthesis of the corresponding alkyl derivatives by hydrogenation of the alkenyl-

Table 6. Photochemical alkenylation of nucleosides.

Entry	Substrate	Reagent	Product (a mixture of <i>E</i> - and <i>Z</i> -isomers)	Yield (%)	Ref.
1	39	$\text{H}_2\text{C}=\text{CHCO}_2\text{Me}$	 (69)		
			69 , R = Rib	38	85
2	38	$\text{H}_2\text{C}=\text{CHCO}_2\text{Me}$	69 , R = dRib	41	85
3	39	$\text{H}_2\text{C}=\text{CHCN}$	 (70)		
			70 , R = Rib	12	85
4	38	$\text{H}_2\text{C}=\text{CHCN}$	70 , R = dRib	14	85
5	 (71) Rib	$\text{H}_2\text{C}=\text{CHCO}_2\text{Me}$	 (72)		
			72 , R = Rib	22	86
6	52	$\text{H}_2\text{C}=\text{CHCO}_2\text{Me}$	72 , R = dRib	24	86
7	71	$\text{H}_2\text{C}=\text{CHCN}$	 (73)		
			73 , R = Rib	18	86
8	52	$\text{H}_2\text{C}=\text{CHCN}$	73 , R = dRib	20	86

Note: The reaction was carried out in three steps: (1) HMDS, Py, Ar, 18 h; (2) alkene, MeCN, $h\nu = 254 \text{ nm}$, 24 h; (3) H_2O .

ated product over Pd/C. Alkenyl fragments are added to the trimethylsilylated 5-iodonucleoside upon irradiation of the reaction mixture with light of the wavelength of 254 nm in deoxygenated and dry acetonitrile for 24 h.

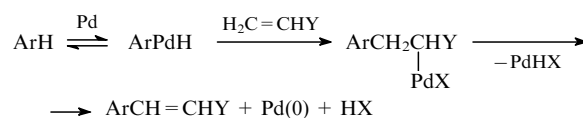
IV. Alkenylation of non-substituted nucleosides and their analogues

Pyrimidine nucleosides and their analogues that are not substituted at positions 5 and 6 of the heterocycle can also enter into the alkenylation reaction. Three versions of this reaction are known, *viz.*, oxidative coupling of alkenes (predominantly, activated ones), cross-coupling with vinyl triflates (both reactions are carried out in the presence of Pd compounds) and nucleophilic addition of alkenylmagnesium derivatives at position 6 of the pyrimidine ring.

1. Oxidative coupling of activated alkenes

Oxidative coupling of alkenes (the Fujiwara reaction⁸⁷) is carried out in the presence of 1 equiv. of Pd(OAc)₂ on boiling in acetonitrile or at room temperature (Table 7). The mechanism of this reaction seems to consist in the formation of an arylpalladium

hydride intermediate followed by insertion of the alkene at the Ar–Pd bond and reductive elimination of PdHX to give Pd(0).⁸⁸

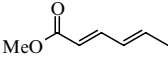
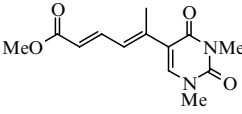
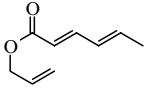
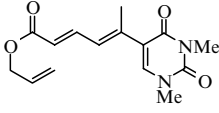
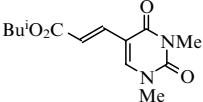
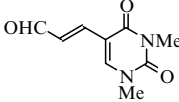
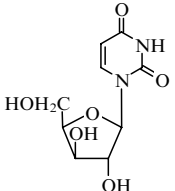
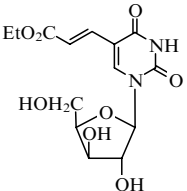


Reactions of 1,3-dimethyluracil with activated alkenes (methyl acrylate, acrylamide, methyl vinyl ketone and styrene) give uracil derivatives substituted at position 5 in good yields; all these reactions result in *trans*-isomers. In the case of non-activated alkenes, *gem*-isomers are formed as admixtures. It is of note that acrolein diethyl acetal also enters into the reaction, which permits one to introduce an alkenyl substituent with a terminal aldehyde group into the pyrimidine base (Table 7, entry 13). It should be remembered that this reaction cannot be realised with mercurio-nucleosides. The products of coupling nucleosides with acrolein diethyl acetal could not be obtained thus far. In general, nucleosides add alkenes less readily in this reaction (Table 7, entries 6, 7 and 14). Only in the case of 2',3'-*O*-isopropylidene-protected nucleosides could the methyl acrylate group be introduced at

Table 7. Alkenylation of non-substituted nucleosides with activated alkenes.

Entry	Substrate	Reagent	<i>t</i> /h	Product	Yield (%)	Ref.
1		H ₂ C=CHCO ₂ Me	24		92	89
2	74	H ₂ C=CHCN	16		73	89
3	74	H ₂ C=CHCOMe	16		74	89
4	74	H ₂ C=CHPh	13		86	89
5	dU	H ₂ C=CHCO ₂ Me	32	20	56	89
6	dU	H ₂ C=CHPh	62	13 , R = H	35	89
7	Urd	H ₂ C=CHCO ₂ Me	72	12	47	89
8		H ₂ C=CHCO ₂ Me	53 ^a		74 + 23	89
9	74		24		36 + 10	90

Table 7 (continued).

Entry	Substrate	Reagent	<i>t</i> /h	Product	Yield (%)	Ref.
10	74		24		25	90
11	74		24		23	90
12	74	H ₂ C=CHCO ₂ Bu ^t	24		—	90
13	74	H ₂ C=CHCH(OEt) ₂	24 ^a		80	90
14		H ₂ C=CHCO ₂ Et	24		40	90

Note: The reaction was carried out in the presence of 1.2 equiv. of Pd(OAc)₂ in boiling acetonitrile. Urd is uridine (1-β-D-ribofuranosyluracil). ^a The reaction was carried out at room temperature.

position 5 of the pyrimidine ring (Table 7, entry 8); the target product was obtained in good yield (74%).

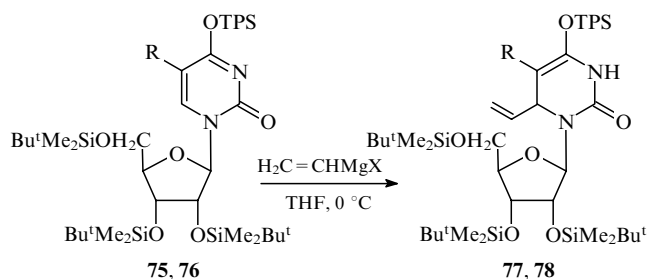
2. Oxidative coupling with vinyl triflates

Vinyl triflates react with non-substituted nucleosides in the presence of a catalyst [(Pd(PPh₃)₄) (~0.05 equiv.)] and an excess of LiCl in THF to give the corresponding alkenyl derivatives in moderate yields (Table 8). This reaction, as the coupling with organoelement alkene derivatives, permits one to introduce non-activated alkenyl substituents into position 5 of the pyrimidine

ring. Depending on the structure of the vinyl triflate reagent, one can obtain various regio- and stereoisomers.

3. Addition of alkenylmagnesium derivatives

Vinylmagnesium bromide and chloride are added at position 6 of the pyrimidine ring of the protected nucleosides; this reaction gives 6-alkenyldihydropyrimidine derivatives of nucleosides in good yields. Thus reaction of protected uridine **75** with vinylmagnesium chloride^{83,92} and reaction of the 5-bromo derivative **76** with vinylmagnesium bromide (Ar, 1 h) give their 6-vinyldihydro derivatives **77** and **78** (yields 61% and 96%, respectively).



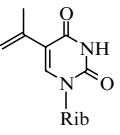
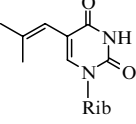
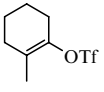
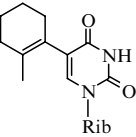
R = H (**75, 77**), Br (**76, 78**).

The attempts⁸³ to oxidise reaction products to pyrimidine derivatives of nucleosides were unsuccessful.

V. Conclusion

Numerous methods for C-alkenylation of nucleosides and their analogues are currently known, which differ in complexity, reaction conditions and the possibility of obtaining substituted nucleosides with a predetermined structure. In our opinion, the most promising approaches involve reactions of organoelement alkene derivatives, in particular, organotin (in non-aqueous

Table 8. Alkenylation of non-substituted nucleosides with vinyl triflates.⁹¹

Entry	Reagent	Product	Yield (%)
1	H ₂ C=C(Me)OTf		54
2	Me ₂ C=CHOTf		43
3			45.7

Note: Reaction conditions: LiCl, Pd(PPh₃)₄, THF, N₂, 48 h; Urd, uridine (1-β-D-ribofuranosyluracil) as a substrate.

solvents) and organoboron derivatives (in H₂O or aqueous-organic media). Organosilicon derivatives of alkenes seem to be promising reagents that might replace toxic organotin compounds in future, although their cross-coupling is insufficiently developed yet. Mercury derivatives of nucleosides used to introduce alkenyl substituents will hardly lose their significance by virtue of their availability, which can be attributed to the ease of their preparation and the presence of a large body of experimental material that helps selecting the conditions for a specific synthesis. However, in more distant future this method will most likely be replaced by analogous procedures, e.g., the Heck-type coupling of iodonucleosides with alkenes, which affords higher yields of the target products and precludes the use of toxic substrates. The methods of oxidative coupling of nucleosides with activated alkenes and alkenyl triflates also attract attention owing to their experimental simplicity. At the same time, literature data concerning these methods are scarce, which makes difficult their application in the synthesis of novel compounds and long-range prognoses. And finally, the use of photochemical alkenylation of nucleosides for preparative purposes will, most probably, hardly have any practical significance.

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Molecular structure descriptors in the computer-aided design of biologically active compounds

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Abstract. The current state of description of molecular structure in computer-aided molecular design of biologically active compounds by means of descriptors is analysed. The information contents of descriptors increases in the following sequence: element-level descriptors—structural formulae descriptors—electronic structure descriptors—molecular shape descriptors—intermolecular interaction descriptors. Each subsequent class of descriptors normally covers information contained in the previous-level ones. It is emphasised that it is practically impossible to describe all the features of a molecular structure in terms of any single class of descriptors. It is recommended to optimise the number of descriptors used by means of appropriate statistical procedures and characteristics of structure–property models based on these descriptors. The bibliography includes 371 references.

I. Introduction

The empirical regularities in the variation of properties of compounds as functions of their structure established by the middle of the XIX century underlay the concept of the structure–property relationship for chemical compounds. The Periodic Law discovered by D I Mendeleev can be considered as the scientific base of the structure–property concept, and the prediction of physical properties and existence of new elements, unknown at that time, is the first stable predictive model based on this relationship.¹

Systematic studies on the relationship between the structure and the biological activity of organic compounds started at the end of the XIX century^{2–4} and by now, they have become widespread. The recognised founder of the research on the

quantitative structure–activity relationship (QSAR) carried out nowadays is C Hansch, who reported in 1964, together with T Fujita, a relation that has found the most extensive use in the studies on the structure–biological activity correlations.² However, whilst acknowledging the merits of this scientist, one should also remember his numerous predecessors. In particular, it was noted³ that as early as 1944, N V Lazarev proposed⁴ that the partition coefficients of chemical compounds in oil–water systems be used to establish the quantitative structure–activity relationships. The intense progress in computational hardware and its adoption for research practice, including that in the field of science in question, promoted the formation of a border line of research — computer-aided design of biologically active compounds. Many concepts of this rapidly progressing field are being modified and improved. Therefore, it is necessary to analyse at intervals the current state of studies dealing with this subject. The previous review on this topic⁵ was published in this journal in 1988.

With allowance for the structure–activity relationship concept, three main stages can be distinguished in the computer-aided design of biologically active compounds.

(1) Formation of a trial set of compounds having a specified property (activity) or a set of properties;

(2) description of the molecular structure of compounds in this set;

(3) elucidation of the structure–biological activity relationship followed by creation of a stable prognostic model suitable for predicting the properties of new compounds.

This review analyses the modern approaches to the quantitative description of molecular structures of chemical compounds within the framework of computer-aided design of biologically active compounds in terms of independent variables characterising structural features of molecules or their parts (substituents, fragments). These variables are called descriptors.

The progress in computational hardware has a crucial influence on the development of this line of research. It should be noted that computer-aided molecular design faces the problem of processing the data on molecular structures in a unified form with their information content being retained as fully as possible after the data have been entered in the computer.

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Complex natural processes are studied by developing their models. Advantages of these models over the original are that they are easier to investigate, can be better manipulated and monitored and that the investigations are cheaper.⁶ The models can be classified into iconic (ensuring similarity regarding the form), analog (ensuring similarity regarding the form and functions) and abstract (symbolic, conceptual) models, which provide the correlation with the original by virtue of symbols.

The modern views on the molecular structure are certainly not exhaustive and, in the future, they will be improved with the aid of various models. Here, it is pertinent to quote M Dewar, who said that we don't know and, perhaps, shall never know what molecules actually are. Our understanding of molecules is based on models, which reproduce their properties sufficiently well to be useful.⁶

Description of models, which are used in chemical research, can be found in the literature.^{6–8} In this review, molecular structure descriptors are considered briefly with allowance for the above classification of models.

II. Classification of descriptors

Various types of classification of descriptors are possible. Three types of classification are considered in a paper by Charton.⁹ According to the first type, descriptors are classified into simple (describing one effect of interatomic interactions) and composite ones (describing two or more effects). Composite descriptors, in turn, can be divided into unicomposite (describing effects of the same type) and multicomposite descriptors (reflecting the sum of effects of various types).

The second classification is based on the way in which descriptors are estimated, *i.e.*, experimental and theoretical ones.

The third classification takes into account the sort of effect described by a given descriptor. Three sorts of effects are distinguished — electronic (electric), steric and intermolecular effects. A specific case of using this type of classification is provided by the classical Hansch equation,^{2,10–14} which represents biological activity as a function of Hammett constants (electronic effects), Taft constants (steric effects) and hydrophobicity constants (transport effects arising due to intermolecular interactions).

For visualisation of the description of chemical structures, Testa and Kier¹⁵ used geometrical figures corresponding to the level of structure being considered: element level → two-dimensional structure → three-dimensional structure → bulk properties → stereodynamic structure → stereoelectronic structure → interactions with the environment. The information content of each subsequent level embraces the information content of the preceding one. Apparently, a similar approach in a somewhat different form could be used in this review to discuss descriptors. Figure 1 shows a chart for several levels of descriptors in which each subsequent level covers the information content of the preceding one. In this representation, it is assumed that structural formula descriptors carry the whole body of information contained in the element-level descriptors; electronic structure descriptors carry the information contained in the structural formula descriptors and descriptors of intermolecular interactions cover the whole body of information provided by all of the preceding levels. In some cases, descriptors do not bear the information of the previous level (*e.g.*, some descriptors of intermolecular interactions such as polarisability and hydrophobicity are often calculated without allowance for the three-dimensional structure), but in general, this approach to the classification of descriptors is visual and reflects the degree of their complexity and, thus, it is convenient for the analysis. In this review, each class of descriptors is considered. It should be noted that a descriptor of any level can characterise both a molecule as a whole and its part (fragment, screen, functional group, substituent).

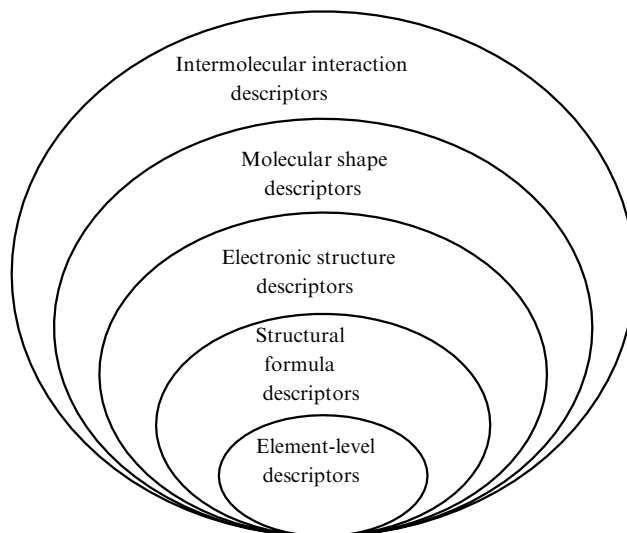


Figure 1. Information contents of molecular structure descriptors.

III. Element-level descriptors

The gross formula bears the information about sorts of atoms that make up the molecule and the number of atoms of each sort. The only property that can be predicted precisely based on the gross formula is molecular weight (MW), which can be regarded as an element-level descriptor. The number of atoms of a particular sort is sometimes taken as another descriptor of this level.¹⁶ An example of using such descriptors can be found in the Appendix [see Eqn (A.1)].

A legitimate construction of the structure–property correlation should be carried out for related compounds. Therefore, the structure variation within a series of compounds being considered reduces to variation of substituents. Hence, the properties of substituents can be regarded as structural descriptors. In particular, the atomic weights of substituents can also be considered to be element-level descriptors. Generally, descriptors of this level carry too little information on the molecular structure and, hence, they cannot be used alone for elucidation of the real structure–property relationships.

IV. Structural formula descriptors

The structural formula of a molecule is the most widespread way of describing a chemical compound. As a model of molecular structure, this formula contains elements of iconic, analog and abstract models⁶ and provides the basis for the construction of many types of descriptors, most of all, topological descriptors (Fig. 2).

1. Topological indices

Topological descriptors (indices) are calculated based on the description of a structural formula of a compound by a molecular graph G , which is a two-dimensional representation of the molecule (the vertices correspond to atoms and the edges match the chemical bonds).¹⁷ Normally, the skeleton atoms and the bonds between them are considered, hydrogen atoms being erased. The matrix form of the graph is used to estimate the topological indices. The adjacency matrix $A(G)$ and the distance matrix $D(G)$ are used most often. The adjacency matrix elements a_{ij} are equal to either unity or zero depending on whether or not vertex i of graph G is incident to vertex j . The number of units in an i th line or j th column of the matrix is equal to the vertex degree.

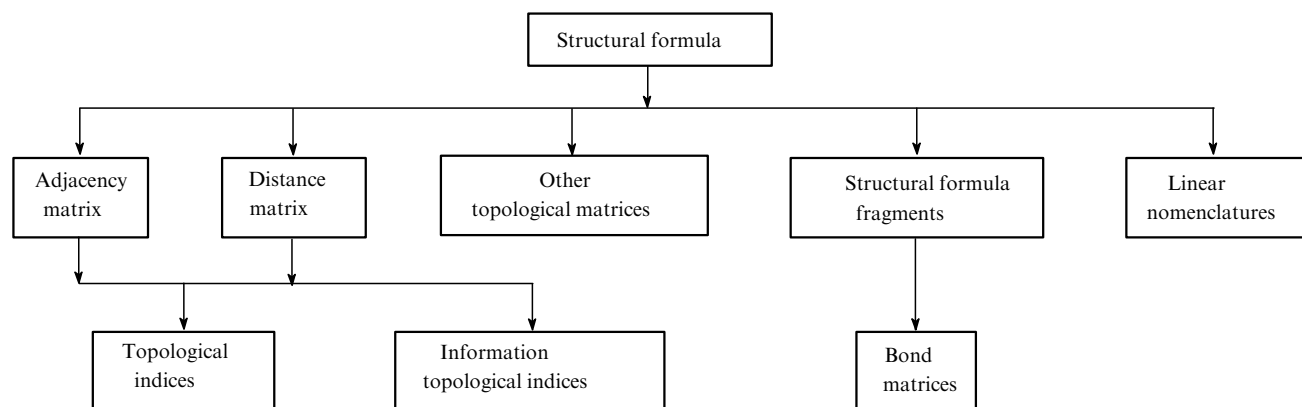


Figure 2. Elements of molecular structure description based on the structural formula.

Each element in the distance matrix $D(G)$ represents the number of edges connecting vertex i to vertex j via the shortest route and is denoted by d_{ij} . The adjacency and distance matrices for pentane, 2-methylpentane, cyclopentane and furan are shown in Scheme 1. Note that the adjacency and distance matrices for the two last-mentioned compounds are identical because the molecular graphs are identical.

Scheme 1

Compound	Molecular graph	Adjacency matrix	Distance matrix
<chem>CH3(CH2)3CH3</chem>		$\begin{array}{c ccccc} & 1 & 2 & 3 & 4 & 5 \\ \hline 1 & 0 & 1 & 0 & 0 & 0 \\ 2 & 1 & 0 & 1 & 0 & 0 \\ 3 & 0 & 1 & 0 & 1 & 0 \\ 4 & 0 & 0 & 1 & 0 & 1 \\ 5 & 0 & 0 & 0 & 1 & 0 \end{array}$	$\begin{array}{c ccccc} & 1 & 2 & 3 & 4 & 5 \\ \hline 1 & 0 & 1 & 2 & 3 & 4 \\ 2 & 1 & 0 & 1 & 2 & 3 \\ 3 & 2 & 1 & 0 & 1 & 2 \\ 4 & 3 & 2 & 1 & 0 & 1 \\ 5 & 4 & 3 & 2 & 1 & 0 \end{array}$
<chem>CH3CH(CH3)(CH2)2CH3</chem>		$\begin{array}{c cccccc} & 1 & 2 & 3 & 4 & 5 & 6 \\ \hline 1 & 0 & 1 & 0 & 0 & 0 & 0 \\ 2 & 1 & 0 & 1 & 0 & 0 & 1 \\ 3 & 0 & 1 & 0 & 1 & 0 & 0 \\ 4 & 0 & 0 & 1 & 0 & 1 & 0 \\ 5 & 0 & 0 & 0 & 1 & 0 & 1 \\ 6 & 0 & 1 & 0 & 0 & 1 & 0 \end{array}$	$\begin{array}{c cccccc} & 1 & 2 & 3 & 4 & 5 & 6 \\ \hline 1 & 0 & 1 & 2 & 3 & 4 & 2 \\ 2 & 1 & 0 & 1 & 2 & 3 & 1 \\ 3 & 2 & 1 & 0 & 1 & 2 & 2 \\ 4 & 3 & 2 & 1 & 0 & 1 & 3 \\ 5 & 4 & 3 & 2 & 1 & 0 & 4 \\ 6 & 2 & 1 & 2 & 3 & 4 & 0 \end{array}$
Cyclopentane		$\begin{array}{c ccccc} & 1 & 2 & 3 & 4 & 5 \\ \hline 1 & 0 & 1 & 0 & 0 & 1 \\ 2 & 1 & 0 & 1 & 0 & 0 \\ 3 & 0 & 1 & 0 & 1 & 0 \\ 4 & 0 & 0 & 1 & 0 & 1 \\ 5 & 1 & 0 & 0 & 1 & 0 \end{array}$	$\begin{array}{c ccccc} & 1 & 2 & 3 & 4 & 5 \\ \hline 1 & 0 & 1 & 2 & 2 & 1 \\ 2 & 1 & 0 & 1 & 2 & 2 \\ 3 & 2 & 1 & 0 & 1 & 2 \\ 4 & 2 & 2 & 1 & 0 & 1 \\ 5 & 1 & 2 & 2 & 1 & 0 \end{array}$
<chem>c1ccoc1</chem>		$\begin{array}{c ccccc} & 1 & 2 & 3 & 4 & 5 \\ \hline 1 & 0 & 1 & 0 & 0 & 1 \\ 2 & 1 & 0 & 1 & 0 & 0 \\ 3 & 0 & 1 & 0 & 1 & 0 \\ 4 & 0 & 0 & 1 & 0 & 1 \\ 5 & 1 & 0 & 0 & 1 & 0 \end{array}$	$\begin{array}{c ccccc} & 1 & 2 & 3 & 4 & 5 \\ \hline 1 & 0 & 1 & 2 & 2 & 1 \\ 2 & 1 & 0 & 1 & 2 & 2 \\ 3 & 2 & 1 & 0 & 1 & 2 \\ 4 & 2 & 2 & 1 & 0 & 1 \\ 5 & 1 & 2 & 2 & 1 & 0 \end{array}$

The most commonly used topological indices calculated from the adjacency matrix are the Platt index $F(G)$ (the sum of degrees of each edge in graph G); the Gordon–Scantlebury index $Y(G)$ (the number of paths of length 2); the full adjacency index $A'(G)$ (the sum of all the non-zero elements in the adjacency matrix); the Randic connectivity index $\chi(G)$ (it will be discussed below); and the Zagreb group indices $M_1(G)$ and $M_2(G)$. The indices that should be mentioned as the descriptors calculated from the distance matrix are the Wiener index $W(G)$, the Hosoya index $Z(G)$, the polarity number $P(G)$, the distance sum index $S(G)$ and the index of distances between the vertices $VDI(G)$. The formulae for the calculation of these widely used descriptors and other topological indices estimated based on the adjacency and distance matrices as well as examples of using these descriptors in the

structure–property correlations can be found in original publications.^{18–20}

The above matrices and topological indices reflect only topological features of molecules without allowance for the types of atoms and the real distances between them. The imperfection of this description of the structures of compounds becomes clear if one recalls that the adjacency and distance matrices (and, hence, all the topological indices mentioned above) for cyclopentane and furan coincide.

In addition to the adjacency and distance matrices described above, the extended distance matrix E ,²¹ connectivity matrix C ²² and Wiener matrix W ²³ are used.

Many researchers use various descriptors estimated based on connectivity matrix C ; therefore, we shall briefly consider them here. In 1975, Randic proposed that the connectivity index $\chi(G)$ be determined in the following way:²⁴

$$\chi(G) = \sum (v_i v_j)^{-1/2}, \quad (1)$$

where v_i and v_j are the degrees of vertices i and j in graph G , respectively. Summation is carried out over all edges of graph G .

Kier and Hall²⁵ have employed the Randic scheme as the basis for the development of a general method for the description of structures of organic compounds and proposed the concept of molecular connectivity for this purpose.²⁵ The first equation for a topological index was as follows:

$${}^1X = \sum (\delta_i \delta_j)^{-1/2}, \quad (2)$$

where δ corresponds to the number of neighbouring atoms (with hydrogen atoms being omitted). This equation is identical to Eqn (1). However, the researchers made this approach more versatile by extending it not only to bonds but also to atoms (${}^0X = \sum (\delta)^{-1/2}$) and to fragments with several bonds. For example, when a molecular graph is cut into two-bond fragments, the index ${}^2X = \sum (\delta_i \delta_j \delta_k)^{-1/2}$ is estimated, when it is cut into three-bond fragments, the index ${}^3X = \sum (\delta_i \delta_j \delta_k \delta_l)^{-1/2}$ is determined and so on. In addition, calculation of these indices for molecules containing heteroatoms was started. The hydrogen atoms attached to heteroatoms were ignored (like those attached to carbon).

Later, Kier and Hall²⁶ proposed a general equation for the estimation of δ for any atom

$$\delta_v = Z_v - h, \quad (3)$$

where Z_v is the number of valence electrons with allowance for the electrons of lone electron pairs and h is the number of hydrogen atoms attached to the given atom (which are present in the structural formula but lacking in the molecular graph). Thus the δ_v value for a carbon atom of benzene is equal to three (the atom has four valence electrons and is linked to one hydrogen atom); the δ_v value for the oxygen atom in alcohols is equal to five (the atom

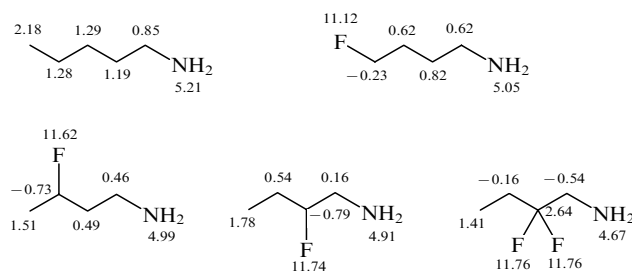
has six valence electrons and is linked to one hydrogen atom) and that for the oxygen atom in ethers is six (the same number of valence electrons but no hydrogens at the heteroatom).

In the subsequent studies, Kier and Hall^{27–30} proposed using electronic state indices (S) to describe quantitatively the mutual influence of atoms. The S value for any atom is estimated by the formula

$$S = I + \Delta I, \quad (4)$$

where $I = (\delta_v + 1)/\delta$ and $\Delta I = (I_i - I_j)/r_{ij}^2$ (r is the number of bonds between the two atoms considered). The indices of the electronic topological state for some substituted amines are presented below (Scheme 2).

Scheme 2



The Kier and Hall indices have been used rather widely in the search for quantitative structure–property relationships [see, for example, the Appendix, Eqns (A.2) and (A.3)]. These indices became very popular because they can be easily calculated and provide clear representation of the structural formulae of compounds. Several recent publications should be noted.^{31–39}

However, description of the electronic structure by the number of valence electrons and description of interatomic distances by the number of bonds between the atoms are too simplified to ensure elucidation of the true molecular structure. This accounts for the criticism levelled at the attempt of using these indices for establishing the real structure–biological activity correlations.⁴⁰

A commonly used index calculated from the distance matrix is the Wiener index $W(G)$, which is the first topological index used in chemistry. It is defined as the half-sum of the elements of the distance matrix D . The Wiener index and related topological indices are often used in the structure–property studies to characterise the compactness of a molecule.^{41–43} However, it should be borne in mind that in matrix D , the distance between atoms is expressed as the number of bonds separating these atoms. In order to bring the structure description in terms of the distance matrix closer to the real situation, it has been proposed to use averaged (typical) distances between atoms in molecules placed in a three-dimensional grid^{44–47} or distances found from experimental data or by quantum-chemical calculations^{48,49} as the off-diagonal matrix elements.

Molecular graphs serve as the source of diverse topological indices. Thus Kier^{50–54} proposed various kappa-indices for coding the shape or configuration of molecules. Description of some other new indices can be found in several publications.^{55–64} Particular correlations of these topological indices with various physical properties and biological activity have been considered.^{65–72}

Information topological indices have also been used for structure description. The estimation of these indices is based on the separation of the set of graph vertices into equivalence classes taking account of the closest environment of the vertices.^{18,73} Within the framework of this approach, a number of topological indices of the theoretical-information type have been devised, namely, ${}^1\text{IC}$ (information content), ${}^1\text{SIC}$ (structural information content), ${}^1\text{BIC}$ (binding information content) and ${}^1\text{CIC}$ (complementary information content), which are calculated from the following equations:

$${}^1\text{IC} = - \sum \frac{n_i}{n} \log_2 \frac{n_i}{n}, \quad (5)$$

$${}^1\text{SIC} = \frac{{}^1\text{IC}}{\log_2 n}, \quad (6)$$

$${}^1\text{BIC} = \frac{{}^1\text{IC}}{\log_2 q}, \quad (7)$$

$${}^1\text{CIC} = \log_2 n - {}^1\text{IC}, \quad (8)$$

where n_i is the number of vertices in the i th equivalency class, n is the number of graph vertices for the molecule and q is the number of graph edges. Examples of using the information topological indices for describing structures of organic compounds in elucidation of structure–property correlations including structure–biological activity correlations have been reported.^{74–80}

2. Encoding of structural formulae by linear nomenclatures and bond matrices

The necessity of automating the processing of information on the structures of chemical compounds, the amount of which has sharply increased in recent years, initiated the development of some new methods for representation of the structural formulae of chemical compounds, namely, various linear nomenclatures and bond matrices, which can be regarded as abstract models of molecules.⁶

According to the linear nomenclature, a structural formula is encoded by a string of characters, which, in turn, encode particular fragments of the structure. Each linear nomenclature is characterised by a definitely specified sequence of characters. The character set of a linear notation usually includes standard characters. The initial stage of development of linear nomenclatures is associated with the name of Wiswesser. As an example, we present the Wiswesser codes for the structures of some compounds:



The Wiswesser linear nomenclature has been described in detail.¹⁶

In Russia, a similar approach is practised by Avidon,^{82,83} who uses the SSFC language (substructure superposition fragmental code).

At present, the most widespread linear nomenclature used to represent structural formulae of organic compounds is contained in the SMILES system,^{84–86} which is used, in particular, to reveal the structural similarity of compounds.⁸⁷ A linear nomenclature suitable for the description of not only the structural formula but also the stereoisomerism also deserves attention.⁸⁸ In this nomenclature, a compound is represented by a canonical line code consisting of two parts; the first part describes the structural formula and the second part characterises the stereochemical features of the molecule.

When a structural formula is described using a connectivity matrix, each atom, each bond and each type of atoms are coded directly. Connectivity matrices are similar to adjacency matrices and distance matrices. The main diagonal of a connectivity matrix normally includes codes for the atoms in the structural formula, while off-diagonal elements are the codes for the types of bonds. These matrices were used rather widely in the 1970s and 1980s; they have been described in a monograph.¹⁶ A connectivity matrix of descriptor centres (CMDC) has been proposed;⁸⁹ in this matrix, the codes of atoms are replaced by codes of functional groups (descriptor centres) and the off-diagonal elements correspond to the numbers of bonds between the descriptors instead of the bond codes. In order to perfect the language of structure description in terms of CMDC, later it has been proposed to use computable distances between the descriptor centres.⁹⁰

3. Structural fragments as descriptors

The topological indices and various matrices described above provide certain information on a chemical compound as a whole. However, the crucial role in the interaction of a compound with other chemical and biological objects is sometimes played by separate fragments of molecules; therefore, in the elucidation of the structure–property and structure–biological activity correlations, the structures of compounds of a given series are often described fragment-by-fragment. A structural fragment can comprise one atom, a substituent, a functional group or a particular combination of atoms (with indication of the hybridisation types).⁹¹ Each structural fragment can be used as an independent descriptor. Further detailing can be attained by specifying the local characteristics of atoms forming the fragment (see, e.g., classification of the descriptor centres in terms of their donor–acceptor properties).^{92,93} Numerous approaches to the computer-aided construction of new substances based on structural fragments of compounds having a common property have been developed. Various substructure analysis descriptors,^{94–97} topological pharmacophores in the LOGANA programme package procedure,^{98–100} substructure descriptors,^{101,102} descriptors of the structural language of the DARC system,^{103,104} chemical functionality descriptors¹⁰⁵ and *de novo* design descriptors¹⁰⁶ can be cited as examples.

V. Descriptors of the electronic structure of molecules

Quantum-chemical calculations for complex molecules make use of atomic and molecular quantum-chemical descriptors. The methods for calculation, the potential and limitations of these descriptors have been described in detail in a review.¹⁰⁷ In this Section, we consider briefly only quantum-chemical descriptors related to intramolecular electronic properties.

Atomic charges are quantum-chemical descriptors used most often to elucidate the structure–property correlations. If chemical interactions are divided into electrostatic and covalent components, atomic charges characterise the electrostatic component. The full charge on an atom can be regarded as a non-directional descriptor, whereas the σ - and π -electron densities characterise the possible orientation of chemical interactions; therefore, they can be regarded as directional descriptors.¹⁰⁸ Examples of successful use of these descriptors can be found in the literature.^{109–111} When the charges on atoms are known, a new set of descriptors of this type can be used in each particular study.

The energies of the highest occupied (E_{HOMO}) and lowest unoccupied (E_{LUMO}) molecular orbitals are descriptors that are frequently used in calculations of electronic structures of molecules.^{112–114} It was found that in some cases, the E_{HOMO} values are directly correlated with the ionisation potential (I) and characterise the susceptibility of the molecule to electrophilic attack. The E_{LUMO} values correlate with the electron affinity (A) and characterise the susceptibility of the molecule to nucleophilic attack. Note that I and A are also used as independent electronic structure descriptors.^{115,116} The $E_{\text{HOMO}} - E_{\text{LUMO}}$ difference is believed to reflect the molecule's stability.¹¹⁷ The notions of softness and hardness of molecules are associated with exactly these electronic structure descriptors.¹¹⁸ The molecular hardness descriptor (η)

$$\eta = \frac{I - A}{2} \quad (9)$$

has also found use in the structure–property correlations (see, for example, Ref. 119).[†]

[†] Hardness as a measure of energy stabilisation has been defined by some researchers as the half-sum of the E_{HOMO} and E_{LUMO} values¹²⁰ or as the difference between E_{HOMO} and E_{LUMO} taken with a minus.^{121,122}

Dipole moment and related descriptors. The polarity of a molecule is described by its dipole moment (μ). The magnitude of this descriptor can be determined experimentally or calculated using a quantum-chemical method. This descriptor is used rather widely in elucidation of structure–property correlations.^{12,112,123–125} However, the vector summation of the dipole moments of several polar groups in a molecule can result in a small value. Therefore, in addition to μ , the greatest difference between the charges of two atoms, the topological electronic index, the local dipole index, the quadrupole moment tensor, *etc.* are sometimes used as polarity descriptors.¹⁰⁷

Examples of using electronic structure descriptors in structure–biological activity relationships are given in the Appendix [Eqns (A.4) and (A.5)].

VI. Molecular shape descriptors

It is now obvious that features of the three-dimensional structure of molecules need to be taken into account in elucidating the structure–property relationships. Suffice it to say that almost all of the modern automated systems for the search for new compounds contain, as obligatory elements, various procedures for comparison of the spatial structures of molecules.^{126,127}

The description of the three-dimensional structure of a molecule by a single quantitative descriptor (or a set of descriptors) is a fairly complicated task. Let us consider the simplest situation when the compounds under consideration have the same framework and different substituents at the same position. In 1976, Verloop and coworkers proposed a set consisting of five steric constants (STERIMOL parameters) for 243 different substituents; the constants were calculated based on standard bond lengths and bond angles.¹²⁸ These simple parameters have found fairly wide use in structure–property studies.^{129–131} A similar approach based on estimation of shape parameters of substituents has been proposed in another study.¹³²

Amoore¹³³ was the first to analyse the projections of molecular structures onto the three orthogonal planes in a study dealing with the relationship between the structure and odour of compounds. An approach describing the shape of a molecule in terms of six descriptors $S_1 - S_6$ has been proposed.¹³⁴

The main problem arising in the comparison of 3D structure parameters of various molecules is associated with conformational mobility. The appearance of an additional internal rotation axis results in an exponentially increased number of possible conformations; therefore, certain restrictions are required as well as special procedures for selecting real conformations and comparing their shapes.

Several methods for the estimation of molecular shape descriptors currently exist. These methods are briefly described below.

The distance geometry approach has been developed since the late 1970s, being constantly modified by Crippen *et al.*^{135–141} The consecutive steps of the procedure used to compare the 3D molecular shapes can be outlined as follows.

1. Generation of 3D structures for the compounds considered; the initial structure is based on the bond lengths and angles found in an X-ray diffraction experiment.

2. Ascribing of definite physico-chemical properties to atoms in the molecules.

3. Elucidation of low-energy regions in the conformational space for each of the compounds.

4. Determination of the geometrically possible superpositions of molecules onto the reference structure. First, all combinations of three atoms in the reference structure and in the molecule being analysed are considered. After the best correspondence of distances between some three-atom groups in the pair of compounds being compared has been found, superposition of these three pairs of atoms is fixed and the process of spatial superposition is continued for other atoms.

5. Analysis of a great number of 'good' superpositions of compounds on the reference structure makes it possible to compare the molecular shapes of the compounds; as this is done, the concept of the molecular shape descriptors is visualised and the shape of the binding site in a potential receptor is evaluated.

The binding site approach.^{142–144} This approach represents the binding sites of a potential receptor as non-overlapping areas covering the whole space rather than as points (as in the previous method). With such representation of a spatial structure, each atom should be located in one (and only one) area and the binding site model should include the list of areas (descriptors) in which each atom is located. Fig. 3a shows the binding site model calculated for compounds exhibiting competitive properties in relation to the protein isolated from mouse liver,¹⁴⁵ and Fig. 3b presents the optimum binding model for benzopyrene.

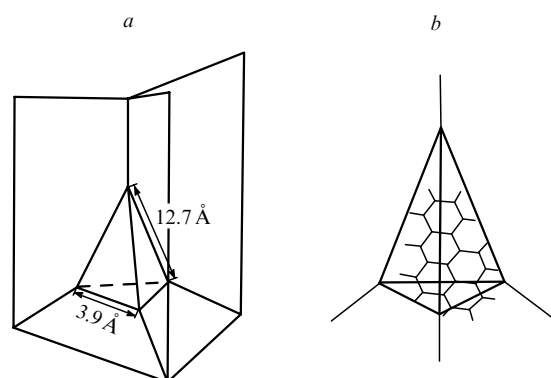


Figure 3. Binding site model for compounds exhibiting competitive properties towards a protein (a) and optimum binding model for benzopyrene (b).¹⁴⁵

Molecular shape analysis. This approach has been developed during the last 15 years in the studies of Hopfinger *et al.*^{146–155} The procedure for the quantitative comparison of the spatial structures of the molecules of various compounds includes six consecutive stages.

1. Conformational analysis with allowance for the internal rotation about all the single bonds and calculation of the energy for each 10° increment. This is done using methods of molecular mechanics with a force field comprising contributions of dispersion, steric and electrostatic interactions and, whenever possible, hydrogen bonds.

2. Selection of individual conformations. The real set of possible conformations for each compound is determined by the chosen difference between the conformation considered and the global energy minimum.

3. The choice of the reference compound and the active conformation by pairwise comparison of the molecular shapes in the series of compounds under consideration.

4. Superposition of each molecule in the series of compounds under consideration onto the molecule of the reference compound.

5. Quantitative comparison of molecular shapes. The following descriptors characterising the molecular shape similarity have been proposed:

the common overlap steric volume (V_0) determined from the following equation

$$V_0 = V_u \cap V_v, \quad (10)$$

where V_u and V_v are the space occupancy by the molecules of the compound considered and the reference compound, respectively;

the relative measure of the degree of similarity defined as the function

$$f_0 = \frac{V_u \cap V_v}{V_u}. \quad (11)$$

These descriptors do not contain information regarding the intramolecular stability of each conformation of the pair of compounds. Therefore, one more descriptor, the shape commonality index (I_c), has been proposed:

$$I_c = S_{(u,v,w)} - \frac{\Delta E_u}{[\Delta E_u^*(\Delta E_u^* + \Delta E_v^* + \varepsilon)]^{1/2}} + \frac{\Delta E_v}{[\Delta E_v(\Delta E_u^* + \Delta E_v^* + \varepsilon)]^{1/2}}, \quad (12)$$

where $S_{(u,v,w)}$ is wV_0 or wf_0 , w is the shape similarity parameter, ΔE is the difference between the conformation energies, $\Delta E_v^* = 1 \text{ kcal mol}^{-1}$, ΔE_u^* is taken to be 1, 3 and 6 kcal mol^{-1} in three separate calculations and ε is a correction factor.

The hypothetical active site lattice.^{156–160} This method is based on the assumption that a molecule can be described by descriptors characterising the space that it occupies and the nature of atoms that occupy this space. Three-dimensional space is defined as a set of regularly arranged points in a three-dimensional lattice. Translation of the molecule to the set of these points occurs with retention of those points of the lattice that fall within the van der Waals radius of each atom in the molecule. The resulting molecular lattice consisting of points carries information on the type and properties of atoms in the molecule. The type of atoms is defined simply: the value +1 is attributed to atoms rich in electrons, the value –1 is attributed to atoms poor in electrons and electrically neutral atoms are denoted by 0.

Estimation of molecular positions.^{161–163} In this approach, the comparison of spatial shapes of molecules also starts with the search for low-energy conformations and selection of energetically stable shapes for each compound in the series under consideration. Molecular position is defined as a specific conformation associated with the activity exhibited by this compound. The molecular position is described by several descriptors.

The weighted holistic invariant (WHIM) molecular descriptors are constructed in such a way as to cover the information on the three-dimensional structure as fully as possible including the size, shape and symmetry of molecules and the distribution of atoms in them.^{164–169} The calculation algorithm includes the analysis of the main components of the centred molecular coordinates using the weighted covariant matrix derived from various weighted schemes for atoms.

Different covariance matrices and principal axes are obtained depending on the type of the weighted scheme used. For example, when the atomic weights are used as the weighted scheme, the directions of the three principal axes coincide with the principal inertia axes.

For each weighted scheme, a set of statistical indices of atoms projected onto each principal component t_m ($m = 1, 2, 3$) is calculated. The invariance of the calculated parameters with respect to translation is attained by the procedure of centring the atomic coordinates, while the invariance with respect to rotation is ensured by using the principal components.

The directional WHIM descriptors are statistical indices calculated based on each individual principal component (1, 2, 3). The non-directional WHIM descriptors are found directly from directional descriptors. The latter type of descriptors characterise the overall shape of the molecule, any information related to the principal axes being lost in this case.

Eleven directional descriptors ($\lambda_1, \lambda_2, \lambda_3, \vartheta_1, \vartheta_2, \gamma_1, \gamma_2, \gamma_3, \eta_1, \eta_2, \eta_3$) characterising the molecular properties within each weighted scheme have been proposed.^{164–169} Thus, the total number of directional WHIM descriptors is 66. In the case of planar structures, only eight directional ($\lambda_1, \lambda_2, \vartheta_1, \vartheta_2, \gamma_1, \gamma_2, \eta_1, \eta_2$) and

five non-directional descriptors (T , A , V , K , D) should be taken into account for each weighted scheme.

Analysis of the shape of electron cloud.^{170–174} This method is based on the assumption that the shape of the electron cloud carries the whole body of information on the properties of compounds. This approach was used primarily to analyse molecular surfaces. The surface of a molecule is cut into areas according to the local curvature properties. Convex D_2 , saddle-like D_1 and concave D_0 local areas are distinguished. The ratios of these descriptors determine groups of molecular shapes, which include two- one- and zero-dimensional truncated surfaces obtained from the initial surface by removing all areas of a given type (D_2 , D_1 or D_0). The quantitative measure for the similarity of shapes of 3D molecules can be found by comparing the numerical codes of shapes. This procedure is performed automatically using a computer without subjective visual comparison of the shapes of objects.

Examples of using molecular shape descriptors in structure–biological activity correlations are given in the Appendix [Eqns (A.9) and (A.12)].

VII. Intermolecular interaction descriptors

Quantitative description of the intermolecular interactions in the elucidation of structure–biological activity correlations can be accomplished using the free energy difference (ΔG).^{175, 176}

$$\Delta G = G_f - G_i, \quad (13)$$

where G_f and G_i are the free energies of the final and initial states, respectively.

A more detailed quantitative description of intermolecular interactions is provided by using the enthalpy (ΔH) and entropy (ΔS) differences, which are related to ΔG as follows:

$$\Delta G = \Delta H - T\Delta S, \quad (14)$$

where T is the reaction temperature. By measuring experimentally the equilibrium constant (K), one can determine ΔG

$$\Delta G = \Delta G^\circ - RT \ln K, \quad (15)$$

where ΔG° is the free energy change for a reaction under standard conditions.

The ΔG , K , ΔH and ΔS values for a reaction or interaction can be regarded as descriptors of intermolecular interactions. For example, dissociation constants of acids and bases (pK_a) are used fairly frequently in the modelling of structure–activity correlations.^{177–180}

A large group of intermolecular interaction descriptors estimated from experimental data on reactivity comprises various constants describing the electronic influence of substituents on the reactivity of chemical compounds. This line of studies was initiated by Hammett who defined the parameter σ (Hammett constant) based on the relation¹⁸¹

$$\sigma_X = \log K_X - \log K_H, \quad (16)$$

where K_X is the corresponding constant for *meta*- (σ_m) or *para*-substituted (σ_p) benzoic acid, K_H is the ionisation constant for benzoic acid in water at 25 °C. By now, a great number of constants have been proposed to describe the electronic effects of substituents. For example, the inductive (σ_i) and resonance (σ_r , σ^+ , σ^-) constants, the inductive Taft constant (σ^*) and the Swain and Lupton constants^{182–184} are widely used as descriptors of intra- and inter-molecular interactions.

The reactivity descriptors, calculated by quantum-chemical methods, constitute an important group of intermolecular interaction descriptors. First of all, mention should be made of indices of electrophilic (S_e) and nucleophilic (S_n) superdelocalisabilities on a reaction centre (r), which are estimated from the equations

$$S_e(r) = 2 \sum_k^{\text{vac}} \sum_{\sigma(r)} \frac{(C_{\sigma k})^2}{0.5(E_{\text{HOMO}} + E_{\text{LUMO}}) - E_k}, \quad (17)$$

$$S_n(r) = 2 \sum_i^{\text{occ}} \sum_{\sigma(r)} \frac{(C_{\sigma i})^2}{E_i - 0.5(E_{\text{HOMO}} + E_{\text{LUMO}})}, \quad (18)$$

where the numerators contain coefficients for the atomic orbitals and denominators contain the energies of the corresponding molecular orbitals.

Some other descriptors such as self-atom polarisability $\pi(r)$,¹⁸⁵ reflecting the influence of the variation of electronegativity of atomic orbitals on the charge of the same atom

$$\pi(r) = 4 \sum_i^{\text{occ}} \sum_k^{\text{vac}} \sum_{\sigma(r)} \frac{C_{\sigma i}^2 C_{\sigma k}^2}{E_k - E_i}, \quad (19)$$

and atom–atom polarisability $\pi(\text{AB})$,¹⁰⁷ reflecting the effect of a perturbation at one atom (A) on the charge of another atom (B)

$$\pi(\text{AB}) = 4 \sum_i \sum_a \sum_p \sum_r \frac{C_{\pi}^A C_{pa}^A C_{ri}^B C_a^B}{E_i - E_a}, \quad (20)$$

can be used as well to describe intermolecular interactions.

These descriptors have also found application in the description of structure.^{107, 186–188}

Molecular refraction and polarisability. When a molecule is placed in an external electrostatic field, the charge distribution in it changes. The resultant dipole moment is determined from the relation

$$\mu = \alpha E, \quad (21)$$

where α is the molecular polarisability and E is the electric field intensity. The polarisability can be estimated experimentally based on the expression relating it to the molecular refraction (MR)

$$\text{MR} = \frac{4\pi N_A \alpha}{3}, \quad (22)$$

(N_A is the Avogadro number) and the relation of the molecular refraction to the refractive index (n)

$$\text{MR} = MV \frac{n^2 - 1}{n^2 + 2}, \quad (23)$$

where MV is the molecular volume. The MR and α values are estimated either based on the additivity of the experimentally determined contributions of separate atoms and fragments¹⁸⁹ or by quantum-chemical calculations.^{191–194}

Lipophilicity. The group of intermolecular interaction descriptors used most commonly to analyse the structure–activity correlations is related to the notion of lipophilicity, which characterises the transport properties of compounds in biological objects. In the vast majority of cases lipophilicity is described quantitatively in terms of the partition coefficients (P) of compounds in the model octanol–water system. The $\log P$ value for the neutral form of the compound is used as the descriptor for this system. The corresponding descriptors for the cationic, anionic and zwitter-ion forms are designated by $\log P^+$, $\log P^-$ and $\log P^{+/-}$.¹⁹⁵ The partition of ionised compounds between octanol and water depends on pK_a of the compound itself and pH of the medium. The distribution of substances in biological media is characterised by the index $\log D$ with indication of the pH, instead of $\log P$. In the vast majority of publications, $\log D$ refers to a physiological medium with pH 7.4.

The relationship between the descriptors $\log D$, $\log P$, $\log P^+$, $\log P^-$ and pK_a is given by the following expressions:¹⁹⁶ for the equilibrium $\text{XH} \rightleftharpoons \text{X}^- + \text{H}^+$,

$$\log D = \log P_{\text{XH}} - \log(1 + 10^{-pK_a - \text{pH}}); \quad (24)$$

for the equilibrium $\text{X} + \text{H}^+ \rightleftharpoons \text{XH}^+$,

$$\log D = \log P_{\text{X}} - \log(1 + 10^{-pK_a - \text{pH}}); \quad (25)$$

for the equilibria $X^- + H^+ \rightleftharpoons XH + H^+ \rightleftharpoons XH_2^+$,

$$\log D = \log(A_0 + A_1 + A_2), \quad (26)$$

where

$$A_0 = \frac{P_{X^-}}{1 + 10^{pK_{a2}-pH} + 10^{pK_{a1}+pK_{a2}-2pH}}, \quad (27)$$

$$A_1 = \frac{P_{XH}}{1 + 10^{pH-pK_{a2}} + 10^{pK_{a1}-pH}}, \quad (28)$$

$$A_2 = \frac{P_{XH_2^+}}{1 + 10^{pH-pK_{a1}} + 10^{2pH-pK_{a2}-pK_{a1}}}. \quad (29)$$

The experimental methods used to estimate the lipophilicity parameters have been described in detail in reviews.^{197–199}

Lipophilicity can be calculated using several schemes, for example, based on the additivity of the contributions of lipophilic constants of atoms²⁰⁰ or fragments^{202, 202} or using conformationally dependent approaches,^{203, 204} molecular descriptors²⁰⁵ and various solvatochromic parameters.²⁰⁶ The octanol–water partition of compounds is mainly governed by two factors — the molecular volume and the capacity of molecules to form hydrogen bonds.^{207, 208}

The contribution of the molecular volume to the lipophilicity has been described quantitatively^{209, 210} using several descriptors such as molecular weight MW, molecular volume MV, total molecular surface area SA, the integral of the van der Waals interaction spectra VWI, molecular refraction MR and molecular polarisability α . To describe quantitatively the contribution of hydrogen bonds, free energy factors for hydrogen bond donors and acceptors C_d and C_a were employed, which are considered in greater detail below. Since the descriptors corresponding to the contribution of the molecular volume are correlated with one another, only one of them can be included in the regression equation. The best result was obtained by using the polarisability and the sum of the factors for the hydrogen bond acceptor capacity [see the Appendix, Eqn (A.14)]. This approach to the quantitative description of the lipophilicity makes it possible to estimate the contributions of polarisability and hydrogen bonding acting in the opposite directions and thus to modify the structure of compounds in order to optimise their properties. Table 1 presents the values for lipophilicity of some chemicals determined experimentally and calculated by Eqn (A.14) and the contributions to the lipophilicity of the two parameters mentioned above.

Analysis of numerous computer programmes meant for the calculation of $\log P$ (see^{211–213}) demonstrated that they provide satisfactory accuracy in the calculation of the lipophilicities of

simple neutral organic compounds but in the case of complex compounds, especially medicines, the accuracy is fairly low. This may be due to the fact that most of the calculations are based on the additivity of the logarithms of the contributions of atoms and fragments rather than on an accurate additive scheme for the contributions of the octanol (oct)–water partition coefficients of compounds. In addition, only a few experimentally determined lipophilicities of compounds containing several cationic and/or anionic groups have been published. Meanwhile it is these data that could provide the basis for precise calculations of the lipophilicities of complex ionised compounds.

The application of Eqn (A.14) to the calculation of $\log P_{oct}$ values for various neutral organic compounds has resulted in the following expression

$$\log P_{oct}(\text{exp.}) = 1.00 (\pm 0.02) \log P_{oct}(\text{calc.}), \quad (30)$$

$$N = 2781, R = 0.971, S = 0.32 \text{ (see } \S \text{)}.$$

Comparison of the lipophilicities calculated from Eqn (A.14) with those determined experimentally for compounds that had been tested with 14 appropriate commercial programmes gave the following results: for 90 simple organic compounds, $R = 0.993$; for 48 medicines, $R = 0.935$ and for all the 138 chemicals tested, $R = 0.971$. These statistical criteria are commensurable with those attained in the best of the programmes tested. This outcome, together with the possibility of calculating the full pH-dependent profile for ionised compounds, attests to the value of the above-mentioned physico-chemical approach to the estimation of lipophilicity.

In recent years, in addition to the above 'classical' descriptors, another descriptor called molecular lipophilicity potential (MLP),^{214–218} which quantitatively describes lipophilicity in three-dimensional space, has been widely used. The lipophilicity potential at a given point in space is a result of intermolecular interactions governed by the lipophilicity of all fragments of the molecule. Two components are needed to calculate the lipophilicity potential, namely, the fragment lipophilicities and a function of distance describing the variation of lipophilicity in space²¹⁴

$$MLP_k = \sum_{i=1}^N f_i f_{ct}(d_{ik}), \quad (31)$$

where k is the label for a given point in space, i is the label of the fragment, N is the total number of fragments in the molecule, f_i is the lipophilicity constant for fragment i , f_{ct} is the distance function and d_{ik} is the distance between fragment i and point k in space.

A large number of examples in which the lipophilicity parameters have been used successfully as intermolecular interaction descriptors in the elucidation of structure–property correlations have been reported in a book¹⁸⁴ and in papers.^{214–224} Examples of using $\log P_{oct}$ in structure–property (activity) regression equations are given in the Appendix [Eqns (A.14)–(A.16)].

It should be noted that the majority of procedures used to calculate both descriptors of intermolecular interactions and energies of reactions are based on the assumption of additivity of contributions of various types of intermolecular interactions¹⁷⁵

$$\Delta G = \Delta G_{\text{solvent}} + \Delta G_{\text{conf}} + \Delta G_{\text{int}} + \Delta G_{\text{motion}}, \quad (32)$$

where $\Delta G_{\text{solvent}}$ is the solvent contribution, ΔG_{conf} is the change in the free energy caused by conformational changes in the reacting molecules, ΔG_{int} is the change in the free energy due to specific interactions and ΔG_{motion} is the change in the free energy of the molecule caused by changes in the translational, rotational and vibrational constituents.

‡ From here on, N , S and R are statistical criteria of equations: N is the number of observations, S is the standard deviation and R is the correlation coefficient; the Fischer criterion F is also used.

Table 1. Experimental and calculated values for lipophilicity and polarisability and acceptor capacity contributions in the formation of hydrogen bonds.²¹⁰

Compound	$\sum C_a$	α	$\sum C_d$	α	$\log P$	
					calculation	experiment
Chloracetamide	3.80	8.00	−2.57	1.99	−0.59	−0.53
Acetaldehyde oxime	2.64	5.59	−1.79	1.39	−0.41	−0.12
Ethanolamine	4.16	6.43	−2.82	1.60	−1.23	−1.30
Nicotinamide	5.88	13.19	−3.98	3.28	−0.71	−0.37
Hydroquinoline	3.00	11.32	−2.04	2.82	0.77	0.59
Dimethyl sulfite	1.50	10.44	−1.02	2.60	1.57	1.77
Acyclovir	10.90	21.44	−7.39	5.34	−2.06	−1.52
Sephopyrazone	24.10	60.97	−16.34	15.18	−1.17	−0.84
Fluorouracil	5.78	10.32	−3.92	2.57	−1.36	−0.85
Hydroflumethiazide	9.31	25.16	−6.31	6.26	−0.06	0.04
Paracetamol	5.49	16.01	−3.72	3.99	0.26	0.64
Warfarin	7.41	32.83	−5.02	8.17	3.14	2.47

Specific interactions are calculated on the assumption that the contributions of various types of interaction obey the additivity principle. At present it is believed that the greatest contributions to the specific interactions are made by steric (st) and electrostatic (el) effects and hydrogen bonds (hb). Within the framework of this assumption, the free energy of specific interactions can be represented as follows:²²⁵

$$\Delta G_{\text{int}} = \Delta G_{\text{st}} + \Delta G_{\text{el}} + \Delta G_{\text{hb}}. \quad (33)$$

Below we consider the parametrisation of these three types of specific interactions, analyse the existing descriptors and describe computer programmes used to calculate the energies of these interactions.

1. Parametrisation of steric effects

The first steric parameter E_s was proposed by Taft.²²⁶ When studying the reactivity of esters, he obtained the following relation:

$$E_s = \log \frac{k_R}{k_{\text{Me}}}, \quad (34)$$

where k_R and k_{Me} are the rate constants for hydrolysis of the compounds R^1COOR^2 and MeCOOR^3 , respectively. It is assumed that the inductive and electronic effects have no influence on the system under consideration. Tables containing refined E_s values are presented in the study cited. Examples of successful use of this steric parameter can be found in the literature.^{15, 184}

In the simplest case, steric effects can be characterised by van der Waals radii. Empirical steric parameters based on these radii have been developed in greater detail by Charton.^{182, 227, 228} The one-parameter method, which is the simplest among those proposed by this researcher, uses steric parameter v , which depends on the van der Waals radii and expresses the steric effect of the first atom in the substituent. In the case of atomic groups having different substituents at the atoms through which the hindered internal rotation axis passes, it is proposed to describe steric effect either by sets of effective steric parameters for certain reactions or by branching equations, which are empirical in their character.

Note that the empirical approach developed by Charton involves many simplifications and requires introduction of additional empirical constants and coefficients when considering new sets of compounds.

The Lennard–Jones potential takes into account the steric constituent of the total energy of an interaction E_{1j} , which is represented as a combination of the attraction and repulsion forces²²⁵

$$E_{1j} = \frac{A}{d^{12}} - \frac{B}{d^6}, \quad (35)$$

where d is the distance between a pair of non-bonded atoms. When d is small, the term A/d^{12} accounts for the predominance of the repulsion forces and, as a consequence, positive E_{1j} values. When d is large, the term B/d^6 is greater. The minimum E_{1j} value corresponds to the optimum distance between a pair of non-bonded atoms. The Lennard–Jones potential can be used as a self-contained descriptor of intermolecular interactions and also as a measure of the contribution of steric interactions to the total interaction energy. In particular, it has been shown that for a series of substituted esters of acetic acid, a steric descriptor based on the Lennard–Jones potentials is well correlated with the Taft parameter E_s .

2. Description of electrostatic interactions

Electrostatic interactions are described using the Coulomb's law for point charges located on atoms and using standard molecular-mechanics approaches.¹⁷⁵

When comparing the capacity of molecules for electrostatic interactions $V(R_i)$, molecular electrostatic potential (MEP) is used

almost always; this parameter can be calculated at each point R of the space surrounding the molecule²³⁰

$$V(R_i) = - \int \frac{\delta(R)}{|R_i - R|} dr + \sum \frac{Z_l}{|R_i - R_l|}, \quad (36)$$

where $\delta(R)$ is the electron density, r is the distance, Z_l are the charges of the nuclei and R_l are the coordinates of the nuclei in the molecule. The results of the calculations of MEP can be represented graphically as maps. Comparison of the MEP maps for a number of compounds having the same type of activity (examples of these studies can be found in Refs 231–235) may prove useful for judging the character of specific electrostatic interactions of these compounds with a biological target exhibiting the given type of activity. However, it should be borne in mind that visual comparison is subjective.

In recent years, formal approaches based on comparison of quantum-chemical parameters related to electrostatic interactions have been vigorously developing. First of all, molecular quantum similarity measures (MQSM) should be mentioned.^{236–239} According to this approach, quantum-chemical similarity of two molecules is identified by considering the electron density functional $Z_{AB}(\Omega)$

$$Z_{AB}(\Omega) = \int \rho_A(\mathbf{r}_1) \Omega(\mathbf{r}_1, \mathbf{r}_2) \rho_B(\mathbf{r}_2) d\mathbf{r}_1 d\mathbf{r}_2, \quad (37)$$

where $\rho_A(\mathbf{r}_1)$ and $\rho_B(\mathbf{r}_2)$ are the electron densities of molecules A and B, and Ω is a positively defined operator. Various operators can be chosen. It is convenient to present the operator in the form

$$\Omega(\mathbf{r}_1, \mathbf{r}_2) = \delta(\mathbf{r}_1 - \mathbf{r}_2), \quad (38)$$

which transforms the integral in Eqn (37) into an integral of the product of density distributions in the given pair of molecules.

$$Z_{AB} = \int \rho_A(\mathbf{r}) \rho_B(\mathbf{r}) d\mathbf{r}. \quad (39)$$

If molecules A and B being compared are identical, we obtain a self-similarity measure

$$Z_{AA} = \int \rho_A^2(\mathbf{r}) d\mathbf{r}. \quad (40)$$

The self-similarity measure is used to construct similarity indices, which can be regarded as normalised values of MQSM. The Carbo index was the first similarity index to be proposed²⁴⁰

$$C_{AB} = \frac{Z_{AB}}{(Z_{AA} Z_{BB})^{1/2}}. \quad (41)$$

This value ranges from zero (for comparison of dissimilar molecules) to unity (when the molecules are identical). Examples of using the Carbo index for elucidation of similarity of electronic structures have been reported.^{241–244}

3. Quantitative description of the ability of compounds to form hydrogen bonds

Hydrogen bonding plays a crucial role in the formation of many molecular and ionic complexes in important chemical and biological processes including enzymic catalysis. The most glaring example demonstrating the significant role of hydrogen bonding in biological systems can be found in a monograph²⁴⁵ in the description of DNA replication. This process is accompanied by a new binding of purine and pyrimidine bases *via* the formation of two (binding of adenine with thymine) or three (binding of guanine with cytosine) hydrogen bonds. Even a rather rough calculation of the free energy difference for this complexation, carried out by Pauling (it was assumed that one hydrogen bond provides an energy benefit of 20 kJ mol^{−1}), demonstrated that this system of hydrogen bonds ensures a ratio of the numbers of 'correct' and 'false' recognitions equal to ten million to one!

Despite this important role of hydrogen binding in the formation of the properties of substances, until recently this intermolecular interaction has been taken into account mainly at the level of an indicator variable.^{12, 13, 246–248} Therefore, in this review it is pertinent to discuss the quantitative approaches to the description of hydrogen bonding in detail.

According to Eqn (14), full thermodynamic description of a hydrogen bond requires a pair of parameters, namely, enthalpy and entropy or enthalpy and free energy. Four combinations of the changes in the enthalpy (ΔH) and the entropy (ΔS) are possible.^{249–252} Note that in the majority of studies devoted to hydrogen bonding in complexes, the change in the entropy is either totally neglected or considered to be proportional to the enthalpy change. The roughness of this approach becomes clear from the examples given in a review.²⁵¹

The development of the empirical scales of hydrogen bonding based on the experimental values of thermodynamic parameters started in the 1960s. Let us consider two approaches, the additive-multiplicative and multiplicative ones. In the additive-multiplicative method, the enthalpy change accompanying the formation of a hydrogen bond is described by six parameters^{253–255}

$$-\Delta H_{\text{hb}} = e_A e_B + c_A c_B + t_A t_B, \quad (42)$$

where e is a parameter reflecting the electrostatic contribution, c is a parameter related to the covalent interaction, t is a parameter describing the charge transfer and indices A and B correspond to Lewis acids (hydrogen bond donors) and bases (hydrogen bond acceptors), respectively. Most of studies dealing with the structure–biological activity correlations present no exact data on the molecular structure of one partner of the interaction (*e.g.*, receptor, biological target). This fact hampers the use of Eqn (42). The method describing the thermodynamic parameters of hydrogen bonds based on the multiplicative approach is more widely distributed. The enthalpy of the hydrogen bond is described by the equation²⁵⁶

$$\Delta H_{ij} = \Delta H_{11} P_i E_j, \quad (43)$$

where ΔH_{11} is the enthalpy change upon the formation of a hydrogen bond between phenol and diethyl ether (standard hydrogen bond partners) in tetrachloromethane,[§] P_i is a dimensionless factor for an i th hydrogen bond donor and P_j is a factor for a j th hydrogen bond acceptor.

The change in ΔH_{ij} can also be described using the donor (E_d) and acceptor (E_a) factors for the enthalpy of a hydrogen bond, which have opposite signs^{92, 257}

$$\Delta H_{ij} = \Delta H_{11} E_d E_a. \quad (44)$$

The E_d and E_a values for various neutral and ionised compounds have been estimated.^{258–270}

Similar equations have been proposed to describe the change in the free energy (ΔG) upon the formation of a hydrogen bond^{271, 272}

$$\Delta G = a C_d C_a + a_0, \quad (45)$$

where a and a_0 are coefficients and C_d and C_a are the donor and acceptor factors for the free energy of the hydrogen bond; and to describe the complex formation constant for hydrogen bonding^{273–276}

$$\log K = b \alpha \beta + b', \quad (46)$$

where b and b' are coefficients and α and β are the donor and the acceptor factors for the hydrogen bond formation constants. Taft *et al.*²⁷⁷ have estimated a large number of β values for phosphoryl compounds based on the data of several publications.^{261–263} With

§ Most of the experiments on the thermodynamics of hydrogen bonding have been carried out in tetrachloromethane. This solvent is non-polar and therefore convenient for determining the values of the thermodynamic factors described below.

allowance for the relationship between the change in the free energy and the constants [see Eqn (15)], it is obvious that the difference between Eqns (45) and (46) reduces to the factor $2.302RT$. In the case where the same array of experimental data is considered and the same method is used to estimate the hydrogen bond parameters, there should be a strict correlation between C_d and α and between C_a and β . No general correlation has been found between E_d and C_d or between E_a and C_a ; however, these correlations do exist for separate groups of compounds.²⁷²

Development and successful use of the empirical approaches described above are possible only when the set of experimental data on the thermodynamics of hydrogen bonds is being extended. A detailed description of an extensive set of data of this type has been reported.²¹⁰ The C_a and C_d values were calculated by selecting 414 hydrogen bond donors and 1298 hydrogen bond acceptors for which experimental thermodynamic parameters for interaction with several partners were available.²⁵¹ The matrix generated consisted of 414 columns and 1298 rows. This permitted rigorous calculations of the C_a and C_d values.

The factors for the free energy of hydrogen bonding for some compounds are presented below

Compound	C_d	Compound	C_a
CF ₃ COOH	−4.78	CCl ₃ CN	0.55
CCl ₃ COOH	−4.75	C ₄ H ₉ Cl	0.60
CHCl ₂ COOH	−4.28	C ₆ H ₅ OCH ₃	1.07
3,5-(NO ₂) ₂ C ₆ H ₃ OH	−4.09	CH ₃ OH	1.76
C ₆ F ₅ COOH	−3.82	CH ₃ C(O)CH ₃	1.92
3-NO ₂ C ₆ H ₄ OH	−3.49	(CH ₃) ₂ SO ₂	2.01
(CF ₃) ₂ CHOH	−3.31	C ₃ H ₅ N	2.45
CF ₃ C(O)NHC(O)CF ₃	−2.98	(C ₂ H ₅) ₃ N	2.57
C ₆ H ₅ OH	−2.50	(CH ₃) ₂ NC(O)N(CH ₃) ₂	2.96
CH(CN) ₂ Br	−2.06	(CH ₃) ₂ SO	3.13
4-NO ₂ C ₆ H ₄ NH ₂	−1.82	(C ₆ H ₅) ₃ PO	3.65
CH ₃ C(O)SH	−1.62	[(CH ₃) ₂ N] ₃ PO	4.00
C ₂ H ₅ OH	−1.42	(C ₄ H ₉) ₂ NO	4.25
C ₆ H ₅ NH ₂	−1.04		
CHCl ₃	−0.81		
2-CH ₃ C ₆ H ₅ NH ₂	−0.50		
C ₂ H ₅ SH	−0.24		
C ₆ H ₅ ≡CH	−0.12		

It should be emphasised that the limits of variation of the factors for the free energy of hydrogen bonding for functional groups overlap (Table 2). This indicates that substituents at a donor or acceptor atom play an exceptionally important role in the formation of the capacity of these atoms for hydrogen bonding.

Comparison of the experimental values for enthalpy and free energy with the values calculated using Eqns (44) and (45) proves

Table 2. Minimum and maximum free energy factors for hydrogen bonds for various functional groups.

Hydrogen bond donors	$C_d^{\min}$	$C_d^{\max}$	Hydrogen bond acceptors	$C_a^{\min}$	$C_a^{\max}$
R ¹ R ² R ³ C—H	−2.06	−0.12	R—O—R	0.78	2.01
RS—H	−1.92	−0.24	R—S—R	0.57	1.51
R ¹ R ² N—H	−3.32	−0.50	R ¹ R ² R ³ N	0.58	3.65
PhO—H	−4.24	−0.76	RC≡N	0.55	2.77
AlkO—H	−3.50	−1.06	R ¹ R ² R ³ P=O	2.40	4.02
RC(O)O—H	−4.78	−2.50	R ¹ R ² S=O	1.16	3.25

the adequacy of the multiplicative approach to the quantitative description of the thermodynamics of hydrogen bonding²⁵¹

$$\Delta H(\text{calc.}) = -0.49 (\pm 0.29) + 0.99 (\pm 0.08) \Delta H(\text{exp.}), \quad (47)$$

$$N = 2787, R = 0.970, S = 2.40, F = 44350,$$

$$\Delta G(\text{calc.}) = -0.07 (\pm 0.12) + 1.04 (\pm 0.05) \Delta G(\text{exp.}), \quad (48)$$

$$N = 3301, R = 0.991, S = 1.12, F = 175000.$$

In the case where charge transfer makes a significant contribution to the hydrogen bond in a particular complex, the values calculated in this way may deviate from experimental results.²⁷⁸

Using the known C_d values for 414 hydrogen bond donors and C_a values for 1298 hydrogen bond acceptors, one can calculate ΔG_{hb} for 537 372 hydrogen-bonded complexes. When a similar approach was used to calculate the constants of formation of hydrogen bonds, the α values for 150 hydrogen bond donors and the β values for 500 hydrogen bond acceptors were determined; this permitted the calculation of K_{hb} for 75 000 complexes.²⁷⁹

A whole series of descriptors have been proposed for the multiplicative description of the thermodynamic parameters of a hydrogen bond, including the donor and acceptor factors for the hydrogen bond free energy and enthalpy for the strongest donor and acceptor sites in a molecule ($C_a^{\text{max}}, C_d^{\text{max}}, E_a^{\text{max}}, E_d^{\text{max}}$), the sum of the free energy and enthalpy factors over all the donor and acceptors sites in a molecule ($\sum C_a, \sum C_d, \sum E_a, \sum E_d$) and the four last-mentioned descriptors divided by the molecular weight ($\sum C_a/\text{MW}, \sum C_d/\text{MW}, \sum E_a/\text{MW}, \sum E_d/\text{MW}$).^{280, 281} These descriptors have been used to model the structure–property relationships in complex processes such as complex formation,^{91, 282–286} solubility in water,²¹⁰ lipophilicity,²¹⁰ inhibition of cholinesterase,^{287, 288} inhibition of dopamine back capture,²⁸⁹ determination of the boiling points of hydrocarbons and acids,²⁹⁰ insecticide activities of nitrogen and phosphorus organic compounds,²⁹¹ ionophoric activity of macrocycles,²⁹² fungicidal activity of phenols and β -adrenergic activity of alicyclic acids and phenols,²⁹³ toxicity against *Golden orfe fish*²⁹⁴ and permeability of biological membranes.^{210, 295} Descriptors based on α and β factors have been described in a review.²⁷⁹ Similar indices for hydrogen bonding have been reported in one more study.²⁹⁶

VIII. Indicator descriptors

Indicator descriptors (sometimes called *de novo* constants) have found fairly wide use in modelling the structure–property (activity) relationships. It is difficult to classify these descriptors into any particular class because they can encode in an implicit form various structural features of compounds (properties of hydrogen bond donors and acceptors, the presence or absence of hydrogen bonds within the molecules, *ortho*-effects, *cis*–*trans* isomerism, stereoisomerism, various fragments, *etc.*).

The expediency of using indicator variables in some cases has been demonstrated in a review.²⁹⁷ Thus for two sets of papain ligands, similar two-parameter relations were obtained [see the Appendix, Eqns (A.7) and (A.8)], having fairly close coefficients at MR and σ but substantially different constant terms. By combining these equations and by using the indicator variable I ($I = 1$ for mesylamides and $I = 0$ for benzamides), the researchers derived a common relation applicable to both series [see the Appendix, Eqn (A.24)].

Other examples of using indicator descriptors can also be found in the literature.^{298, 299}

Indicator descriptors are especially useful at initial stages of investigations. These descriptors can be used for tentative combinations of compounds to give various subsets of compounds with a particular property, which is needed to form a training set meant for the modelling of the structure–property relationship based on a more extensive structure description.

In analyses of the structure–biological activity relationships, various physico-chemical molecular properties or experimental

parameters obtained by various physical methods are often used as structure descriptors.¹⁵ The use of physicochemical properties as descriptors has been discussed in the preceding Sections. A more detailed discussion of these descriptors can be found in the literature.³⁰⁰

IX. Modern computer software for the calculation of descriptors

At present the market of computer software meant for chemistry and, in particular, for molecular design is filled by diversified programme products. Therefore, to be competitive, every new programme must have obvious novelty elements or obvious advantages over other programmes.

1. MOLSURF is a generator of chemical descriptors for QSAR.¹⁹³ This programme has three distinctive features.

Firstly, it is assumed that a researcher prefers describing molecules using chemical terms such as hydrogen bonds, nucleophiles, electrophiles, bases, acids, hydrophobicity, polarisability, π -interaction, *etc.* rather than using quantum-chemical terms (HOMO, LUMO, electrostatic potential, force fields, *etc.*). Therefore, the MOLSURF programme calculates the descriptors related the above chemical notions.

Secondly, the programme is based on correlations of the calculated values of descriptors with experimental data.

Thirdly, the programme prefers descriptors of substituents to molecular descriptors, because the former reflect more accurately the variation of properties upon structure modification and because their values can be calculated more precisely.

2. The calculations and the use of theoretical descriptors within the framework of the concept of linear correlations of free energy have been described in a number of publications.^{301–306} In this fairly simple approach, a property is described by regression equations containing descriptors related to steric interactions, polarisability and hydrogen bonding as independent variables. The steric interactions are estimated quantitatively using the van der Waals volumes V_{mc} . A descriptor called polarisability index (π) is defined as polarisability divided by volume. To describe hydrogen bonds, the researchers distinguish two constituents, the acidic and basic ones. Each constituent is divided in turn into covalent and electrostatic components. The covalent contribution is assumed to be determined by the energy of the highest occupied molecular orbital (HOMO). The electrostatic contribution to the basicity is characterised by the formally most negative atomic charge (q_-) in the molecule (it is assumed that the most negative atom should interact most efficiently with the proton in a neighbouring molecule). The covalent component in the acidic constituent (ϵ_a) is characterised by the energy of the lowest unoccupied molecular orbital (the difference between the LUMO energy of the compound and the HOMO energy of water divided by hundred). A smaller ϵ_a value points to a higher tendency to form hydrogen bonds (the ϵ_b component) with water. The contribution of the electrostatic component to the acidity is determined by the most positive charge of a hydrogen atom in the molecule (q_+).

According to this approach a property (P) can be described by the following six-parameter equation

$$\log P = \log P_0 + \frac{AV_{\text{mc}}}{100} + B\pi_1 + C\epsilon_b + Dq_- + E\epsilon_a + Fq_+. \quad (49)$$

where A, B, C, D, E and F are coefficients.

This method has been used to describe the properties and biological activity of chemical compounds and gave formally rather good results. Nevertheless, this approach seems to be based on a simplified physical model. In addition, when initialising sets are relatively small, multiparameter regression equations of this type are not stable and may lead to faulty results when used to predict the properties of compounds.

3. The CoMFA programme (Comparative Molecular Field Analysis) is currently the most widespread computer programme

used to calculate the energies of intermolecular interactions in terms of the corresponding descriptors establishing the structure–property relationships.³⁰⁷

The parameters calculated initially include the energies of steric and electrostatic interactions between the compound considered and a probe atom being placed into various points of a regular three-dimensional grid. The size of this grid should be sufficiently large to accommodate the largest molecule of the initialising set. The size of the cell in this grid is usually taken to be 2.0 Å and, in some cases, 1 Å (the smaller the grid dimensions, the larger the number of descriptors and the time it takes to calculate them). An sp^3 hybridised carbon atom with the charge +1.0 was used initially as the probe atom; later, various atoms and groups have been used (see, e.g. Ref. 308). It is clear that these calculations give an enormous number of descriptors, exceeding the number of compounds in the initialising set by a large factor. Most of the descriptors thus obtained are correlated with one another. Under these conditions, a stable model can be designed only by using a special procedure. The PLS (Partial Least Squares)³⁰⁹ method permits selection of orthogonal components. During the design of stable models, the number of these components can be optimised by calculating the correlation coefficients for predictive models, formed by the cross-validation procedure.

During the last decade, the CoMFA programme has been constantly improved. For example, several studies have been devoted to the methodological aspects of the programme development^{310, 311} (description of non-linear CoMFA, the use of various semiempirical methods for optimisation of the calculations of the geometry and the properties of compounds). The programme has been used to study many types of biological activity of various compounds, for example, the relationship between the structure of 2-hetarylquinoline-4-amines and their biological activity against HIV,³¹² the structures and steric and electronic effects of phosphorus ligands³¹³ and the structure–inhibitory activity correlations for various compounds,³¹⁴ steroid inhibitors,³¹⁵ melatonin receptor ligands³¹⁶ and calcium blocking agents.³¹⁷

However, the CoMFA programme is not free from drawbacks. First of all, it should be noted that until recently it had been unable to calculate the energies of hydrogen bonds, which play a crucial role in many biological processes. In addition, based on the parameters that act as independent variables in the final regression equation, it is hardly possible to construct any useful physical model for a structure–property relationship because these variables are linear combinations of many thousands of descriptors. Yet another drawback of this programme is that it cannot be run on a personal computer.

4. The GRID programme,²²⁵ having some common features with CoMFA, also uses atoms and functional groups of various natures as the probe atoms to estimate the intermolecular interactions with the macromolecules under study, which are put in a three-dimensional grid. It is significant that this programme, unlike CoMFA, takes into account not only steric and electrostatic interactions but also hydrogen bonds (E_{hb}). Initially this has been done using a direction-dependent 6–4 function with a broad energy minimum^{225, 318}

$$E_{hb} = \left(\frac{C}{d^6} - \frac{D}{d^4} \right) \cos^m Q, \quad (50)$$

where Q is the DHP angle (D is the donor atom of the protein, H is a hydrogen atom and P is the probe electron-withdrawing atom); m is usually taken to be 4.

If the interaction involves two identical atoms, the interatomic separation d_{min} is determined by tabulated values for C and D . If different atoms interact, the geometrical mean of their individual D values and the arithmetic mean of their separations (d_{min}) are used. Later, the 6–4 function has been replaced by a 8–6 function.^{319–320}

$$E_r = \frac{C}{r^8} - \frac{D}{r^6}, \quad (51)$$

where r is the distance between the probe atom and some atom in the compound considered. The hydrogen bond energy is represented by the following expression:

$$E_{hb} = E_r E_\tau E_p, \quad (52)$$

where E_τ and E_p are angle functions taking account of the mutual arrangement in space of the hydrogen atom and the lone electron pair of the hydrogen bond acceptor.

The GRID programme has been used successfully to design models of various biological receptors.^{321–327}

5. As an alternative to the CoMFA and GRID programmes, approaches reflecting a three-dimensional structure and the capacity for intermolecular interactions as a spectrum of interatomic distances or interatomic interactions can be considered.^{251, 270, 328–340} In these cases, a molecular structure is represented as a radial scattering curve, which can be constructed for a molecule of any complexity provided that its Cartesian coordinates are known. A similar approach is employed in gas phase electron diffraction studies of molecular structures. The radial distribution function $[M(s)]$ in the spherical approximation for atoms i and j and in the absence of intramolecular vibrations is a spectrum of interatomic distances, the intensity of the spectrum being determined by the natures of the atoms spaced at a given distance and by the dynamics of the variation of this distance during intramolecular vibrations

$$M(s) = \sum_{i=1}^N \sum_{j>i}^N C_{ij} \frac{\sin sr_{ij}}{sr_{ij}}, \quad (53)$$

where C_{ij} is a coefficient characterising the scattering capacity of this pair of atoms, s is an angle parameter: $s = (4\pi/\lambda)\sin(Q/2)$ (λ is the electron wavelength and Q is the scattering angle) and r_{ij} is the interatomic distance in the molecule.

It can be said that the radial distribution function obtained in an electron diffraction experiment is the pattern ‘seen’ by an electron interacting with the molecule in a scattering event. This analogy has been extended to the case where a receptor interacts with molecules of a substance administered into an organism.³²⁸ It is known that a receptor interacts with parts of the molecule that are complementary to the active sites of the receptor rather than with the whole molecule. The governing factors are the distances between the active sites and the susceptibility to intermolecular interactions of the atoms located at these distances from one another in the reagent molecules. A sort of scattering of the reagent molecules on the active sites of the receptor occurs, i.e. the receptor ‘sees’ the molecule as a radial distribution function. In this approach, the radial distribution function can be modified in such a way as to take into account quantitatively the ability of atoms of the reagent to undergo various intermolecular interactions. This approach was embodied in some studies^{251, 340} and in the MOLTRA (Molecular Transform Analysis) programme package, which can be used to calculate the spectra for the steric interactions of atoms; interactions of positively charged atoms with one another, negatively charged atoms with one another and positively charged atoms with negatively charged atoms; interactions of hydrogen bond donors with one another, hydrogen bond acceptors with one another and hydrogen bond donors with hydrogen bond acceptors. Each of these spectra is a superposition of bands corresponding to pairs of atoms in the molecule. The positions of the band maxima are matched by the equilibrium distances between these atoms and the areas below the band contours are proportional to the products of the given local properties for a given pair of atoms.

Figure 4 shows the spectra for the interactions of hydrogen bond acceptors in some macrocyclic polyethers. Each point in the spectra presented can be considered as a descriptor of intermolecular interactions describing the interaction of hydrogen bond

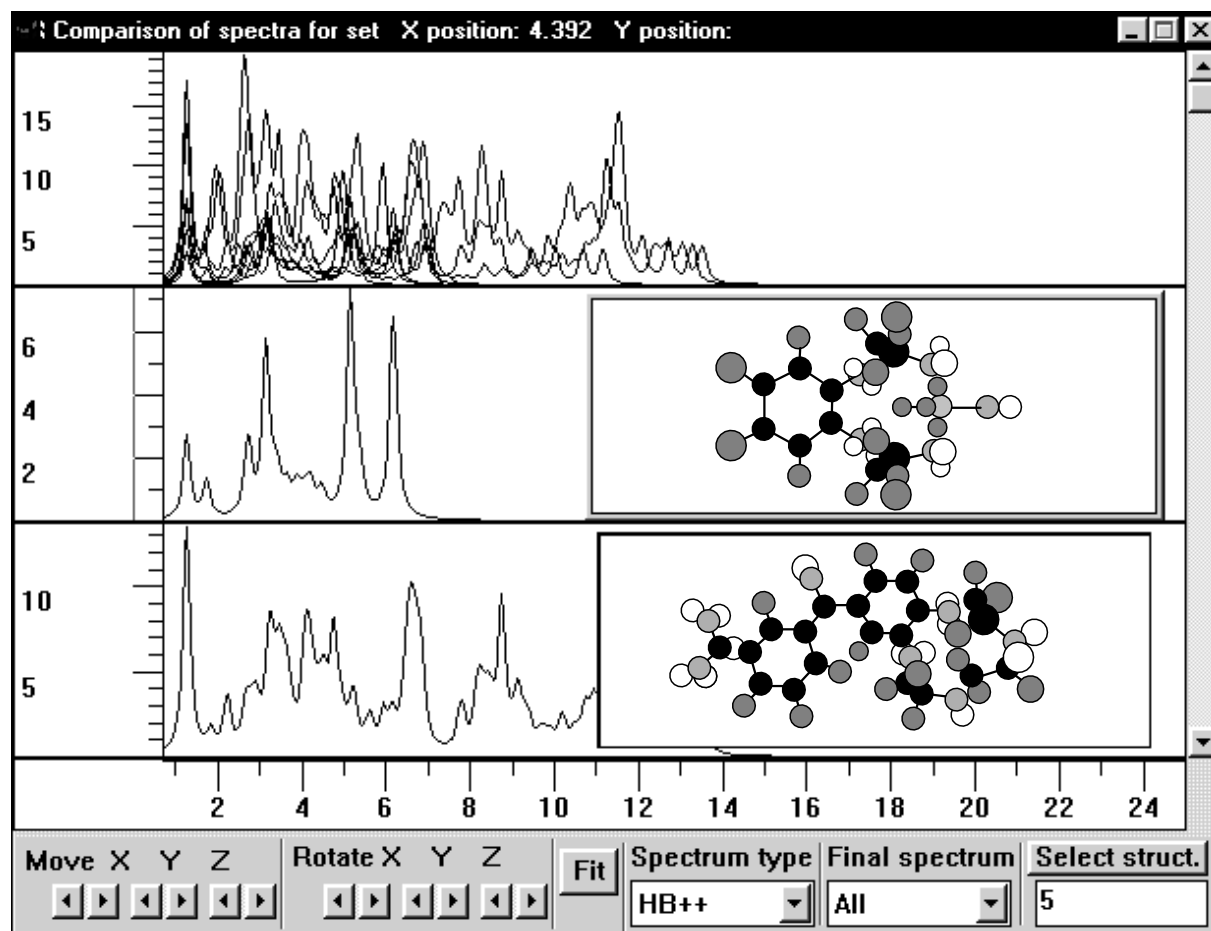


Figure 4. General view of the spectrum of interactions of hydrogen bond acceptors in some macrocyclic polyethers.

acceptors located at a given distance. For distances ranging from 1.1 to 20.0 Å and with a step of 0.1 Å, each spectral pattern provides 190 descriptors. Seven spectral patterns permit the description of the possible steric and Coulomb interactions and hydrogen bonds in terms of 1340 descriptors.

X. The necessary properties of descriptors

A great number of descriptors have been reported by now. It is clear that the extension of the views on molecular structure stimulates the design of new structure models and new descriptors reflecting these views. The attempts of developing new descriptors which, having been introduced in computer programmes, would preserve and utilise the information on the molecular structure better than the earlier descriptors are also justified.

Nevertheless, the introduction of new descriptors is expedient only in two cases — either when none of the existing descriptors or their combination provides the elucidation of stable structure–property correlations for the training set used or when the new descriptor ensures a substantial improvement of the statistical criteria of the model.⁹

New descriptors should be readily calculable, convenient to use and versatile; they should ensure comprehensive description of a given structural feature and be interpretable.³⁴¹

Unfortunately, the above requirements are by far not always taken into account.

The efficiency of descriptors of various classes used in establishing the structure–biological activity correlations becomes clear upon comparison of the statistical criteria of the models designed using these descriptors. For example, Raevsky *et*

al.^{290, 293} compared the models for classification of agonists and antagonists among substituted phenylethylamines based on a number of topological and physico-chemical descriptors using linear discriminant analysis, a discrete regression model²⁹⁰ and significant cluster analysis.³⁴² In all of these types of classification, the best results were attained by using hydrogen bond descriptors. Other examples can also be found in the literature.^{14–16, 337, 343, 344}

In this review, the descriptors were introduced in the order of increasing amount of information on the molecular structure contained in them. However, this does not mean that the use of a more informative descriptor guarantees better results in elucidation of the structure–property correlations. Indeed, there are many examples of successful employment of topological descriptors for the calculation of the melting and boiling points, evaporation enthalpies and other ‘simple’ physical properties within narrow series of related compounds, which differ, for example, in the length of the chain in the alkyl substituent. In these cases, the statistical criteria of regression equations containing more informative descriptors as independent variables prove sometimes to be inferior to those for equations based on simpler descriptors, because the magnitudes of more informative descriptors are estimated with lesser accuracy and because they carry ‘excessive’ information for the set considered. The foregoing leads to the following conclusions: it is expedient to use combinations of known descriptors with different information contents; it is useful to develop new descriptors and perfect the procedures to attain more precise calculations of all descriptors; well-founded selection of descriptors for a particular set of compounds is necessary.¹

Note that comprehensive description of a molecular structure cannot be attained in terms of any single descriptor. One descriptor can predominantly take into account one feature of

the electronic or steric structure or one type of intermolecular interactions. For this reason, description of a molecular structure using several descriptors and construction of structure–property models based on several independent variables appears expedient.

In the construction of structure–biological activity models, the modern views on the processes occurring in an organism with participation of chemical compounds play an important role in the selection of appropriate descriptors. For example, it is currently believed that the complex mechanism of action of a substance on an organism consists of three stages — pharmacologic, pharmacokinetic and pharmacodynamic stages.³⁴⁵ The pharmacologic stage is associated with the administration of a substance into an organism and includes disintegration of the preparation. The pharmacokinetic stage is determined by the transport of the substance from the administration site to the particular biological target and includes the processes of absorption, distribution, metabolism and excretion. At this stage, the reactivity of the initial compounds and their capacity for complex formation are important. The pharmacodynamic stage is characterised by the interaction of the initial substance or the products with biological targets responsible for the particular type of biological activity. At this stage, the three-dimensional structure of the interacting partners is the most important factor.

The exceptional popularity of the Hansch–Fujita three-parameter equation is due most of all to the fact that it uses descriptors of the electronic structure (Hammett constants), steric interactions (Taft steric constants), and transport properties (octanol–water partition coefficients). At present, similar models and the corresponding equations are also used successfully in the molecular design of biologically active substances.^{346–349} For example, for a series of bicyclic compounds, an equation describing their ability to bind the muscarinic receptor based on three descriptors has been derived²¹⁰ [see the Appendix, Eqn (A.23)]. One descriptor characterises the transporting properties of the compounds, the second descriptor is related to the solubility of the compounds in water and the ability to form hydrogen bonds with the donor sites of the receptor and the third one points to the important role of the distance between two particular hydrogen bond acceptors in the formation of the substrate–receptor complex.

The development of models requires the observance of formal criteria. From the statistical viewpoint, the number of compounds considered should exceed the number of descriptors by a large factor. The information contents of the descriptors must be sufficiently large and, simultaneously, they should not correlate with one another. This can be attained by several procedures including experimental design,³⁵⁰ the SIMCA/PLS method^{351,352} and the principal component and factor analyses.³⁵³

XI. Conclusion

At present, molecular structure descriptors constitute an integral part of the majority of studies dealing with structure–property (including biological activity) correlations; they are widely used to optimise characteristics of compounds in the molecular design. The Appendix to this review presents examples of successful application of various types of descriptors for quantitative description of diverse properties and types of biological action.

It should be emphasised that the molecular structure descriptors used should finally provide the design of structure–property models, which satisfy certain requirements. These models should be consistent with the laws of Nature, be relatively simple and have a clear physical meaning; in addition, they must be stable and hence possess predictive capacity and provide the possibility of identifying the relationships that were not specified in an explicit

form when the model was developed. All these points broach one more important section of the computer-aided molecular design, namely, modelling of the structure–property relationships, and require separate discussion.

XII. Appendix

Examples of successful application of molecular structure descriptors in structure–property (biological activity) correlations are presented below.

1. Element-level descriptors

Solubility of gases in water, $\log L^w$ (see³⁵⁴).

$$\log L^w = 42.37(\pm 1.11)\text{HDCA}(2) + 0.65(\pm 0.02)[2n(\text{N}) + m(\text{O})] - 0.16(\pm 0.02)\Delta E + 0.12(\pm 0.01)\text{PCWT}^E + 0.82(\pm 0.01)N_{\text{ring}} + 2.65(\pm 0.22), \quad (\text{A.1})$$

where HDCA(2) is a hydrogen bond descriptor, $[2n(\text{N}) + m(\text{O})]$ is a descriptor characterising the number of nitrogen and oxygen atoms in the molecules of compounds studied, $\Delta E = E_{\text{LUMO}} - E_{\text{HOMO}}$, PCWT^E is an electronic topological index, N_{ring} is the number of aromatic rings; $N = 406$, $R = 0.971$, $S = 0.52$, $F = 1300$.

2. Topological descriptors

Lipophilicity of organic compounds (based on topological and information topological indices), $\log P$ (see³⁵⁵)

$$\log P = 0.19P_{10} - 1.46\text{IC}_0 + 1.09\text{CIC}_2 - 0.77\text{CIC}_3 - 1.36^6X_b + 5.34^0X^V - 3.41^1X^V + 0.55^4X^V - 0.41^3X_C^V + 1.10X_w - 0.17W - 5.60, \quad (\text{A.2})$$

$N = 219$, $R = 0.955$, $S = 0.35$, $F = 194$.

β -Blocking activity of medicines, pLD_{50} (see³⁵⁶).

$$\text{pLD}_{50} = 1.79^1\chi - 1.81^1\chi^V + 0.36^2\chi + 2.37^4\chi_p^V - 2.76^4\chi_p + 1.56, \quad (\text{A.3})$$

where χ are Kier and Hall connectivity indices; $N = 17$, $R = 0.905$, $S = 0.208$, $F = 10.1$.

3. Descriptors of the electronic structure of molecules

Binding of an estrogen receptor, pEC_{50} (see³⁵⁷).

$$\text{pEC}_{50} = 3.38(\pm 0.12)D^2 + 3.22(\pm 0.20)\text{Gap} - 44.3(\pm 1.8) \quad (\text{A.4})$$

where D is the Balaban topological index, Gap is the $E_{\text{LUMO}} - E_{\text{HOMO}}$ difference; $N = 33$, $R = 0.99$, $S = 0.30$, $F = 595.0$.

Toxicity against Daphnia magna, EC_{50} (see³⁵⁸).

$$\text{EC}_{50} = -3.63 \frac{V_{\text{mc}}}{100} - 45.8\pi + 3.71q_- - 2.0q_+ + 11.4, \quad (\text{A.5})$$

where V_{mc} is the molecular volume, π is the polarisability index, q_- is the electrostatic basicity, q_+ is the electrostatic acidity; $N = 38$, $R = 0.977$, $S = 0.37$, $F = 176$.

Fungicide activity of phosphonates, pEC_{50} (see³⁵⁹).

$$\text{pEC}_{50} = 0.296(\pm 0.124)\sum \pi - 0.047(\pm 0.012)\text{MR}(\text{R}^2) + 0.543(\pm 0.331)\sum F' + 3.556(\pm 0.215), \quad (\text{A.6})$$

where π is the hydrophobicity constant, $\text{MR}(\text{R}^2)$ is the molar refraction of the second substituent, F' is the Swain–Lupton electronic parameter; $N = 57$, $R = 0.851$, $S = 0.290$, $F = 46.32$.

Binding of papain ligands by phenyl N-mesylglycinates (see²⁹⁷).

$$\log \frac{1}{K_m} = 0.529(\pm 0.230)\text{MR} + 0.379(\pm 0.200)\sigma + \quad (\text{A.7})$$

¶ An expert can rely not only on the generally recognised views on the mechanism of formation of the property being considered but also on the knowledge not yet formalised and even on intuition.

+ 1.877(±0.130),
where σ is an electronic constant; $N = 13$, $R = 0.935$, $S = 0.105$,
 $F = 34.51$.

Binding of papain ligands by phenyl N-benzoylglycinates (see²⁹⁷).

$$\log \frac{1}{K_m} = 0.771(\pm 0.670)MR + 0.728(\pm 0.370)\sigma + \quad (\text{A.8})$$

$$+ 3.623(\pm 0.340),$$

$N = 7$, $R = 0.971$, $S = 0.148$, $F = 32.85$.

4. Molecular shape descriptors

Inhibition of ligand binding, pIC₅₀ (see³⁶⁰).

$$\text{pIC}_{50} = 10.25(\pm 0.97)V + 1.43(\pm 0.56), \quad (\text{A.9})$$

where V is the shape index; $N = 26$, $R = 0.912$, $S = 0.462$,
 $F = 111.1$.

Sweetness of aniline derivatives, logRS (see³⁶¹).

$$\log RS = 0.52L - 1.37W1 + 3.71, \quad (\text{A.10})$$

where L and $W1$ are STERIMOL parameters; $N = 20$, $R = 0.90$,
 $S = 0.32$.

Psychomimetic activity of phenyl-2-aminopropane derivatives, logMU (see³⁶²).

$$\log MU = 1.99(\pm 0.13) - 1.78(\pm 0.17)MTD + \quad (\text{A.11})$$

$$+ 0.93(\pm 0.10)S_3 - 0.77(\pm 0.12)q_4,$$

where MTD is the minimum topological difference, S_3 is the
electron topological index for the atom with number 3 in the
benzene ring, q_4 is the charge on atom 4 of the benzene ring;
 $N = 49$, $R^2 = 0.885$, $S = 0.241$, $F = 84.7$.

Inhibition of hepatic receptors, pEC₅₀ (see¹⁶⁹).

$$\text{pEC}_{50} = 0.447Tm + 0.242Ts - 0.158Vu + 2.361, \quad (\text{A.12})$$

where Tm , Ts and Vu are WHIM descriptors; $N = 71$, $R = 0.914$,
 $S = 0.64$.

Inhibition of photosystem II, pIC₅₀ (see³⁶³).

$$\text{pIC}_{50} = 1.081 \log P - 0.57\sigma(Y, Al) + 0.29L(Y, Al) - \quad (\text{A.13})$$

$$- 0.95T(Y, Al) - 2.21T(Y, Ar) - 0.32W(X) +$$

$$+ 1.02I_u + 8.16,$$

where Y and X are substituents, Al is alkyl, Ar is aryl, L , W and T
are shape descriptors, I_u is an indicator variable (1 for urea
derivatives and 0 for all other compounds); $N = 69$, $R = 0.921$.

5. Intermolecular interaction descriptors

Lipophilicity of various compounds, logP (see²⁰⁹).

$$\log P = -0.01(\pm 0.08) + 0.249(\pm 0.005)\alpha - \quad (\text{A.14})$$

$$- 0.68(\pm 0.02)\sum C_a,$$

where α is the molecular polarisability, $\sum C_a$ is the sum of the
factors for the hydrogen bond acceptor capacity; $N = 234$,
 $R = 0.961$, $S = 0.34$, $F = 1383$.

Effect of protein binding, log HSAI (see³⁶⁴).

$$\log HSAI = 0.59(\pm 0.03)\log P + 0.27(\pm 0.08), \quad (\text{A.15})$$

$N = 57$, $R = 0.92$, $S = 0.28$, $F = 283$.

Toxicity against Daphnia, log(1/IC₅₀) (see³⁶⁵).

$$\log \frac{1}{IC_{50}} = 0.809 \log P + 1.64, \quad (\text{A.16})$$

$N = 23$, $R^2 = 0.84$, $S = 0.30$, $F = 118$.

Bactericidal activity, pMIC (see³⁶⁶).

$$\text{pMIC} = -0.35 \text{pK}_a + 0.68, \quad (\text{A.17})$$

$N = 8$, $R = 0.973$, $S = 0.063$.

Ligand-receptor binding, ΔG (see³⁶⁷).

$$\Delta G = 0.06(\pm 0.01)E_L - 0.05(\pm 0.02)\Delta E_{\text{solv}} + 7.74(\pm 0.57), \quad (\text{A.18})$$

where E_L is the change of the intramolecular energy of the ligand
upon binding, ΔE_{solv} is the change of the solvation upon binding;
 $N = 10$, $R = 0.92$, $F = 20.61$.

Inhibitory activity of aryl-substituted piperazine and piperylene, log(1/EC₅₀) (see³⁶⁸).

$$\log \frac{1}{EC_{50}} = 0.62(\pm 0.04)\log P - 0.39(\pm 0.05)\sum C_a - \quad (\text{A.19})$$

$$- 2.16(\pm 0.18),$$

$N = 17$, $R^2 = 0.90$.

Toxicity of carboxylic acids against Xenopus embryos, pLC₅₀
(see³⁵⁸).

$$\text{pLC}_{50} = 0.696 \log P - 0.358 \text{pK}_a - 0.541, \quad (\text{A.20})$$

$N = 44$, $R = 0.947$.

Membrane permeability (human red cell basal), logBP (see³⁶⁹).

$$\log BP = -0.70(\pm 0.64) + 1.08(\pm 0.16)\sum C_d, \quad (\text{A.21})$$

$N = 10$, $R = 0.983$, $S = 0.433$.

Membrane permeability (cells of the alga Chara ceratophylla), log Per (see³⁶⁹).

$$\log \text{Per} = 0.83(\pm 0.57) + 0.59(\pm 0.12)\sum C_d, \quad (\text{A.22})$$

$N = 27$, $R = 0.903$, $S = 0.49$.

Binding of the muscarinic receptor by bicyclic ligands, log K
(see²¹⁰).

$$\log K = 1.28(\pm 0.15)\log P - 0.09(\pm 0.06)\sum C_a + \quad (\text{A.23})$$

$$+ 0.27(\pm 0.08)\text{HBA5.3A} - 4.58(\pm 0.48),$$

where HBA5.3A is a descriptor characterising the interaction
between two hydrogen bond acceptors spaced 5.3 Å apart;
 $N = 27$, $R = 0.918$, $S = 0.38$, $F = 41.1$

6. Indicator descriptors

Binding of papain ligands by phenyl N-mesylglycinate and N-benzoylglycinate, log(1/K_m) (see²⁹⁷). (The combination of Eqns
(A.7) and (A.8) with the aid of an indicator variable I ($I = 1$ for
mesylamides and $I = 0$ for benzamides)).

$$\log \frac{1}{K_m} = 0.57(\pm 0.26)MR + 0.56(\pm 0.19)\sigma - \quad (\text{A.24})$$

$$- 1.92(\pm 0.15)I + 3.74(\pm 0.17),$$

$N = 20$, $R = 0.990$, $S = 0.148$, $F = 272.04$.

Inhibition of HIV-RT, pIC₅₀ (see³⁷⁰).

$$\text{pIC}_{50} = 1.47I + 0.41\mu + 2.69 \log MW - 4.36, \quad (\text{A.25})$$

where I is the indicator variable, MW is the molecular weight,
 $N = 14$, $R = 0.94$, $S = 0.42$, $F = 27.4$.

Cytotoxic activity, pIC₅₀ (see³⁷¹).

$$\text{pIC}_{50} = 0.73(\pm 0.46)I_2' + 1.14(\pm 0.38)I_5' + \quad (\text{A.26})$$

$$+ 1.12(\pm 0.43)I_{xy} + 3.15,$$

where I_2' , I_5' , and I_{xy} are indicator variables; $N = 22$, $R = 0.915$, $S = 0.32$, $F = 30.78$.

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Expert systems for structure elucidation of organic molecules by spectral methods

M E Elyashberg

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Abstract. The state-of-the-art of the investigations aimed at creating expert systems for establishing the structure of organic molecules from IR, ^1H and ^{13}C NMR spectra is analysed. Computer methods used for identification of molecular fragments, generation of their structure and spectra prediction are considered. Principles of the creation of modern expert systems and general strategy of solving structural problems are discussed. The bibliography includes 174 references.

I. Introduction

More than 30 years have elapsed since the publications^{1–5} in which the problem of using mathematical methods and computers for establishing the structure of organic molecules from their spectra were first considered. Even in these articles it was shown that the structural-group analysis (SGA) can be formalised using methods of mathematical logic and performed on a computer,^{1,2} while application of graph theory and combinatorial analysis makes it possible to generate automatically (perform mathematical synthesis) structural formulae from fragment sets.³ In this time, many interdisciplinary sciences have united on the basis of mathematical algorithms as computer programs to form a new line of investigation, application of artificial intelligence (AI) to the determination of molecular structures from spectral data.

Since World War II, spectral methods have received wide acceptance in chemistry. It will not be an exaggeration if we say that IR, NMR spectroscopy and mass spectrometry revolutionised the methodology of chemical investigations and ‘chemical’ thinking and have become one of the main sources of structural information for chemists. Unquestionable are the advantages of spectral methods, *viz.*, their versatility, fast operation, ease of constructing a computer interface and the use of well developed theories (this particularly concerns IR and NMR spectroscopy). It is these features, as well as the accumulation of a great body of information on empirical spectrum – structure correlations (SSC),

that have stimulated investigations on the application of AI in chemistry.

To formalise the process of molecular structure determination, it was necessary to find mathematical tools adequate to the problem considered. Since a molecule has a discrete nature and its energy levels are discrete too, mathematical logic, graph theory and combinatorial analysis were chosen as appropriate mathematical tools. It is discrete mathematics which describes the models of the ‘black box’ type that has become one of the main instruments of mathematical chemistry, which has progressed intensively in the last decades.

At first, mathematical synthesis of the structures from the atoms and fragments seemed to be merely a stage in the identification process of organic compounds; however, soon it became clear that its importance goes far beyond the scope of the problem considered. In fact, innumerable sets of organic molecules designed by the structure generator can be interpreted as enumeration of logical implications from a system of axioms that form a basis of the theory of molecular structure. At the same time, knowing only the structural formula of a compound, one can predict a number of its important properties. This made it possible to pose a problem of the development of mathematical methods for predicting the structure of the compounds with desired properties and, *vice versa*, the properties of compounds from a structure given (studies of N S Zefirov’s scientific school in this line of investigation have gained world-wide acceptance). Rich experience accumulated by chemists shows that most predictions on the possibility for unknown compounds to exist in nature and to be synthesised, made on the basis of the classical theory of the structure of organic substances, were borne out, the percentage of wrong predictions being relatively small.⁶

Formalisation of chemical research based on integration of many sciences has become an important result of the studies on the application of AI in molecular spectroscopy.

By and large, the development of concepts and methodological approach in this new area of study was completed by the early 1980s, which was embodied in a number of monographs^{7–10} and reviews.^{11–15} The efforts of investigators from many countries have resulted in general principles for creating AI systems [currently, they are called expert systems (ES)] and in developing corresponding algorithms which were tested on a large number of problems.

About twenty ES for molecular spectroscopy have been documented. They differ in their possibilities, use different algorithms and instrumental tools and are aimed at the applica-

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tion of different methods of spectral analysis. However, common to these systems is the fact that they simulate reasoning of an expert (spectroscopist) when solving an identification problem. This thinking process involves the following main stages:

- (1) structural-group analysis of an unknown compound;
- (2) generation of possible structural formulae from the fragment sets found;
- (3) test for the correlation between structural formulae and experimental spectra (and additional information) using spectra prediction of the assumed structures.

Each stage is simulated by a corresponding block of an expert system. The above-mentioned blocks are relatively independent and their functions are usually realised using different mathematical methods. Currently, methods for identification of the fragments, structure generation and prediction of their spectra have become almost independent divisions of computer spectroscopy and mathematical chemistry.

To come as close to solving actual problems using ES as possible, it was necessary to investigate the nature of the structure determination problem. Peculiarities of this problem were considered¹⁶ as an example of the inverse problem.¹⁷ As is known, the inverse problems belong to the so-called ill-posed problems: they do not have a unique solution unless *a priori* restrictions are imposed.¹⁸ Important conclusions were drawn that it is impossible to perform a structure determination without the attention of a chemist and that all problems should be solved in the interactive mode. At that time, it was also appreciated that information on the spectra–structure interrelations is usually ‘fuzzy’ (ambiguous). With this in mind it was suggested¹⁹ that methods of fuzzy mathematics²⁰ should be used for SGA formalisation and approximate spectra prediction. The results obtained by different research groups up to the early 1990s have been reported in reviews.^{21–23} At about the same time a considerable interest has been expressed by investigators in algorithms of artificial neural networks (ANN),^{24–27} the application of which in different areas of computer chemistry seems to be rather promising. The number of studies in this investigation line grows rapidly. It appeared to be so new for chemistry and chemometrics that no mention of ANN was made, *e.g.*, in a ‘Chemometrics’ monograph²⁸ published in 1986.

At the same time it became clear that ES have a chance to become an analytical tool of organic analysis only if they ‘learn’ to operate on large non-additive structures (*e.g.*, the structures of natural compounds) and possess a high degree of user-friendliness. The efforts of several research groups focussed on this line of investigation have led to the creation of new ES (see, *e.g.*, Refs 29–32).

In the present review, the experience mostly accumulated in the last decade in the area of creation of the ES oriented to the molecular structure determination from IR, ¹H and ¹³C NMR spectra is generalised. First, methods for identification of fragment sets, structure generation and prediction of their spectra are considered and then strategies of structure determination are analysed taking the most perfect ES as examples. Particular emphasis is placed on discussing the problems that arose in the course of ES operation and analysing possible ways of overcoming these problems.

II. Methods for identification of structural fragments

To identify the structural fragments, most ES use characteristic features of functional groups and other structural elements in the molecular spectra. Usually, the knowledge base of an ES consists of molecular fragments, ranges of changes in their characteristic features (frequencies in IR spectra and chemical shifts in NMR spectra) and the rules relating the spectra to the structure. In a number of systems, libraries of the structures and corresponding spectra are included in the knowledge bases in addition to molecular fragments. Depending on the type of the knowledge

base, different methods of structural information retrieval are used.

1. Formal logic method

It has been shown^{1,33} that the scheme of relations between the elements of molecular structure and their spectral features can be described by a discrete structural model, therefore application of mathematical logic in the studies of the spectrum–molecular structure interrelation naturally follows from the nature of the object studied. It is assumed that the molecule is additive or partially additive and each fragment A_i of a set A of fragments related to the problem given is characterised by one or several intervals of changes of characteristic features $\omega_i \in \Omega$ (Ω is a set of spectral features).

Boolean algebra was used as a mathematical tool of the theory of SGA. This made it possible to derive in the general form logical relations connecting structural elements to their characteristic spectral features and to construct a model of reasoning when identifying structural fragments.

Boolean algebra deals with elementary propositions and their combinations, which are called Boolean functions. Combinations of elementary propositions are constructed using ‘and’ (conjunction), ‘or’ (disjunction), negation and implication operations. The latter has a meaning of a complex proposition ‘if..., then ...’ and is denoted by an arrow ($\rightarrow$). For instance, the sentence ‘if a molecule contains a fragment A_i , then feature ω is observed in its spectrum’ is represented by the $A_i \rightarrow \omega$ implication. Elements of Boolean algebra and SGA theory are reported in the monograph.⁷

In the general case, reasoning of an expert who performs SGA seems to be as follows: if a Boolean function $T(A, \Omega)$ correctly reflects interrelation between the spectrum and molecular structure, then the presence in the spectrum of a combination of spectral features, which is described by a Boolean function $R(\Omega)$, indicates the presence in the molecule under study of at least one combination of the structural elements defined by a Boolean function $f(A)$, *i.e.*

$$T(A, \Omega) \rightarrow [R(\Omega) \rightarrow f(A)].$$

This expression is a general formulation of the problem of qualitative spectral analysis in terms of Boolean algebra, it is a logical equation with respect to function $f(A)$. Solution of the logical equation is reduced to calculating the function $f(A)$ using an algorithm which is based on the concept of designation numbers and reported in the monograph.⁷ Function $f(A)$ contains fragment sets, each of which can explain characteristic features in experimental spectra.

The approach described serves as the basis for the SGA block in several generations of the RASTR system^{34–36} and is used in the X-PERT,²⁹ CHEMICS,³⁷ EXPIRS^{38,39} and other systems. This makes it possible to select successively possible fragments for producing logically consistent sets appropriate for further structure generation. However, such an approach has a drawback consisting in too ‘rigid’ logical determinacy. For instance, a small deviation of a characteristic feature of the fragment in the experimental spectrum from the limits of a given interval leads to the loss of the corresponding fragment. In addition, the knowledge base of the algorithm remains to a great extent similar to correlation tables and, hence, vast information presented in terms of natural language in numerous monographs on molecular spectroscopy (regularities, empirical rules, *etc.*) is not used. In this connection attempts have been undertaken to create such an ES in which SSC are described in more detail.^{19,40}

2. Methods of predicate logic

To create an ES which operates on the knowledge presented in terms of a natural language with professional restrictions, it is necessary to find appropriate mathematical tools. The requirements placed on such mathematical tools are caused by the character of the knowledge formulated in terms of natural language. On the one hand, descriptive (declarative) knowledge,

in particular, in the field of IR spectroscopy (see, *e.g.*, Ref. 41), is characterised by some fuzziness and ambiguity. The statement that, usually, stretching vibrations of the C=C bond are observed in the IR spectrum in the region near 1650 cm^{-1} ; however, sometimes they are shifted to the region 1685 cm^{-1} can serve as an example.⁴¹ On the other hand, logical inferences in the course of solving qualitative problems are also performed in terms of a natural language with inherent ambiguity and hidden estimates of reliability (*e.g.*, 'often', 'rarely', 'sometimes', *etc.*). The man thinks using fuzzy concepts rather than numbers. Therefore, theoretical tools appropriate for adequate simulation of our knowledge and reasoning must meet the requirement figuratively formulated by L. Zadeh who initiated fuzzy mathematics:⁴² 'The theory of nature must reflect the fact that nature paints by arbitrary strokes rather than by a ball pen'.

To represent the knowledge on IR spectroscopy, applied logical calculus^{19,40} (ALC) based on the theory of first-order predicates⁴³ and theory of fuzzy sets^{20,42} was proposed. The basic principles of ALC are as follows.

A logical function $P(X_1, X_2, \dots, X_n)$, where $X_i \in M(X_i)$, which takes a 'true' or 'false' value on substituting the objects belonging to a certain object domain is called an n -place predicate. Most often, the predicate reflects properties of the objects and relations between them. For instance, let predicate $P(X)$ reflect the property of the substances to have a strong IR absorption band near 1700 cm^{-1} and let $X_1 = \{\text{acetone}\}$ and $X_2 = \{\text{propylene}\}$. Then, obviously, $P(X_1) = 1$ ('true') and $P(X_2) = 0$ ('false'). If $M(X_i)$ is a set, then a fuzzy subset F of the set $M(X_i)$ is defined as a set of ordered pairs $\{X_i, \mu_A(X_i)\}$, where $\mu_A(X_i)$ is a characteristic membership function, which varies from 0 to 1 and indicates to which degree the element X_i is a member of the subset F . For instance, the membership function of the proposition 'there is a band near 1710 cm^{-1} in the IR spectrum' will be written as follows: $\mu_A(1710\text{ cm}^{-1}) = 1$. In this case it is assumed that there exist certain bounds, *e.g.*, 1700 and 1720 cm^{-1} , and beyond them the function $\mu_A(X_i)$ is zero.

If predicate variables are assigned the meaning of the elements of fuzzy sets, then we get fuzzy predicates. Each n -place predicate symbol is associated with mapping M^n into a set of the values of a characteristic membership function, which in the case of ALC is called a truth function μ_p , $0 \leq \mu_p \leq 1$.

A system of predicates describing the IR spectrum–structure interrelation was developed to describe the spectrochemical knowledge. In particular, predicates characterising the IR spectrum ('there is a band of vibrations of the type ζ of a structural group g in the spectrum; the band is characterised by frequency X_i , intensity Y_i and halfwidth Z_i) and molecular structure ('the molecule contains a fragment R_1 ', 'the molecule contains a fragment R_1 separated by n_1 bonds from m_1 fragments R_2 ', 'the molecule contains a ring of size j , which includes a fragment R_3 ', *etc.*) were introduced. Specific predicates characterise the state of aggregation of the substance, solvent type, *etc.* To describe changes in the data, second-order predicates are introduced, and using them it is possible to indicate the direction of changes in the variables which appeared in the first-order predicates (*e.g.*, 'increases', 'decreases', 'disappears', 'becomes split into d components', *etc.*).

Using such a system of predicates and conventional logical operations, it is possible to formalise declarative knowledge to a great extent. For instance:

(1) 'stretching vibrations ν_s of compounds with one double C=C bond and alkyl substituents (Alk) absorb in the region $1640\text{--}1680\text{ cm}^{-1}$ '

$\text{STRUCT}(\text{C}=\text{C}, \text{Alk}) \rightarrow \text{SPECTR}(\nu_s, \text{C}=\text{C}, 1640, 1680);$

(2) 'conjugation of double bonds of two alkyl-substituted groups results in splitting of the band of stretching vibrations ν_s into two bands'

$\text{Q}_1[\text{STRUCT}, \text{C}=\text{C}, \text{Alk}(\text{C}=\text{C})] \rightarrow$
 $\rightarrow \text{Q}_2[\text{SPECTR}, \nu_s, \text{C}=\text{C}, X_1(\text{SPL}, 2)].$

The logical formula G and the predicate symbol P are associated with a set of outside values of the truth function μ_e , $0 \leq \mu_e \leq 1$. The external value of the function μ_e reflects the knowledge quantification ('often', 'sometimes', 'in some instances', *etc.*). For instance, the statement 'stretching vibrations of the C=C bond are often observed in the region $1640\text{--}1660\text{ cm}^{-1}$ ' is represented by elementary formula $[0.8]\text{SPECTR}(\nu_s, \text{C}=\text{C}, 1640, 1660\{10\})$, where $[0.8]$ is the external value of the truth function, $\{10\}$ is the segment length (in cm^{-1}) on both sides of the bounds of the region $1640\text{--}1660\text{ cm}^{-1}$, on which the trapezoidal membership function decreases to zero. To determine the value of the truth function μ_i appeared in the elementary formula, it is necessary to multiply the external value of μ_e by those of the membership functions of fuzzy constants and variables in this formula. In this case, taking into account the properties of a triangle, we get $\mu(X) = 0.5$ at $X = 1665\text{ cm}^{-1}$; at $\mu_e = 0.8$, the μ_i value will be equal to $0.5 \times 0.8 = 0.4$.

Spectrochemical knowledge can be divided into facts (expressions containing constants) and regularities (expressions containing at least one logical variable). It is convenient to operate on structured knowledge. To structure the knowledge, a class is specified of general regularities that are valid for most organic molecules (*e.g.*, 'there are no small rings containing a triple bond in organic chemistry'). Principal functional groups possessing characteristic spectral features (C=C, C $\equiv$ C, C=O, C $\equiv$ N, OH, *etc.*) are accepted as structuring units of other knowledge. The molecular fragment is described by its core (C=C, C $\equiv$ C, *etc.*) to which surrounding atoms are successively added, thus respectively forming first-, second-, third-level fragments, *etc.* The knowledge hierarchy thus formed is a tree graph called a declarative knowledge network. The description of a network node contains the fragment structure, possible types of its vibrations, regularities and facts for each type of vibrations and those characteristic of the given fragment.

If declarative knowledge is considered as a system of axioms of the theory used for solving an applied problem, the SGA problem is represented in terms of statements (theorems) that should be proved or rejected. It has been shown⁴³ that the classical resolution method adapted to the theory of fuzzy predicates can be used for automated proof of the theorems (automated SGA).

The formalism suggested makes it possible to solve SGA problems as well as those of structural interpretation of IR spectra. The results of interpretation can be used for self-learning of declarative knowledge, in the course of which the facts and regularities are tested, values of characteristic membership functions are changed and new facts and regularities are revealed.

The approach described was realised as a research prototype of an ES written in the Prolog algorithmic language.⁴⁴ The system reveals consistent fragment (network node) sets that explain the spectrum. Simultaneously, interpretation of the IR spectrum is performed: each frequency is assigned to a certain type of vibrations of corresponding fragments with an indication of the value of the truth function μ_p for the assignment given.

Predicate logic and Prolog algorithmic language were also used for structural interpretation of IR spectra in the EXPEC system.^{45–47} The knowledge base of the system includes a rule interpretation generator. As in the preceding system,⁴⁴ fragments included in the knowledge base are hierarchically structured in the form of a network of declarative knowledge. When interpreting the spectrum of unknown compound, the network is scanned to find the rule for each fragment, according to which the relation between the fragment and spectrum is analysed. Each result obtained is associated with its probability. Explanatory facilities make it possible to trace the reasoning process of the program.

The knowledge base of the system is formed on the basis of SSC known from the literature and is supplemented using the rule interpretation generator,⁴⁵ as well as due to input of expert's knowledge. To perform automated rule generation, a library of IR spectra of organic compounds belonging to the CHO class is used. The program generates a set of potential rules, selects the least correlated ones and minimises their number.

The presence of the rule generator⁴⁵ is an advantage of the EXPEC system. Automated rule generation involves four steps: (1) selection of structural fragments; (2) database retrieval to find all structures containing a S_i fragment; (3) search for the intervals of characteristic features for S_i and (4) selection of intervals appropriate for using interpretation rules. The problem of the knowledge base formation is of fundamental importance for creating an efficiently operating ES, therefore the above-mentioned approach to automatization of this process appears to be rather promising.

The interpreter (inference machine) selects only those network fragments for which the presence of groups in the network nodes was validated. For instance, the rules concerning detection of phenol compounds can be used only after the presence of benzene ring and hydroxy group was confirmed. For each substructure, the probability of its presence is calculated using a trapezoidal probability distribution function for a given interval (*e.g.*, this shape was chosen for the band membership function of the absorption region^{19,40}). Selected fragments are arranged in order of decreasing the probability of their presence.

The investigators from different research groups suggest different rules for selecting possible fragment sets (see, *e.g.*, Ref. 48). It seems that these studies will progress and make it possible to come right up to creating ES for the molecular spectral analysis that interact with a chemist in terms of a natural language with professional restrictions. However, on this way the investigators will inevitably face many difficulties. Overcoming them will require joint efforts of the experts who carries out interdisciplinary research such as, *e.g.*, mathematical linguistics, mathematical logic, knowledge technology, *etc.*

3. Application of artificial neural networks

Beginning in the early 1990s, the attention of chemists was drawn to the possibilities of new promising mathematical tools of computer chemistry, *viz.*, artificial neural networks (ANN). Particularly rapid is the increase in the number of studies on the application of ANN to interpretation and classification of spectral data.

A neural network is a simplified model of the human brain, consisting of several layers of neurons that send signals to other neurons depending on the input signals received. Such networks function according to the 'black box' type and possess a common ability to construct empirical models of the systems for which theoretical dependences between the input and output are too complicated or even unknown. Models are obtained as a result of the network training. In the course of training, the network is represented in the form of input–output pairs related by simulated transformation. A network trained on these examples is capable of predicting the output signals from the input signals not 'seen' at that instant. The training procedure may be time-consuming (tens of hours); however, a network once trained generates the answer or prediction almost instantaneously. For instance, a network can be trained to generate structural information (output) retrieved from a spectrum (input) or to predict a spectrum (output) from structural information (input). By applying this procedure to the spectra, it is possible to establish which functional groups can be present and absent in the specimen and to complement these data with reliability estimates of the results obtained.

Let us consider general principles of designing neural networks^{24,49} in more detail.

Strictly speaking, ANN is a computational structure consisting of a number of interconnected elementary units called nodes or neurons. In a simplified form, a neuron functions as follows.

The 'signal' values s_i ($i = 1 \rightarrow m$) at the neuron input (we will call them inputs) are multiplied by weighting factors w_i and summed up to give the function Net:

$$\text{Net} = s_1w_1 + s_2w_2 + \dots + s_mw_m.$$

Then, the Net value is transformed into the output signal of a neuron using a nonlinear transfer function. The sigmoid function

$$\text{sf} = \frac{1}{1 + \exp(-s_iw_i)}$$

is most often used as a transfer function.

This signal is then used as the input signal for other neurons and the organisation of the connections between neurons defines the network architecture. A large number of neurons and interrelations between them makes the network behaviour more complex. The network can be modified by 'adjustment' of its parameters, among which weighting factors are the main ones. Adjusting the network parameters in order to obtain a desired behaviour is called the network training. This process is carried out iteratively using a learning algorithm on a set of examples. At each iteration, the network outputs are compared with the reference values (examples) and, if they appear to be different, the program performs correction of weighting factors. The network is trained until coincidence of outputs with references.

In the first studies on structural interpretation of IR and NMR spectra, multilayer ANN trained using the back-propagation of errors (BPE) algorithm²⁴ were most often used. In these networks, each neuron is connected to all neurons in the preceding and succeeding layers. The first (input) layer receives the input data and distributes them over the succeeding layer. The last (output) layer, or decision layer, is responsible for outputs of the entire network. Other layers, if any, are called hidden layers (Fig. 1). Information is propagated from the input layer through hidden layer(s) to the output layer. For instance, an IR spectrum encoded as the intensity values taken at points uniformly distributed along the abscissa axis is used as the input vector. The output vector coordinates are certain numerical values (often, zeros and unities) indicating the presence or absence of particular structural features. The number of points used for encoding the spectrum defines the size (the number of nodes) of the input layer while the number of structural features (fragments) introduced determines the size of the output layer. There is no generally accepted rule for setting the number of nodes in hidden layers: it has to be large enough to provide correct data processing; however, increasing the number of nodes increases both the learning time and risk of the network 'over-training'. The latter consists in decreasing the network performance after a certain

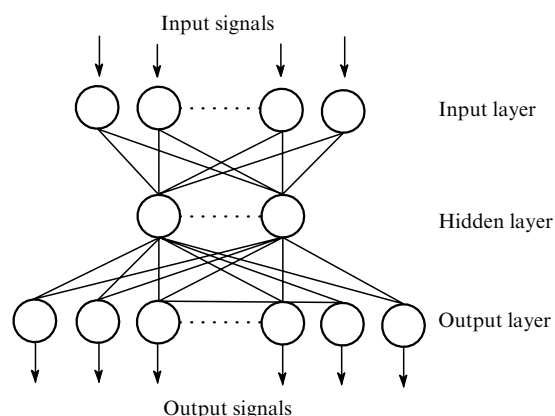


Figure 1. A scheme of neural network.

number of iterations (they are called cycles or epochs) in the course of training.

After random initialisation of the initial values of weighting factors w_i , the network training is performed on a set of spectra of the compounds containing fragments associated with desired outputs. (This set is called the training set.) There are numerous variants of this algorithm; however, all of them are based on the same principle, a steepest-descent minimisation of the total error, calculated as the sum of differences (or the squared differences) between the network outputs and desired results.

To determine the network performance (efficiency), a set of examples (the test set) is used. This set should differ from the training set in order to measure the network capacity for generalisation instead of learning.

The size and composition of the training set strongly affects the learning efficiency. For instance, increasing the number of examples increases the overall performance of the network, but only up to a certain point.⁵⁰ The effect of the composition of the training set appears to be much more complicated. The effect of presents/absents balance for structural features in the molecules, *i.e.*, the proportion of compounds presenting a structural feature to those not presenting it in the training set has been studied.^{49, 51, 52} In particular, it has been found⁴⁹ that increase in the proportion of presents in the training set increases the probability of recognising these fragments in the compound analysed to the detriment of the absents. At the same time, it was found that there is a certain limit of presence under which the network is unable to perform correct classification. The setting of a well-balanced and diversified training set can be difficult, especially if the network to be trained has many outputs.

The number of network outputs is of great significance: according to the reported data,^{50, 53} mono-output networks perform better than the networks with many outputs; moreover, large networks are more difficult to optimise than small ones (networks with smaller number of outputs). Since the best result for each output may occur at a different training time, the ANN training is stopped at a stage where the averaged (but not for each output) network performance will be optimum. The use of many mono-output networks for the determination of a large number of structural features is much more time-consuming than the use of a single network. Therefore, advantages and drawbacks of using a single multi-output network are opposite to those of using several mono-output networks.

A hierarchical system for spectrochemical studies, which should retain the best of both approaches, was proposed.⁵⁴ In such a system, a multi-output top-level network performs a rough classification of the spectra. Depending on the structural feature considered, the hierarchy is extended to deeper levels where further refinement is performed.

The top-level network outputs activate the first-level networks and so forth through the whole hierarchy. The design of a hierarchical system of neural networks can be considered as a compromise between one multi-output network and many mono-output networks. Its main characteristics are also intermediate. It was found that it is easier to balance the components of the training set for each network of the hierarchy than for a single large network (in some sense, as simple as for a mono-output network). In addition, optimisation of the learning time is easier for a smaller number of outputs, and the modular conception makes it possible to modify the system without the entire reconstruction.

A hierarchical system gives information on structural features on different levels: from general characteristics ('a compound contains a CO group') to more specific ones ('a compound contains an acidic group'), the number of networks to be activated in each particular case remaining small. For instance, there is no need to find out whether a compound is a primary or tertiary alcohol if the OH group has not been recognised by the top-level network. However, mention has been made⁴⁹ that the adjustment of a hierarchical network is a complex task and

requires *a priori* knowledge and consideration of the dependence of sub-level networks on upper-level network performance.

Let us consider the results of studying a hierarchical system as an analytical tool for determination of the fragments using IR spectra.⁴⁹ The experiments were carried out using a set of 8620 compounds and their IR spectra taken from the Sadtler Bio-Rad library. Calculations were performed on an IBM RS6000 workstation. The system was trained to recognise 33 structural groups whose hierarchy is shown in Fig. 2. As can be seen, recognition of carbonyl group was carried out using two specially designed networks, one for wide-spread structural features (carboxyl, ketone, ester and amide) and another for rare structural features (acid chloride, anhydride and aldehyde).

The following network parameters were used.

Input vector. The IR spectrum in the region 500–3596 cm^{-1} was represented as a set of 259 points separated by increments of 12 cm^{-1} . The weighted mean of absorbance in the vicinity of each point was scaled to a 0 to 1 range and used as input.

Hidden nodes. Networks contained only one hidden layer, and the number of hidden nodes was set to 30 for all networks.

Transfer function. The classical sigmoid function was used.

Structure encoding: 0 and 1 were respectively used to encode the absence and presence of a structural feature.

Learning algorithm. All networks were trained using the BPE algorithm with a learning rate $\alpha = 0.05$ and a momentum $\mu = 0.90$ (Ref. 24).

Decision making. Since the network outputs were real values from the 0–1 range, two thresholds were necessary for decision about the presence or absence of each structural feature f in the molecule: accept level (presence threshold) AL_f and reject level (absence threshold) RL_f of a structural feature. If the output number is between RL_f and AL_f , the answer is considered ambiguous and the fragment is reported as 'not classified'. These decision thresholds were optimised individually for each network.

Training and test sets elaboration. The sets of examples required to train 10 networks constituting a hierarchical system were built by random selection from initial population with the constraints to reach a prescribed proportion of compounds containing preset structural features. For the top-level network,

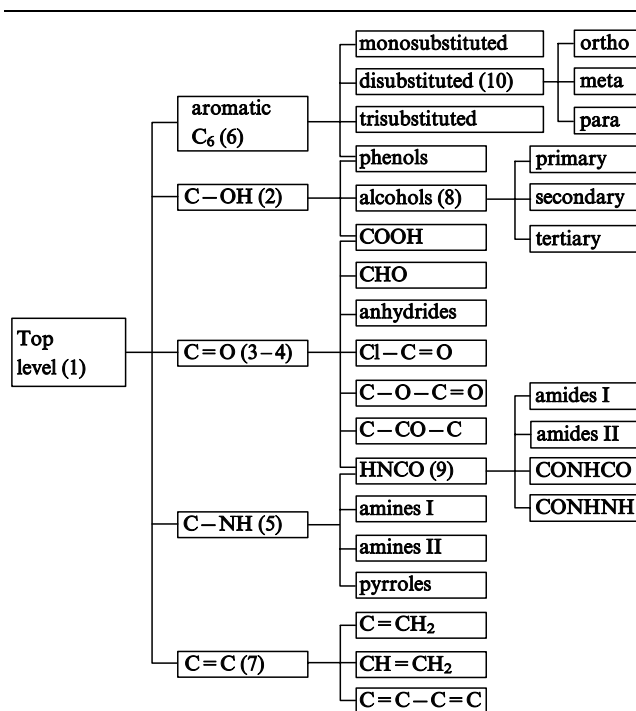


Figure 2. Hierarchical organisation of networks. The numbers of activated networks are given in parentheses.

the whole collection of spectra was used. Sub-level networks were trained using specially designed protocols.

As was mentioned above, in hierarchical structures the network dedicated to recognition of the fragments belonging to a specific class is activated only if it recognised the example as a member of this class. For a structural feature, two types of misclassification are possible: (1) the fragment was identified in the compound in which it does not occur; this case is called false present (AdP); and (2) the fragment was not identified in the compound containing it; this case is called false absent (PdA). False absents are not propagated through the hierarchy, since the structural feature is considered as absent. However, false presents raise a new problem: sub-level networks must refine classification of the fragment which actually is not contained in the compound.

Special experiments showed that the hierarchical system is robust and bears the change of networks without losing the global capability of the hierarchy. The best training was found to occur for the training sets of 1000 examples and the number of cycles was between 5 and 20. The best results were obtained for C=O and OH groups that are easily recognised in the IR spectra.

The following indices were suggested for measuring the performance of the entire hierarchical system:⁴⁹

Ptf — a general characteristic of the presence of a structural feature (the total present found); it is defined as the ratio of the number of compounds in which the presence of the fragment was correctly identified to the total number of compounds containing the given structural feature;

Atf — the same as above, as applied to the absent structural features (the total absent found);

Pte — the total error of decision of the presence of the structural feature (the total present error), which is defined as the ratio of the number of compounds containing the feature but identified as absent to the total number of the compounds containing the given structural feature;

Ate — the total error of decision of the absence of a structural feature (the total absent error), which is defined analogously to the preceding index.

The results of testing the system using the criteria introduced are shown in Table 1. Comparison with the reported data⁵⁵ shows that, on the whole, the hierarchical system performs better than multi-output network; however, the results qualitatively rank below those obtained using well optimised mono-output networks.

Currently, a few studies dedicated to application of ANN to the selection of molecular fragments has been reported; however, investigations in this area are gathering force. Thus, analyses of IR spectra using ANN were reported.^{52–61} An ANN was used to identify amino acid residues in proteins from their 'fingerprints' in 2D NMR spectra.⁶² Adjustment of the networks in the case of joint application of different spectral methods to elucidation of structural fragments was reported.^{51,63} This investigation line seems to be of particular interest; therefore, let us consider the results reported in the last two articles in detail.

A study⁵¹ was carried out in which IR and ¹³C NMR spectra and molecular formulae of organic substances served as input signals for a neural network preliminarily trained to recognise molecular fragments. The ANN containing 512 inputs, 85 outputs and ~ 50 neurons in the hidden layer was used. The training set comprised 1560 compounds for which IR and ¹³C NMR spectra were known. A total of 128, 294 and 90 inputs were respectively specified for IR spectra, NMR spectra and molecular formulae. Such a distribution was chosen taking into account the estimate of the amount of information contained in each data type. IR spectra were encoded in the same way as in the study by Cleva *et al.*⁴⁹ ¹³C NMR spectra were encoded by present/absent indicators of signals at intervals of 2 ppm. The indicators for signals of different multiplicity were stored in prescribed positions of the input vector (*e.g.*, encoding the chemical shifts of quartets in the spectral range 0–64 ppm was performed using 32 intervals to which positions 128–159 of the input vector corresponded). The molecular

Table 1. Performance of global hierarchy.

Fragment	Atf	Ptf	Ate	Pte
C—OH	93.3	88.3	6.7	16.4
CO—OH	91.2	79.8	1.0	18.0
Ph—OH	92.8	56.4	0.8	32.3
C _{sp³} —OH	91.3	78.6	1.1	18.2
CH ₂ —OH	91.1	71.5	0.7	27.2
CH—OH	90.6	57.2	1.2	41.9
C _{quatern.} —OH	91.6	35.1	0.1	62.9
C=O	94.3	91.8	3.1	5.5
CO—OH	94.1	82.8	1.3	13.7
CO—OR	93.6	77.0	1.6	15.2
CO—R	92.9	50.7	1.7	39.0
CO—NH	91.5	85.5	3.0	11.8
CO—NH ₂	93.4	87.0	2.0	10.5
CO—NHR	94.9	55.5	0.8	35.8
CO—NH—CO	95.6	74.2	0.1	21.4
CO—NH—NH	95.6	47.6	0.3	52.4
CHO	86.8	74.0	6.1	22.1
OC—O—CO	92.2	82.8	1.2	10.0
Cl—CO	94.6	47.0	1.7	48.0
C—NH	92.0	82.7	6.6	15.6
C—NH ₂	91.1	52.4	3.0	43.0
C—NHR	93.4	36.3	1.8	60.3
CO—NH	91.6	66.0	1.3	29.8
Pyrrole	93.8	14.3	0.4	79.8
Aromatic C ₆	79.0	86.4	16.3	5.9
C ₆ —OH	80.9	69.9	2.9	29.7
monosubstituted	80.8	54.0	2.1	35.0
disubstituted	70.0	53.3	10.7	37.8
ortho	73.9	34.9	0.2	62.8
meta	73.7	16.7	0.3	83.3
para	71.7	47.6	1.1	49.0
trisubstituted	76.4	34.8	6.0	59.1
C=C	93.6	42.6	6.3	56.9
C=CH ₂	93.2	30.4	0.9	68.7
CH=CH ₂	93.3	23.0	0.3	75.8
Csp ² —C=C	89.4	34.4	1.8	62.0

formula was encoded by the numbers of present types of atoms, the degree of unsaturation and molecular weight. Structural formulae were encoded by 0 or 1 depending on the presence or absence in the molecule of each of 85 fixed structural elements including functional groups ($-\text{O}-\text{C}=\text{O}$, $\text{C}\equiv\text{N}$, $\text{H}_2\text{C}=\text{CH}$, *etc.*)

and chemical classes (steroids, terpenes, pyridines, *etc.*). Optimisation of parameters and the network training using the BPE procedure were carried out on HP 9000 RISC and other workstations. Performance of the system was studied for different combinations of input data.

It was established that performance of the system in the case of using NMR spectra only is higher than that reached using IR spectra only; the inclusion of molecular formula increases performance of the system for any combination of IR and NMR spectral data; simultaneous use of both types of spectra leads to a substantial increase in performance of the system (*i.e.*, the number of reliably identified groups increases appreciably).

These conclusions were not unexpected; however, the importance of this study⁵¹ is that the procedure for identification of fragments by joint use of IR and ¹³C NMR spectra, based on ANN application was first proposed. This approach can be realised with ease in a fragment selection block of an ES.

Application of ANN to joint interpretation of IR and mass spectra (MS) of gases has been described.⁶³ The network was trained to identify 26 functional groups. The proportion of correctly identified present groups was 86.4% when using com-

bined data; this index was respectively 88.4% and 78.2% when IR spectroscopy and mass spectrometry data were used separately. Among 26 groups, only for 8 did the use of MS lead to improving the recognition quality; the results of determination for the C—Cl bond have been considerably improved. This confirms the known fact that IR spectroscopy is more appropriate for identification of functional groups than mass spectrometry. Absent functional groups were predicted to an accuracy of 95.5% using combined data and IR spectroscopy data only and to an accuracy of 87% using mass spectrometry data only. The results of this study⁶³ show that principles of combining the data obtained by different spectral methods, as applied to ANN, require special investigations to find optimum variants.

It should be noted that, as a rule, different groups of researchers use different indices of network performance, therefore comparison of the results obtained in their studies is difficult. In this connection the problem of the selection of generally accepted indices and standard test sets, which would make it possible to easily compare the efficiency of different classification methods, appears to be topical.

Despite improved capability of ANN to identify fragments, successful application of the networks is to a great extent dependent on the user's skill in adjusting the network parameters (decision thresholds, composition of the training set, *etc.*) to meet specific requirements when solving any problem. Currently, there is no information on the use of ANN in any actual ES dedicated to identification of the molecular structure and the number of structural features that can be recognised using an ANN is unclear (for comparison, it should be noted that spectral libraries of known ES contain hundreds of fragments). Therefore an estimate of actual possibilities of this approach is still ahead. However, it can be stated with certainty that application of ANN to the determination of individual classes of chemical compounds is rather efficient.

4. Methods for recognition of large fragments

To solve the problem of identification of large molecules, an ES must have adequate analytical tools for determination of large fragments. Attempts to create libraries containing large fragments and ranges of variations of their characteristic spectral features are of no promise because of imminent combinatorial explosion and the virtual impossibility to predict the ranges. An actual way of solving the problem is using modern databases containing structural formulae and spectra of substances. The basis of the method is a hypothesis that similar spectra (subspectra) correspond to similar structures (substructures).

Two approaches to identification of large fragments using IR, NMR and mass spectra databases have been described. The algorithm suggested to this end in the first approach is reduced to three main operations:^{64–72} (1) search for structures whose spectra are similar to a given experimental spectrum and ordering the former according to decrease in similarity; (2) selection of a number of structures in the beginning of the list that, according to the basic hypothesis, have the highest resemblance to the structure of the analysed compound; and (3) selection (among these structures) of largest common fragments that can be plausible constituents of the structure of the unknown compound. The probability of correct identification of the fragment increases if the database retrieval system selects the data using several types of spectra and the selected fragments are tested on the basis of coincidence of the predicted subspectra (the latter can be most easily done using ¹³C NMR spectra).

Realisation of the above algorithm requires reliable quantitative criteria for structural and spectral similarity, as well as methods for revealing the largest common subgraph in a set of chemical graphs. Studies on the development of such methods gave rise to an independent investigation line in graph theory and numerous studies on the subject have been reported.

The other method for recognising large fragments found a wide application in practice due to the appearance of large

¹³C NMR spectra databases. In these types of databases the structures are described by 'spherical' code⁷³ while the signals in the spectra are assigned to corresponding carbon atoms. This made it possible (see, *e.g.*, Refs 30, 31, 74) to develop algorithms which can automatically create the subspectrum–substructure correlation libraries used for solving the problem raised. First, the program compares all subspectra of library fragments with the experimental NMR spectrum of the analysed substance. In this case it is necessary that the signal intensity (*i.e.*, the number of carbon atoms) be also indicated in addition to the chemical shifts and signal multiplicities. As a result, only those substructures (fragments) are selected to which subspectra coinciding (within the limits of prescribed deviations) with the query subspectra correspond. Further, the most probable fragments are selected by a detailed analysis of spectral information and ranked in descending order with respect to the number of carbon atoms and skeletal atoms. Thus, the largest fragments appear in the beginning of the list (the use of the described procedure in ES is considered below).

III. Generation of structural formulae of isomers

No more than two dozen of publications concerning the search for ways of increasing the software performance and methods of more efficient use of structural constraints have appeared after the first generators of isomers^{3, 75–78} were developed. This relatively small number indicates stubbornness of the problem rather than a loss of its actuality or interest. The numbers of possible structural formulae and the CPU time grow exponentially as the number of skeletal atoms and fragments involved in the generation process [they are called discrete units of structure (DUS)]⁷ increase. Therefore, all the efforts were aimed at using structural constraints even in the course of rather than after structure generation and at developing new algorithms that make possible improving the efficiency of generation.

This interesting and ambitious problem drew the attention of mathematicians, specialists in the field of graph theory and combinatorial analysis, which resulted in the development of new approaches and appearance of efficient software (COCOA,⁷⁹ MOLGEN,^{80–82} and GENM^{83–86} programs). Parallel to the search for efficient generation algorithms, computer performance has increased swiftly. On the whole, this has led to appreciable increase in dimensionality of the problems which can be solved using modern generators of isomers. Currently, the number of DUS used in the structure generation that takes a 'reasonable' time lies in the range from 10 to 16 depending on the valence of the atoms considered as DUS, the number of free bonds in the fragments, the unsaturation degree of the molecule and several other factors (*cf.* with 7–8 DUS in the 1970s). For instance, it took 3420 s to generate 4347 isomers of composition C₁₅H₃₂ using (the first in the USSR) program generator written by V V Raznikov in codes of an M-20 computer,⁷⁵ whereas a modern GENM program installed on a personal computer equipped with a Pentium CPU solves this problem in a matter of seconds. One more example can be given: generation of 217 isomers of composition C₆H₆ using the MAISS program written in Fortran algorithmic language and installed on a Minsk-32 computer took ~30 min;⁷⁷ the GENM program performs this task for a fraction of a second, which means that the actual rate of structure generation has increased by several orders of magnitude. However, since recognition of the structures of large molecules is of prime interest for practice, the generation stage remains a bottleneck for all ES despite the advances achieved.

Basic requirements for the structure generators have been formulated and realised as long ago as 1970s. The results of these studies were generalised.^{7, 8} The most important requirement is that, irrespective of generation algorithm used, the software suitable for practical use must contain flexible tools for imposing structural constraints among which the following are typical.

1. Fragments — DUS identified at the SGA stage. It is usually assumed that they have no overlapping atoms and the number of

free valence bonds of terminal atoms in such fragments is fixed. Therefore such fragments are also called macroatoms and they participate in structure generation along with free atoms. The DUS sets are designed of atoms and macroatoms and the total number of DUS in the set determines the dimensionality of the problem. Some programs, *e.g.*, GENOA⁸⁷ admit partial overlap of the macroatoms; however, this makes the algorithm more complicated and increases the generation time.

2. Obligatory and forbidden fragments (GOODLIST and BADLIST, respectively). These are structural constraints imposed by a chemist and each structure must meet these requirements. This type of constraint is imposed on the basis of *a priori* knowledge of the compound under study (the origin of the specimen, data of non-spectral experiments, *etc.*). These fragments have a peculiarity consisting in the possibility for their structures to overlap and superimpose on the DUS structure.

3. Constraints associated with the ring size and bond multiplicities make it possible to formulate general requirements for generated structures with consideration of specificity of the DUS set and *a priori* information (the presence of multiple bonds in macroatoms, rings, the inclusion of the unsaturation degree of the molecule, *etc.*).

4. Fragments which are unlikely in organic chemistry. These include small rings containing triple bonds, structures that contradict the Bredt rule, certain strained fused structures with small rings, fragments of the $-O-O-O-$ type, *etc.*

Since 'construction of generators' has become an individual division of mathematical chemistry and combinatorial mathematics, we will restrict ourselves to mentioning some new programs that are of prime interest for the ES creation. Detailed information concerning modern structure generation algorithms can be found in the theses.^{88,89}

The CONGEN generator developed in 1970s⁹⁰ is based on the algorithm generation by building up a chemical graph from its centre. As a result of improving this algorithm, the MOLGRAPH⁸⁰ and MOLGEN⁸¹⁻⁸³ programs have been developed. The MOLGEN program generates structures using nonoverlapping fragments. It has a high performance and is capable of generating stereoisomers. Currently, this generator has received wide acceptance in Europe.

A GENM program^{84-86,88} for generation of structural isomers was developed in the Russian Federation. The parameters of the program are at least as good as and in some instances superior to those of the MOLGEN program. The algorithm used has a number of unique features that make it possible to rule out 'hopeless' branches of the solution in the course of generation in accordance with the constraints imposed. Operating experience of the GENM generator at the Institute of Organic Chemistry (the Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russian Federation) and in the RASTR³⁶ and X-PERT²⁹ systems has shown its high reliability and fast operation.

The SMOG program^{89,91} allows a chemist to analyse different structural hypotheses in the course of investigations of chemical reactions. This program can generate structures containing atoms in unusual oxidation states or carrying formal charges, generate the molecules using both non-overlapping and overlapping fragments and recognise different resonance forms of the same aromatic molecule among the results of generation. The SMOG program can serve as a basis for the development of software tools designed to operate on a special-purpose workstation used in the chemical laboratory; however, the program operates not so fast to be used as a 'conveyer-type' structure generator in ES.

In some instances where the fragments are elucidated independently by using different methods of investigation (IR, NMR, MS, *etc.*) it may appear that the structures of particular fragments have common atomic groups (*e.g.*, $-\text{CH}=\text{CH}-\text{C}=\text{O}$ and $\text{>C}=\text{C}-\text{CH}_3$). In this connection the GENOA program⁸⁷

capable of generating the structures using overlapping fragments was developed to extend the potentialities of the CONGEN program. At the same time, structure generation using overlapping atoms belonging to different fragments is the major condition for operation of a number of recently developed programs.^{30,31,74} This type of algorithm was developed to provide structure generation using a set of fragments identified by means of ¹³C NMR spectra (see Section II.4). The program tries to match the atoms belonging to different fragments and predict the subspectrum of a new, enlarged fragment. If the predicted subspectrum does not contradict the experimental spectrum within the limits of prescribed admissible deviation, an attempt is made to add one more fragment, *etc.*

Thus, structure generation is a successive assembly accompanied by verification of the correctness of all possible combinations of the fragments. Structure generation using this approach does not require knowledge of an empirical formula and even the molecular weight. However, it should be compensated for the absence of empirical formula by ascribing a certain number of carbon atoms to each signal in the experimental NMR spectrum (this cannot be done in all cases, especially for symmetric molecules). This algorithm implicitly uses the $\text{C}_n\text{H}_{(m-k)}$ part of the empirical formula, where k is the number of hydrogen atoms bonded to hetero-atoms. Information on the latter is retrieved in the course of structure generation. However, if the set of selected fragments is not exhaustive with respect to the structure of the entire molecule, the generation fails. Application of this type of generator is considered in detail below.

Mention may be made of a number of studies (*e.g.*, Refs 92-97) in which different principles of structure generation were evaluated. However, their actual efficiency and performance can be assessed only by solving the test problems on clone-type computers, which seems to be difficult.

In some instances, structure recognition is not restricted to determination of the structural formula of the compound, but also involves the establishment of the spatial model of the molecule. To this end, algorithms and programs for generation of stereoisomers,^{83,98,99} and building of spatial models of the molecules⁹⁹⁻¹⁰³ were developed. They use structural formulae of organic compounds as the input information. Building spatial structures can appear to be necessary for prediction of the spectra of candidate structures, thus becoming an important stage of elucidation of the true structural formula of the compound analysed. It should be noted that one of the most efficient 3D-generators, CORINA,¹⁰¹ can be accessed *via* the Internet (the webpage URL is <http://www2.ccc.uni-erlangen.de/services/3d.html>).

IV. Prediction of spectra of probable structures

Prediction of the spectra of isomers to reveal plausible structures is the final stage of the ES operation. In practice, depending on how hard are structural constraints imposed, the answer file may contain tens, hundreds or even thousands of structural formulae that cannot be distinguished taking into account the ranges of changes in characteristic spectral features. This requires prediction of complete molecular spectra. Time-consuming quantum-chemical calculations are inapplicable in this case, so only fast approximate spectra prediction using various empirical correlations, rules and parameters, as well as spectral databases can be used. Numerous studies concerning this problem have been reported. Because of its prime importance for the methodology of the development of ES, let us consider the approaches to prediction of IR, ¹H and ¹³C NMR spectra.

1. Simulation of ¹³C NMR spectra

¹³C NMR spectroscopy is one of the most powerful methods for elucidation of the structure of organic molecules and testing structural hypotheses. Among all types of molecular spectra, it is the ¹³C NMR spectra that can be simulated most easily since in the case of off-resonance they consist of singlets, doublets, triplets and

quartets ($^1\text{H}-^{13}\text{C}$ spin-spin coupling through one bond) and each anisochronal (magnetically equivalent) carbon atom is ascribed a signal with specific chemical shift and multiplicity. Usually, 2D DEPT NMR experiments make possible reliable determination of signal multiplicities even in the case of strong overlap. Prediction of ^{13}C NMR spectra can be performed with different degree of detailisation.

a. Prediction of the number of signals with different multiplicity

Shelley and Munk¹⁰⁴ were the first who suggested use of prediction of the number of signals with different multiplicity for selecting candidate structures. The method is based on the topological analysis of a multigraph on which the structural formula of the molecule is mapped. All skeletal atoms are divided into groups of topologically equivalent atoms. Where all carbon atoms in the structure appear to be unique, the predicted number of signals in the spectrum is equal to the number of carbon atoms in the molecule; in this case the number of different types of multiplets is predicted automatically. If the structure contains several groups of equivalent carbon atoms, the expected number of signals in the spectrum is equal to the number of groups. The authors¹⁰⁴ analysed how stereochemical factors affect the correctness of prediction and suggested a number of rules which make it possible to take into account splitting of the signals of dimethyl groups located near a chiral centre. A simple comparison of predicted and experimental numbers of different types of multiplets allows one to reduce appreciably the number of candidates. However, it should be noted that accidental coincidence of inequivalent signals can occur or unexpected splittings can appear in the spectra. To improve this approach, it was suggested²⁹ that the number of signals with different multiplicity in characteristic spectral regions be predicted, which increased the resolving ability of the method used.

b. Prediction of chemical shifts

Simulation of ^{13}C NMR spectra is based on the prediction of chemical shifts of carbon atoms in the structure under consideration. The model spectrum obtained is compared with the experimental one and the structural hypothesis is accepted or rejected on the basis of calculated mean or standard deviations. There are two most widely used procedures for predicting NMR spectra, based on construction of empirical models¹⁰⁵⁻¹¹⁰ and on application of spectral databases.¹¹¹⁻¹¹⁵ Recently developed software¹¹⁶⁻¹¹⁸ uses both approaches. Attempts to simulate ^{13}C NMR spectra using ANN are also documented.¹¹⁹⁻¹²⁸

Grant and Paul¹²⁹ suggested the first additive linear model for calculating the chemical shifts of carbon atoms in aliphatic hydrocarbons using increments with consideration of the effects of environment up to δ -atoms. Later, linear models were constructed for alkanes, cyclohexanes, alcohols, amines, chlorine-containing compounds, *etc.* The formulae derived and tables of increments were collected in a number of monographs (see, *e.g.*, Refs 130, 131). The approach described provides a rather high quality of prediction, which stimulated the development of software for analysing the candidate structural formula, selecting a corresponding additive model for each carbon atom and calculating the chemical shift. This type of software is of limited utility since chemical shifts can be predicted only for sp^3 -hybridised carbon atoms and the increment values cannot be modified.

Fürst and Pretsch¹¹⁰ removed these restrictions. Using large databases containing structural information and assigned ^{13}C NMR spectra, the authors of this study succeeded in constructing linear models which can be applied to many classes of chemical compounds. The models contain configuration- and conformation-dependent parameters and take into consideration the configuration of C=C bonds and the presence of axial and equatorial substituents in the cyclohexane ring. The software developed allows modification of parameters (reference values and increments) and input of new additive rules. A test of the

program on the set of 170 000 known chemical shifts showed that the rules derived are fulfilled for 97% of the cases. The standard deviation of predicted chemical shifts from experimental values was 5.5 ppm; our experience has shown that calculations of the spectrum of medium size molecules ($\text{C}_{12}-\text{C}_{16}$) on a modern personal computer take no more than a second. Obviously, this program can be used for filtration of the answer files created by an ES.

In another approach,¹¹¹⁻¹¹⁵ databases containing structural information and chemical shifts of carbon atoms are used. For all carbon atoms of each reference compound contained in the database, atom-centred fragments (ACF) with a prescribed number of concentric layers are generated. These fragments and the corresponding chemical shifts are stored as an ordered list. To predict the spectrum of a candidate structure, the program selects all possible ACF existing in the structure, performs a search for their analogues in the database and ascribes the chemical shifts taken from the reference fragments to carbon atoms. If an ACF was not found in the database, the program usually performs 'interpolation' using the available 'most similar' structures. The results obtained using this approach are in very good agreement with experimental ones when using a large database containing a diversified set of structures (see, *e.g.*, Ref. 73). Usually, the difference between predicted and experimental chemical shifts lies within the limits of 1 ppm, which means that the prediction accuracy is rather high.

However, despite its indubitable advantages, the approach described has some drawbacks. The absence of stereochemical information in the database (only structural formulae are available) may strongly affect the prediction quality. As has been shown,¹³² neglect of stereochemical effects may increase the difference between predicted and experimental chemical shifts by more than 10 ppm. Spectral properties of the reference fragments used for extrapolation may appear to be not the closest to those of the fragments of the hypothetical structure. Additionally, the fact that the effect of an atom equally distant from another atom can be different in different compounds is ignored at the encoding stage. Finally, prediction of a spectrum takes a rather long time (tens of seconds and even minutes) depending on complexity of the molecule.

A method is described,¹¹⁷ which is a combination of both above-mentioned approaches. At the first stage, the environments of carbon atom in the reference and target (verified) structures are represented as vectors and the Euclidean distance between these vectors is calculated. After repeated application of this procedure, a test set of carbon atoms whose chemical environment is similar to that of carbon atoms in the target molecule is generated. If the degree of similarity of the chemical environment of the target atom appears to be high, the chemical shift characteristic of its 'twin' in the reference structure is ascribed to this atom in the target structure. Otherwise a linear model is constructed using the test set. To this end, descriptors describing topological, geometric and electronic properties of the environment are introduced. Models are constructed using multiple linear regression (MLR), partial least squares (PLS) method^{28, 133} and principal component analysis.²⁸ The test of the combined approach on the set of 38 500 atoms has shown that the mean deviation is 1.69 ppm, whereas this value was 1.85 ppm in the case of straightforward database retrieval procedure.

It was mentioned above that ANN can be used not only for structural interpretation of the spectra, but also for prediction of spectral pattern corresponding to a particular structure. Attempts to apply ANN for prediction of chemical shifts in NMR spectra have been undertaken taking methyl-substituted cyclohexanes,¹²¹ mono-substituted benzenes,¹²² monosaccharides,¹²⁵ ribonucleosides,¹²⁶ sp^2 - and sp^3 -hybridised α -atoms in acyclic alkenes^{127, 128} *etc* as examples.

Artificial neural networks are trained to predict spectra of compounds belonging to prescribed classes on a training set which includes structures encoded analogously to the procedure

described in Section II.3. In the course of training, the network uses encoded reference structures as input information and the output signals are compared with the ^{13}C NMR spectra of these structures. Training is completed if the deviations of predicted spectra from the reference ones take appropriate values. Let us consider the results of computational experiments¹²⁸ as an example.

The authors trained a network to predict the chemical shifts of sp^3 -hybridised carbon atoms in the α -position with respect to the double bond in acyclic alkenes. Parallel with the training, a MLR-based model was developed. Testing both models showed that the standard deviation lay within the limits from 1.3 to 1.5 ppm for ANN and was 3 ppm for the MLR model, which means that ANN can predict the spectra more correctly than linear models.

Artificial neural networks can be applied only to predict the spectra of compounds belonging to those classes on which the network was trained, whereas the structures included in the answer (output) files created by the ES may contain diversified and unexpected atomic fragments. We believe that the optimum strategy of applying prediction of ^{13}C NMR spectra must include two steps, *viz.*, screening of structures (using fast approximate prediction methods, *e.g.*, linear models¹¹⁰) followed by more accurate (oriented to chemical classes) prediction applied to those structures for which the mean or standard deviation lies within the limits of error of the computational method used and, hence, further refinement is required.

2. Prediction of ^1H NMR spectra

As was mentioned above, relative simplicity of prediction of ^{13}C NMR spectra is associated with the fact that they consist of clearly defined multiplets. It is a much more complicated problem to predict ^1H NMR spectra, because they contain both first-order signals and higher-order multiplets. This is also the reason for difficulties encountered when trying to compare automatically experimental and predicted spectra. That is why information on the methods for prediction of ^1H NMR spectra is scarce.

The Proton Shift program developed¹³⁴ to predict the chemical shifts in ^1H NMR spectra on the basis of simple linear models¹³¹ automatically determines the substructures for which certain rules are applicable and considers the rest part of the molecule as a set of substituents at each of the substructures selected. To extend the area of application of the program, different extrapolation procedures were used, including division of large substructures and replacement of missing substituents by related substructures. The program takes into account *cis-trans*-isomerism of double bonds as well as axial and equatorial positions of substituents in six-membered rings. Linear models are based on a large set of increments and the total number of parameters that can be used in calculations approaches 3000. A test on the set of 583 chemical shifts showed that the mean deviation of predicted values from the measured ones was 0.06 ppm (the standard deviation was 0.18 ppm).

The authors of another study¹³⁵ on evaluation of the quality of the Proton Shift system using a large test set found that the standard deviation of chemical shifts was 0.3 ppm, which is closer to actual values. Using the ASSEMBLE structure generator,¹³⁶ 24 308 isomers with 111 605 different proton environments were generated. The chemical shifts were assessed in 89% of the cases, which can be considered satisfactory. The mean time taken to predict the chemical shifts for one structure on a Macintosh Quadra 650 computer was 0.30 s. When comparing the predicted and experimental spectra, the input of the latter is performed manually as a set of chemical shifts of CH , CH_2 and CH_3 groups. The program compares each experimental chemical shift with the closest value of corresponding chemical shift in the predicted spectrum. Then the standard deviations are calculated to rank the isomers generated. The procedure for comparing the chemical shifts in high-order spectra used in the study cited¹³⁵ remains unclear. Most likely, the approach described can be used only for

preliminary rough selection of structures in the answer file ranked after predicting the ^{13}C NMR spectra.

The ACD/HNMR Predictor program¹³⁷ is designed to calculate automatically the absorbance curve in the ^1H NMR spectrum from the structural formula of the molecule. The program has an internal database containing 180 000 experimental chemical shifts and 25 000 experimental spin-spin coupling constants (SSCC). The algorithm of quantification of spin-spin interactions in organic compounds used by the system is based on parameters found for more than 3000 structural fragments. Each δ_{H} value in the database is assigned to a particular structural fragment and each $J_{\text{H-H}}$ constant is assigned to a pair of interacting structural fragments taking into account the skeleton bonding them. The internal database of assigned δ_{H} and $J_{\text{H-H}}$ values is based on the results of analysis of 48 000 experimental ^1H NMR spectra. The δ_{H} and $J_{\text{H-H}}$ values for fragments not found in the database are calculated using special-purpose algorithms.

Calculations of the spectrum are performed for the basic frequency of the spectrometer, which is considered as a parameter. Calculated chemical shifts and constants are provided with 95% confidence intervals to indicate the reliability of the calculated values. The spectrum is calculated with consideration of second-order interactions and long-range SSCC, which allows simulation of the spectra of strongly coupled spin systems containing up to eight magnetically inequivalent nuclei (if there are magnetically equivalent nuclei, then a larger number of interacting spins can be taken into account). The program recognises *cis-trans*-isomers of alkenes and *syn-anti*-isomers of amides, oximes, hydrazones and nitrosamines.

After input of the query structure whose spectrum should be predicted, the program automatically 'splits' the molecule into a set of unique fragments that are compared with the fragments contained in the internal database. If any structural fragment coincides with a fragment from the database, its experimental δ_{H} values are included into the set of chemical shifts of the structure. If some fragments are not found in the database, the chemical shifts are extrapolated using the parameters of similar fragments.

After composing the final lists of chemical shifts and SSCC, the program composes and diagonalises the spin Hamiltonian matrix to calculate the number of lines, their positions and intensities and to assign the δ_{H} values to the hydrogen atoms of candidate structure. The program generates the spectrum plot (including digitising of positions of the lines and the integrated curve). Calculations of chemical shifts, spectral contour, integrated curve and digitising of maxima take from several seconds to tens of seconds CPU time on a computer with a Pentium type CPU.

The ACD/HNMR Predictor program was developed to interpret experimental spectra and test hypotheses. However, where preliminary ranking of the structures in the answer file created by the ES was already done on the basis of ^{13}C NMR spectra prediction, only 5–10 structures placed at the beginning of the final list require additional testing. Hence, comparison of the calculated spectra with the experimental ones to select the most probable structures can be done with ease by a chemist.

The author of this review has assured himself that the approach used in this program is highly efficient when analysing the answer (output) files for many problems solved using ES.³¹ In all the cases considered, it has been possible either to elucidate the true structure or to reduce drastically the number of alternative structures.

3. Prediction of IR spectra

The nature of IR spectra is such that, in principle, they can be used for selecting candidate structures. This is due to the fact that IR spectrum depends not only on which groups constitute a molecule, but also on their arrangement; in other words, the IR spectrum reflects properties of the entire molecule. Therefore, considerable

efforts of many investigators were aimed at developing methods for prediction of IR spectra of organic molecules.

Semiempirical calculations of an IR spectrum using a computer database of molecular parameters (the geometry, force constants, electrooptical parameters) can be considered as an efficient method for predicting the spectra. A corresponding database as well as computational techniques and software were developed under the supervision of L A Gribov.¹³⁸ The IR spectrum is calculated in the harmonic valence-force field approximation using a semiempirical computational procedure for calculating the band intensities.¹³⁹ The force constants and electrooptical parameters to be stored in the database are found from quantum-chemical calculations followed by solving mechanical and electrooptical inverse spectral problems. Calculated spectra are represented as spectral distributions of the absorption coefficient and can be immediately compared with the experimental curves. Calculations of the IR spectrum of a medium-size molecule take several minutes of CPU time; however, preparation of input data may take from 15 min to several hours depending on the problem complexity. Our experience shows that this approach can be successfully used not only to select preferable isomeric structures, but also to elucidate plausible stereoisomers and conformers.¹⁴⁰

However, the advantages of this method for prediction of IR spectra have their counterpart consisting of at least three drawbacks: the method is not so fast as those used for prediction of NMR spectra and, hence, it cannot be used for 'conveyor-type' calculations of dozens of structures (to say nothing of hundreds and thousands of them); prediction of the spectrum cannot be performed automatically without attention of a chemist; and the method can be applied to recognise small- and medium-size molecules only.

The first two drawbacks are obvious and their influence will gradually decrease with improving the algorithms and increasing the computer performance. The third one is of crucial importance, since it is due to the nature of molecular vibrations rather than to limitations of the software performance imposed by the size of molecules (*e.g.*, a program¹³⁸ makes it possible to operate with the structures containing over 100 atoms). In the general case, the larger the molecule, the more rich its IR spectrum. This statement has a consequence consisting in a nearly uniform distribution of absorption bands of rather large molecules over the 'fingerprint' region, which makes it senseless to compare the calculated spectra of candidate structures with experimental ones. Therefore, it is appropriate to use straightforward calculations of IR spectra in those cases where it is impossible to make unambiguous decision using fast prediction methods.

Prediction of IR spectra of three isomers with closely related structures, for which standard deviations of predicted ¹³C NMR spectra appeared to be within the limits of admissible errors of computational procedure, is illustrated in Fig. 3. The structures are ordered in accordance with decreasing similarity between the predicted and experimental NMR spectra. Comparison of calculated and experimental IR spectra shows that the calculated spectrum of the structure shown in Fig. 3*b* is closer to the experimental spectrum than the calculated spectra of the other structures (see the region from 10 to 14 μm). The same result was obtained using the ACD/HNMR software package¹³⁷ developed for prediction of ¹H NMR spectra. Thus, three methods for prediction of spectra indicate the priority of the first structure (2,4-dimethylanisole).

Impossibility of using semiempirical methods for fast automated prediction of IR spectra has stimulated the search for another approaches. Dubois *et al.*¹⁴² suggested the simplest procedure for simulating the IR absorbance curve. A database containing 700 substructures with fixed expected absorbance regions in the IR spectra was created within the framework of the DARC system. The expected intensities and band shapes are indicated for each interval. The prediction method includes the search for reference fragments in the candidate structure and

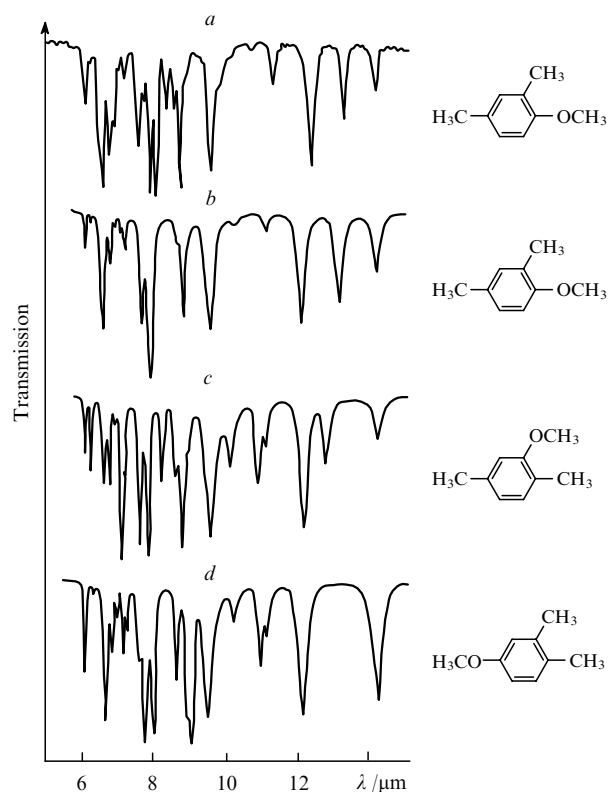


Figure 3. Experimental (a) and calculated (b–d) IR spectra of candidate structures.¹⁴¹

graphical representation of the spectrum of the molecule as superposition of the bands on the intervals corresponding to the fragments found. It is obvious that this approach leads to inevitable loss of many bands of skeletal vibrations in the 'fingerprint' region, as well as overtones and combination bands, and that the influence of molecular symmetry on the band intensities in the region of functional groups is ignored. It is also clear that the fragment library is far from exhausting all possible atomic combinations.

It should be kept in mind that, as a rule, characteristic spectral features of isomers included in the answer (output) file of ES correspond to experimental spectra. However, structurally similar isomers can be recognised first of all using noncharacteristic IR bands containing encoded structural information and observed in the 'fingerprint' region'. In practice, the most likely structure is chosen on the basis of careful comparison of frequencies and intensities of no more than five bands in the experimental and predicted IR spectra (see Fig. 3). Therefore the approach suggested¹⁴² should be considered unacceptable for the analysis of the answer structural files.

An attempt to use ANN for predicting the IR absorbance curves of organic compounds from numerically encoded structural formulae has been undertaken.¹⁴³ It has been possible to predict satisfactorily absorbance in the regions characteristic of functional groups; however, this approach appeared to be unacceptable for prediction of the 'fingerprint' region. It is likely that the failure can be explained by application of too rough a coding procedure, which, in particular, completely ignores the spatial structure of the molecules.

An analogous conclusion was also drawn by Weigel and Herges¹⁴⁴ who attempted to simulate IR spectra using an ANN trained on a set of spectra obtained from experiments and semiempirical quantum-chemical calculations.

In contrast to the above-mentioned failures, a new approach^{145, 146} seems to be encouraging. Taking into account

that IR spectra are strongly dependent on the spatial structure of molecules, the authors attempted to train the ANN on a training set composed of three-dimensional models of organic molecules. Since all models should be described by vectors of equal dimensionality, the impossibility of using Cartesian atomic coordinates in this case is obvious. To describe the spatial structure of molecules with different numbers of atoms using the same number of descriptors, it was subjected to a transformation based on the equation used for analysing experimental data on electron diffraction. This made it possible to find a procedure for coding any spatial structure by a vector with 32 or 64 coordinates (the 3D MoRSE code). Using the CORINA program¹⁰¹ for fast transformation of structural formulae into three-dimensional models, the authors studied the spatial structure–IR spectra correlations using ANN. The structural formulae from the training set and the target structures were first transformed into spatial models and then encoded using the 3D MoRSE code.

Experiments show that this methodology makes it possible to simulate adequately the IR spectra of specified classes of compounds throughout the absorption region including the region of ‘fingerprints’. The experimental and predicted IR spectra of a quinoline derivative are shown in Fig. 4 as an example (in this case, the ANN used for prediction was trained by the BPE method on a set of more than 50 quinoline and isoquinoline derivatives). The similarity of experimental and calculated spectral curves for this non-additive complex molecule shows that the approach has a chance to become an analytical tool for choosing plausible structures. However, it should be kept in mind that in this case successful results were obtained after training the network on the set of related compounds.

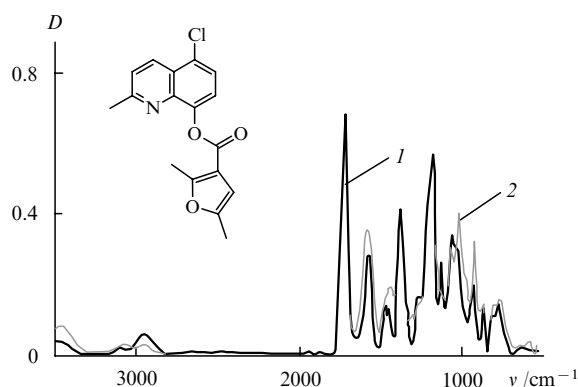


Figure 4. IR spectra of trisubstituted quinoline: experimental (1) and predicted using ANN (2).¹⁴⁶

It is noteworthy that, in principle, this approach also makes possible solving the ‘inverse’ problem, *viz.*, construction of the spatial model of a molecule using its IR spectrum. This was illustrated taking 1-phenylbutan-1-ol¹⁴⁶ and cholesterol¹⁴⁷ molecules as examples (in the latter case, the model found from the IR spectrum appeared to be fairly close to the structure obtained from semiempirical quantum-chemical calculations).

Yet another method¹⁴⁸ for prediction of IR spectra seems to be promising. On the basis of the search for nearest neighbours of a target molecule in the library containing structures and corresponding IR spectra the authors proposed to develop a method for simulation of IR spectra in the region 2250–550 cm^{−1}. The prediction mechanism is based on a reasonable assumption that similar IR spectra correspond to similar structural features. Thus, it is assumed that it is highly probable for compounds assigned the highest similarity rank to have IR spectra similar to that of the target molecule. The predicted spectrum is composed of the spectra of the neighbours (the nearest neighbours in the structure space) if they meet specific requirements for structural similarity.

The structures and spectra are considered as such, *i.e.*, no substructure–subspectrum correlations are used. This approach is most likely to retain noncharacteristic skeletal vibrations, overtones and combination bands, as well as the bands that are changed depending on the molecular symmetry (usually, these bands are in correlation tables). This method of nearest neighbours has also the advantages that it requires no preliminary classification of reference substances and allows easy elucidation of the target molecules that have no analogues in the reference set, thus indicating impossibility to simulate the spectrum.

Implementation of this idea required choice of such procedures for coding fragments, structures and spectra that would make it possible to introduce quantitative measures of structural and spectral similarity. Two methods of structure representation used in the study cited¹⁴⁸ were the method of ACF with one atomic layer¹⁴⁹ and a method which employs a modified graph-theoretical descriptor designated as the ES vector.¹⁵⁰

The ACF code is a reasonable compromise between the undue increase in the number of fragments and comprehensive description of the molecule. In this case, each atom is characterised by its own type (C, O, *etc.*) and by the types of the atoms and bonds of its nearest neighbours (hydrogen atoms are ignored). The fragment size varies from two atoms and one bond (a terminal group) to five atoms and four bonds for the atoms with four valence bonds. The fragments are ordered in the same way as the coordinates of the *n*-dimensional vector and each molecule is characterised by its own vector. The presence or absence of a fragment in the molecule is represented as a binary 1 or 0, respectively, and the occurrence number of the given fragment in the structure is indicated.

The program selected 180 different fragments in the set of about 9000 compounds for which the IR spectra were known. The structures were coded as vectors with *n* = 180. The molecules consisting of C, N, O, Br and Cl atoms and containing ordinary, double, triple and other bonds were selected. On the average, the structure was described by eight different fragments while the reference molecules were polyfunctional.

Using the ACF code, it is possible to exactly describe various functional groups and, at the same time, impossible to distinguish the variants of mutual orientation of functional groups within the same molecule (*e.g.*, substitution types in benzene ring). Therefore, the ES vector¹⁵⁰ was used as an additional descriptor to simulate the structure in more detail. It is less sensitive to changes in the atomic groups than the ACF code; however, both codes well complement each other. The ES vector code is based on the counting statistics of the number of routes in the coloured molecular graph mapped onto the coded compound. It provides a way for performing a detailed (though highly redundant) description; therefore the principal component analysis²⁸ of encoded data was applied in the next stage. To characterise each molecule, the contributions from the first eight principal components responsible for 99% of changes of complete code were used. Experiments have shown that the structure encoding system¹⁴⁸ is rather well suited in this case.

Various procedures for estimating the degree of structural similarity have been considered.¹⁵¹ In particular, similarity of structures X and Y characterised by vectors $\mathbf{X} = \{x_1, \dots, x_i, \dots, x_n\}$ and $\mathbf{Y} = \{y_1, \dots, y_i, \dots, y_n\}$ can be described using the Tanimoto coefficient

$$S_T = \frac{\sum_i x_i y_i}{\sum_i x_i^2 + \sum_i y_i^2 - \sum_i x_i y_i}.$$

The X and Y vectors can be composed of zeros and unities representing the presence or absence of the fragment, respectively, or of integers representing the occurrence number of the fragment in the structure. As applied to IR spectra, the 0/1 representation is more informative than the integer representation, since the absence of any fragment often changes the entire IR spectrum, whereas the difference in the number of the same structural

fragments usually results in a gradual change in the spectral pattern. Therefore, the structures to be sorted are selected using 0,1 vectors and ranked in accordance with the similarity criterion calculated on the basis of the occurrence number. Ranking of molecules using ES vectors is based on calculations of Euclidean distances from the vector of the target molecule.

Experiments were carried out using the IR spectra recorded in the region $2250\text{--}550\text{ cm}^{-1}$ with a resolution of 2 cm^{-1} and represented as sets of 128 points separated by 13.5 cm^{-1} (this corresponded to the same spectral resolution); at each of the 128 points, the value was averaged over seven points in the experimental spectrum covering the 13.5 cm^{-1} interval. Spectral intensities were normalised so that the absorbance of the most intense band was taken as 1.0.

Reliable estimate of similarity in the IR spectra is by no means easy problem. The spectral pattern seen by a spectroscopist's eye is hard to digitise. To solve this problem, the Pearson rank correlation coefficient and Spearman rank correlation coefficient (the strongest, medium intensity and weakest peaks are respectively characterised by the highest, mean and lowest ranks) were used.¹⁴⁸

The spectrum prediction algorithm was as follows.

1. Search for the nearest neighbours in the structure space. Compare the target structure with all reference structures in the collection and select k nearest neighbours for each of three models of structural similarity (the Tanimoto coefficients for both the 0,1 and integer vectors and the Euclidean distances for ES vectors). Get three lists of coincidences, containing information on k structures each.

2. Rank the selected molecules in accordance with the three measures of similarity. Search for the same structures in the three lists and sum up the individual ranks. If some molecules were found in one or two lists only, then ascribe rank $k + 1$ to these molecules in those lists in which they were not found. Sort molecules in ascending order of complete ranks and generate the final list.

3. Select those molecules whose characteristics either exceed the structural similarity threshold or are below the distance threshold.

4. If the final list contains information on less than two molecules, then terminate the procedure and display the results. Go to step 6.

5. Check the IR spectra of selected molecules for spectral homogeneity using correlation coefficients. If more than 50% of the spectra (*e.g.*, 2 out of 2, 2 out of 3, 3 out of 4, *etc.*) are much alike (*i.e.*, the correlation coefficient value exceeds a certain threshold value), then use the averaged spectrum for prediction. If the checking for homogeneity fails, then return control to the chemist. Go to step 6. In any case, display all available information.

6. Reject automated prediction since no or only one molecule is available. Prompt the chemist to assess the situation and decide between continuation and termination of the program. If a decision to predict the spectrum is made, then prompt the chemist to specify the molecules that were ascribed the highest rank and whose spectra should be used.

Thus, prediction can be performed either automatically or manually. If the chemist makes final decision, the result of prediction is characterised by higher quality. The CPU time is dependent on the number of fragments in the structure and takes several seconds on a personal computer with a Pentium CPU operated at 75 MHz, which is well suited.

Unfortunately, the authors restricted themselves to demonstration of a unique example (Fig. 5), which shows that the predicted and experimental spectra are similar. However, no attempts were made to test the method by sorting actual answer files of the ES, which makes impossible to obtain a statistically justified estimate. In our opinion, this approach has the advantage that its algorithm is free from the 'black box' type elements; therefore, the spectroscopist can easily establish the reasons for change in the prediction quality.

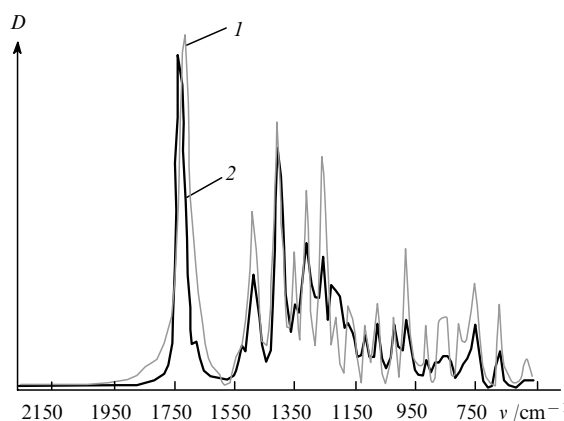


Figure 5. IR spectra: experimental (1) and predicted on the basis of search for the nearest neighbours of the target molecule (2).

V. Pathways of development of expert systems

Among the expert systems created in 1970–1980s, the best known is the DENDRAL system⁸ referred to as a 'classical' example of ES in numerous publications on chemistry and books on AI. Popularity of the DENDRAL system is, on the one hand, to a great extent associated with the fact that this project was worked out under supervision of the Nobel Prize winner J Lederberg and noted scientists in the field of AI. On the other hand, the authors of the project have reported about 40 articles collectively called 'Application of artificial intelligence in chemistry', which could not but draw the attention of many specialists. However, Gray¹⁵² critically analysed the idea behind the DENDRAL system and concluded that this artificial intelligence system is far from being perfect. This problem was hotly debated^{153, 154} with participation of the directors of the project. In contrast to a widespread opinion that the CONGEN program has found extensive application, Gray stated that it used rarely (he knows 8 articles in which application of the system was reported). One of the reasons for not-too-high popularity of the system is probably that it is not user-friendly.

In this review the emphasis is placed on the modern ES appeared in the 1990s. The potentialities of modern ES and those belonging to earlier generations were compared.¹⁵⁵ In the last decade, the efforts of researchers were aimed to improve the methods for retrieval of structural information from the spectra, to search for optimum strategies of computer-assisted structure recognition and to increase the user-friendliness of the systems. Our experience has shown that non-user-friendly ES have no chances to become an analytical tool for the chemist. A user-friendly system must:

- (1) have convenient and operationally simple tools for information interchange with the user, which allows the chemist control over any step of the solution of the problem;
- (2) offer the chemist the possibility of getting explanation of each decision made by the program;
- (3) inform the chemist in case of 'emergency' at any solution step and display messages adequate to the situation;
- (4) have advanced graphical tools for representing spectral and structural information to allow a chemist to quickly assess current status of the program operation and make corresponding decision.

In this review we consider certain ES, which, in our opinion, reflect modern tendencies and new approaches. However, let us first define basic concepts to be used later. Let the empirical formula of an unknown compound be determined and the number of isomers corresponding to the empirical formula be N . In principle, the N value can be found by structure generation using appropriate software. We say that a set of n structures ($1 \leq n \leq N$)

selected after the ES operation is a solution of the problem. The solution is correct if it contains a proper structure, otherwise it is incorrect. A correct solution and proper structure can be found only by checking each structure from the answer file using prediction of its spectra and additional experiments. If the answer file is empty ($n = 0$), the problem has no solution consistent with experimental data, information stored in the knowledge base and system options.

A description of the RASTR expert system created to elucidate the molecular structure using IR and NMR spectra is available (see, e.g., Ref. 22). This system is capable not only of revealing possible structures, but also of generating, constructing and depicting spatial models of all stereoisomers corresponding to a given structural formula. The RASTR system was used as a prototype and basis for a user-friendly X-PERT system²⁹ which operates under MS WINDOWS. Let us consider the most important elements of this ES, which in one form or another are incorporated into several other systems.

1. The X-PERT system

The X-PERT system was created to elucidate the structure of organic molecules containing up to 30–35 skeletal atoms (C, N, O, P, S, B, Si, Hal) using IR, ¹H and ¹³C NMR spectra. The knowledge base of the system comprises a set of libraries of molecular fragments and ranges of changes in their characteristic spectral features. The libraries are composed taking into account that the fragments belong to different classes of chemical compounds and respond specifically toward different types of spectroscopic techniques. Libraries belonging to different categories play different roles. The first category comprises universal libraries used for both fragment selection and structure filtration. Libraries belonging to the second category are adjusted to different types of spectroscopic techniques and are mainly used as filters for structure verification. Each fragment in every library is associated with its characteristic features in IR and NMR spectra, which are also stored in the knowledge base.

There are four hierarchically organised universal libraries.

1. Library of principal functional groups (LPF), e.g., C=O, C≡N, etc. The widest ranges of changes in characteristic spectral features are used for these groups irrespective of the nearest environment of a fragment. These libraries are mainly used for preliminary evaluation of a specimen to assign it to a particular class of chemical compounds and for recognition of the structure of non-additive compounds.

2. Library for structural-group analysis contains functional groups and information on the admissible nearest environment,

e.g., $\begin{array}{c} | \\ -C-CO-C \\ | \end{array}$, $\begin{array}{c} | \\ -C-O-C=O \\ | \end{array}$, $-CH_2-OH$, etc. The library

is used for SGA and structure filtration.

3. Library of aromatic fragments (AROM) contains 12 types of benzene ring substitution.

4. Library of phosphorus-containing fragments.

There are the following specialised libraries:

A library of ¹³C NMR data; three libraries of ¹H NMR data to reveal CH₃, CH₂ and CH groups with consideration of the nearest environment; a library containing fragments (mostly cyclic) characterised by strong specific absorption bands (e.g., four- and five-membered cyclic ketones, lactones, lactams, etc.); and a library of fragments containing an OH group.

For each fragment, the system generates a 'visit card' containing the following information: the fragment structure; ranges of changes in the characteristic features in IR (frequencies, halfwidths and intensities of absorption bands) and NMR spectra (chemical shifts, SSCC, signal multiplicities and corresponding numbers of C or H atoms); structural descriptors used to set the requirements for the fragment environment (additivity conditions) and provide retention of its spectral features on going from one molecule to another. Descriptors characterise the frag-

ment atoms with free valence bonds. The descriptor indicates the possibility of adding a hydrogen atom, hetero-atoms (they can be enumerated), aromatic cycles and multiple bonds to a given atom. The possibility (or impossibility) of the formation of a multiple bond and incorporation of the fragment into cyclic structures of specified size is also indicated.

The descriptor can have three types of meanings: 'possible' (P), 'forbidden' (F) and 'obligatory' (O). The program finds classes of topologically equivalent atoms with free bonds in the fragment structure and colours them using individual colours. Each coloured atom is associated with a column of corresponding colour in the table of descriptors. This makes it possible easily to form, interpret and correct the values of descriptors characterising equivalent atoms. The total number of fragments in the libraries is 450.

Experimental data (the empirical formula or molecular weight and available spectra) can be input manually or imported using the OPUS and WIN-NMR programs. The system checks the data for consistency and prompts the chemist to double-check the reliability of the data in questionable situations. If the empirical formula is unknown or questionable, the program generates all possible molecular formulae corresponding to the specified molecular weight taking into account the constraints imposed on the qualitative and quantitative composition of the substance. In this case the most probable molecular formula is chosen using a recently developed method.^{156†}

From this time on, the system operates in the interactive mode. This makes it possible to use the experience and intuition of the chemist and the capability of computer to perform fast search for necessary information and complex logic-combinatorial calculations. In this case, the basic requirement for ES is also met: at any step in the solution the program can explain the reasons for one or another decision and the user can be prompted to activate a corresponding option.

Prior to starting the operation, the program assesses complexity of the problem and displays messages concerning the method of its solution. If the problem can be solved automatically, the program generates all structural isomers and selects possible structures by passing them through a system of filters.

The first stage of the standard method for solution is generation of fragment sets. First, possible fragments are selected with consideration for their empirical formulae, spectral intervals and the unsaturation degree. In this case, necessary libraries of fragments are chosen by the user. The fragments are selected taking into account that the reliability of finding a fragment is 100% if the experimental band falls into the middle of the characteristic interval. It (reliability) linearly decreases as the interval bounds are approached and decreases to zero on both sides of the bounds. A trapezoidal membership function¹⁹ of the interval is chosen so that the decrease in the reliability near the bounds with increasing the length of the interval be more gradual.

The fragments selected and their reliability indices are displayed. The 'Show Spectra' procedure makes it possible to represent experimental spectra and characteristic intervals for selected fragments in clear graphical form to allow the chemist to assess the reliability of the fragments and to edit the list by adding (if needed) his own fragments. Then the table with interpretation data of all available experimental spectra is displayed. The chemist can analyse logical relations between the fragments and correct the 'reasoning' of the program using his experience and *a priori* information. The final set of consistent logical equations is used as input information for the 'inference machine'. The result of the solution of the logical equations [function f(A), see Section II.1] is displayed as a set or several sets of fragments consistent with the spectra, empirical formula and the unsaturation degree of the compound analysed. The program automatically adds sets of

† See also a recent study by M E Elyashberg, Yu Z Karasev and E R Martirosian *Anal. Chim. Acta* **388** 353 (1999).

microfragments such as CH_3 , CH_2 , *etc.*, which were not included as constituents of the structures of selected fragments. The chemist can also correct the selected fragment sets or compose his own sets. The special-purpose 'Multiple Fragments' procedure allows for the inclusion of a fragment appearing repeatedly in the structure, which reduces dimensionality of the problem.

Structure generation using fragment sets is the next step of the program operation. In this stage, the possibility of imposing structural constraints listed in Section III (GOODLIST, BADLIST, constraints associated with the ring size, bond multiplicities, *etc.*) is provided. There is an additional option which enables or cancels the descriptor control in the course of structure generation. The descriptor control is useful to preclude generation of a large number of wrong (bad) structures. Cancellation of the descriptor control can appear to be useful in the case of repeated solution of the problem if the structures found are questionable. The structure generation is carried out by the program based on the known algorithms.^{84,85} The structure counters allow the chemist to monitor the process and assess the efficiency of the constraints imposed.

Structure generation using fragment sets and free atoms can lead to such substructures whose presence contradicts the spectra and/or concepts of organic chemistry, therefore all generated structures are verified using the following six filters (see Section IV).

1. Checking for consistency with characteristic spectral features.
2. Rough simulation of ^{13}C NMR spectra (see Section IV.1.a).
3. Checking for consistency with principles of structural chemistry and stereochemistry (unlikely fragments, Bredt's rule).
4. Checking each isomer for its appropriateness to be used in interpreting experimental spectra.
5. Search for and exclusion of identical structures.
6. Prediction of chemical shifts in ^{13}C NMR spectra to reveal the most probable structures.

The system chooses necessary libraries on the basis of generalised 'portrait' of the answer file to perform a two-stage check. In the first stage, the list of fragments that contradict the spectra is generated. In the second stage, only contradictory fragments are sifted using structural formulae to save time and reject those structures in which at least one of these fragments is found. Options used in the filtration stage allow the user to specify the parameters determining hardness of constraints imposed (*i.e.*, the degree of fuzziness of the interval bounds).

Structure verification using the first and second filters can be performed in both the standard and supervised modes. The first of them provides automated filtration (the so-called 'blind' filtration). In this case, only messages on the current status of program operation and the running number of 'good' and 'bad' structures are displayed. In the second mode, the filtration process is visualised and the user can control over it as well as get all information necessary to explain the decisions made by the system. Each structural formula to be checked is displayed. If no contradictory fragments are found in the structure (it should be kept in mind that only these are sifted), the structure is indicated as good. Otherwise contradictory fragments found in the structural formula are coloured and information on characteristic spectral features (frequencies, chemical shifts, parameters of bands or signals) not confirmed by the spectra is displayed in the form of a 'visit card' of the fragment.

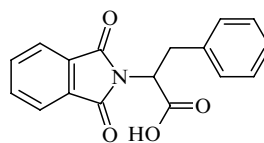
Depending on the number and type of contradictory fragments found in the structure, the user decides to reject the structure as unlikely or accept it for further checking. Structure filtration using this user-friendly mode of the program operation is visualised, fully controllable and understandable.

Checking the number of signals with different multiplicity in ^{13}C NMR spectra in the supervised mode is accompanied by displaying the data on the differences between the number of predicted and observed signals.

After passing the data through the first five filters the system automatically uses the answer file as input data for the SpekEdit program which predicts the chemical shifts in ^{13}C NMR spectra. Then the standard deviations (*S*) of calculated spectra from experimental ones are calculated and the structures are ranked in ascending order of *S*.

The potentialities of the system will be assessed below; here we consider only one example to illustrate the operation of the program.²⁹

Let an unknown compound have a molecular weight of 295 and possible composition $\text{C}_{1-50} \text{H}_{0-120} \text{N}_{0-30} \text{O}_{0-30}$; 197 different molecular formulae correspond to this set of parameters. Using IR and NMR spectral data, the program found the only molecular formula $\text{C}_{17}\text{H}_{13}\text{N}_1\text{O}_4$ and created the fragment sets (1) $\text{C}=\text{O}$, C_6H_5 , 1,2- C_6H_4 and (2) $\text{C}=\text{O}$, C_6H_5 , 1,3- C_6H_4 . These sets were used to generate 6995 structures. The proper structure



was elucidated using spectral and structural filtration.

2. The SpecSolv system

The SpecSolv system[‡] is a new module of the well known SpecInfo system¹⁵⁷ designed for storage and structural interpretation of NMR, IR and mass spectra. In particular, the SpecInfo knowledge base consists of over 200 000 assigned ^{13}C NMR spectra which serve as a basis for the development of the program.

The SpecSolv system is designed to elucidate the molecular structure using the ^{13}C NMR spectrum only and does not require the knowledge of the molecular weight and molecular formula. It uses parameters of ^{13}C NMR spectra [the chemical shifts, signal multiplicities and intensities (the latter as the number of carbon atoms)] as input data. The knowledge base of the system is a library of fragments and their subspectra. The library was created by automated 'cutting off' fragments from the structures stored in the SpecInfo database and contains more than 400 000 fragments encoded by the three-sphere HOSE code⁷³ and more than 100 000 fragments encoded by the two-sphere HOSE code with respect to the central carbon atom. The library is carefully checked by experts.

Information on a fragment includes the connectivity matrix, HOSE codes of all heavy atoms and the subspectrum. Parameters of ^{13}C NMR spectrum (chemical shift, multiplicity, intensity and root-mean-square deviation *R* of the chemical shift) are stored for each carbon atom. The *R* values were calculated for the sets of equivalent substructures in the SpecInfo database. All fragments are completely defined including ring closures in the outer sphere.

The first step of structure elucidation with the program is the fragment search. All subspectra in the library of fragments are compared with the experimental spectrum and the fragments whose subspectra match corresponding regions in the experimental spectrum are selected. A typical case is selection of ~ 500 fragments for a molecule containing ~ 25 heavy atoms.

Fragment search includes three stages: preliminary (pre-search), main and fine search. After the first stage the subspectra are coded as strings encoding the presence of signals with a certain multiplicity within discrete regions of the ^{13}C NMR spectrum. At the second stage it is tested as to whether the number of signals in the regions selected after presearch has a matching number of lines in the experimental spectrum. The fine search includes checking for exact deviations of the chemical shifts in both spectra.

[‡] The first article contained the description of the SpecSolv system³⁰ appeared in 1996 and had an intriguing title 'Fully Automated Structure Elucidation — A Spectroscopist's Dream Comes True'.

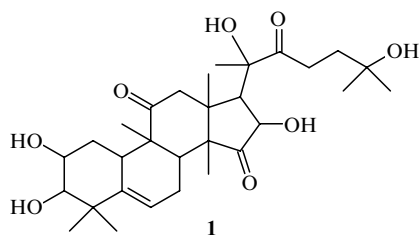
Typically, the deviation is 2 to 5 ppm. The selected fragments are then ranked in descending order of match factor, which is defined as the mean deviation of the chemical shift of each atom from the signals in the experimental spectrum.

Despite the fact that the program can operate without knowledge of the molecular formula, it is necessary to specify possible types of atoms (especially, hetero-atoms) since they cannot be immediately revealed by ^{13}C NMR spectroscopy.

It is essential that there is no need for a chemist to analyse all selected fragments, since bad fragments should be excluded at the stage of structure generation. However, if *a priori* information is available (most often, such is indeed the case), it can be expected that analysing the list will make it possible to exclude the bad fragments to save the working time. The main feature of the generation algorithm used in the SpecSolv system is that the fragments are linked by overlapping common atoms. The largest fragment whose subspectrum best matches a particular region of the experimental spectrum is taken as the first one and the program tries to add successively any other fragment to this fragment. If the new fragment passes the plausibility test, it is accepted and the enlarged fragment is considered as starting structure. Before adding the next fragment, the program predicts the ^{13}C NMR spectrum of the enlarged fragment. This is achieved by simple combination of the subspectra, which provides a high performance of prediction. Intermediate structures for which the deviations of the chemical shifts exceed a prescribed value are excluded. In this fashion the final structure is being assembled at the same time with cross-validation of intermediate structures. The absence of such a verification tool in structure generators that admit assembly of structures from overlapping fragments (e.g., GENOA⁸⁷) is a grave drawback.

The assembly continues until all chemical shifts in the experimental spectrum are assigned and free bonds in the resulting structure are absent. Usually, 10 generation cycles based on the first 10 best (the largest with minimum deviation of the chemical shifts) fragments are sufficient to elucidate the answer structure. This is possible since the selected fragments are ranked by match factor of their subspectra with the experimental spectrum. Most often, only one structure is found after exhaustive search in the entire fragment space, though several isomers of similar structure can also be obtained (in general, if no empirical formula is given, generation of nonisomeric structures is also possible).

Will, Fachinger and Richert³⁰ reported recognition of rather large molecules, e.g., such as **1**.



However, it is obvious that structure generation is possible only if the fragment library contains large overlapping fragments of such molecules. Hence successful identification requires the presence of a rather large number of large molecules related to the molecule to be recognised in the system database. However, even if the database contains appropriate fragments, the absence of common atoms will make generation of the proper structure impossible, which means a strong dependence of the result on the diversity and quality of the database. The program is also very 'sensitive' to the solvent in which the experimental spectrum is recorded and, in addition (this is a grave drawback) does not recognise stereoisomeric forms. These factors can have a determining effect on the results of comparison of predicted subspectra of intermediate substructures and the overall model spectrum with the experimental one. It is reported that the system elucidated the

structure of 80% of all compounds analysed in the laboratory. The system was adapted for exploitation on a VAX 6610 minicomputer.

As can be seen, at present 'a spectroscopist's dream' does not come true with the aid of the SpecSolv system since 20% of all problems remain unsolved. If the system cannot solve the problem, a corresponding message is generated and the program is terminated. Therefore new approaches are required which make it possible to resume the analysis in those cases where the program reaches a deadlock. A procedure for overcoming a deadlock has been implemented in the ACD/Structure Elucidator system.³¹

3. The ACD/Structure Elucidator system

The ACD/Structure Elucidator system integrates the recognition strategy developed by the authors of the SpecSolv system³⁰ and conventional methodology used in the RASTR,²² X-PERT,²⁹ CHEMICS³⁷ and other systems.

Two structure elucidation modes, a standard mode and the classical ES mode are permitted. The first mode is to a great extent based on the known general strategy.³⁰ As in the SpecSolv system, the set of experimental data includes a ^{13}C NMR spectrum, chemical shifts, signal multiplicities and intensities. If it is difficult to indicate the exact number of carbon atoms assigned to a signal, their minimum and maximum values are specified. To facilitate measurements of signal intensities, it is appropriate to record a ^{13}C NMR spectrum with an admixture of a paramagnetic reagent, e.g., $\text{Cr}(\text{acac})_2$, which shortens and equalises the spin-lattice relaxation time T_1 for all carbon atoms including quaternary ones. The experimental spectrum can be imported directly from the spectrometer or the user can input spectral parameters manually. Usually, only an NMR spectrum is required for structure elucidation; however, it is helpful to have IR and ^1H NMR spectral data to facilitate the solution of the problem. The database of the system is a library consisting of more than 400 000 fragments and their ^{13}C NMR subspectra that were derived from 135 000 structures with assigned ^{13}C NMR spectra (the structural database). This ES has an appreciably smaller knowledge base than the SpecSolv system has.

The operation of the program begins with the search for ^{13}C NMR spectrum in the knowledge base. Once a spectrum is found, a corresponding structure is displayed and the program is completed. Otherwise the structure is reconstructed from fragments.

At first, the program selects fragments whose subspectra do not contradict the experimental spectrum. The fragments found are sorted in descending order of the number of skeletal atoms and mean deviations of their subspectra from corresponding signals in the experimental spectrum. Since it is impossible to accept or reject the presence of, e.g., OH, NH and $\text{C}\equiv\text{N}$ groups or to differentiate between δ_{C} of the $\text{O}=\text{C}-\text{N}$ group and aromatic ring signal (150–160 ppm) using the ^{13}C NMR spectrum, then, if the IR spectrum is available, filtration of selected substructures is performed using a library of functional groups having the most characteristic features in the IR spectra. Analogous filtration can be performed using fragments having clearly defined characteristic features in the ^1H NMR spectra. After filtration the number of selected fragments is reduced (in some instances, it becomes halved), which favours placing good fragments at the beginning of the list. Then, beginning with the first fragment, the fragments are checked for the possibility of linking by common atoms to perform successive assembly of the structure. As in the SpecSolv system, linking the fragments is accompanied by prediction of the ^{13}C NMR subspectrum of the enlarged fragment to verify the correctness of the assembly.

The problem is considered solved if after checking of all possible combinations of the fragments the program generates one or several structures. The most promising fragments (*i.e.*, the largest ones whose subspectra match well the experimental spectrum) are placed at the beginning of the list; therefore the answer structure is often generated within minutes after starting

the operation of the program. In the case of good correspondence between the ^{13}C NMR spectrum predicted for the answer structure and the experimental spectrum the process can be terminated before completion of exhaustive search for all combinations of the fragments.

If the attempt to assemble the structure fails (the knowledge base contains no appropriate fragments having common atoms or good fragments were not selected), the program automatically switches on the classical ES mode to operate with DUS.

As was mentioned in Section III, operation in this mode requires knowledge of the molecular formula or at least the molecular weight. If the molecular formula is unknown, the program first selects functional groups that would be present in the molecule analysed. To this end, a library containing a small number of the most characteristic functional groups and their spectral features is used. Then search for selected functional groups in the structure of previously selected fragments is performed. The elemental composition and unsaturation degrees of the verified functional groups, as well as the numbers of carbon and hydrogen atoms counted from NMR spectral data are used by the program for automated determination of structural constraints for the generator of empirical formulae. One or several possible empirical formulae established by this generator are passed to the structure generator for verification.

This structure generator operates with the atoms and fragments having no common atoms. It is based on the known algorithms.^{84–86} The fragment sets are composed as follows.

The first N (reference) fragments in the primary list of selected and filtered fragments (usually, the chemist varies the N value from 10 to 30 on his own) are chosen. Obviously, these are the largest fragments and this set almost always includes those fragments that are constituents of the structural formula of analysed compound. Then, the fact is used that, according to the ranking algorithm, small fragments (most often functional groups with their nearest environment) are placed at the end of the primary list.

The subspectrum of the first reference fragment is compared with the experimental spectrum to select the unmatched chemical shifts in the latter. Then, small fragments appropriate for interpreting these chemical shifts are chosen. Only those combinations of small fragments are added to the first reference fragment that provide the highest degree of interpretation of the experimental spectrum. If thereafter certain signals in the query ^{13}C NMR spectrum remain uninterpreted, the program adds corresponding microfragments (CH_3 , CH_2 , CH , $\text{C}=\text{O}$, *etc.*) to the set. Each of the sets obtained is checked for consistency with the current empirical formula of the molecule. The sets corresponding to the second, third, *etc.* reference fragment are generated analogously. If no small fragments appropriate for composing the sets were found, the latter are formed using microfragments so that the number of sets becomes equal N .

The chemist can add his own fragments to the sets, compose the sets based on one of the reference fragments and use all types of constraints described in Section III. To facilitate this, the program displays a 'generalised portrait' of the molecule under study, *i.e.*, the distribution of typical functional groups over frequency of meeting them in the selected fragments. High frequency of meeting indicates that the group is, probably, a constituent of the molecule, whereas the absent groups are used to generate the BADLIST.

Before starting the structure generation using the current fragment set the program assesses the working time (to this end, the percentage of the job done in a time set using system options, *e.g.*, 20 s, is measured) and, if it appears to be longer than a reasonable time, this set is skipped during the first program run and the program begins testing the next fragment set. All structures resulting from the structure generation process are checked for consistency with the available spectra and principles of organic chemistry and stereochemistry. A special program developed to search for tautomeric structures excludes unstable

forms from the list, which often substantially reduces the size of the answer file.

Then the structures automatically arrive at the input of the program for prediction of ^{13}C NMR spectra (the ACD/CNMR Predictor program¹¹⁸). When prediction is completed, the structures are ranked in ascending order of mean deviations of the predicted spectra from the experimental spectrum. Our experience shows that calculations of the spectrum using a personal computer equipped with a Pentium CPU operating at 133 MHz take from 0.5 to 1 s, so prediction of the spectra of 1000 structures takes only 5 to 15 min depending on the number of carbon atoms. Testing of the system showed that in the majority of cases the proper structure is ranked 1st or 2nd from the beginning of the answer file or is at least placed among the first dozen of the structures. However, if the difference between the chemical shift deviations of the preferred structure and the succeeding structure lies within the accuracy of the calculation of the ^{13}C NMR spectrum, further verification of the solution is required.

To this end, automated prediction of ^1H NMR spectra is performed using the ACD/HNMR Predictor program¹³⁷ (see Section IV.2). As a rule, only the spectra of the first dozen of structures are predicted, so the CPU working time is relatively short (~ 10 – 60 s per structure depending on the complexity of the spin systems calculated). Experimental and calculated ^1H NMR spectra are compared by a chemist who makes the final choice of the preferred structure or makes a decision on the necessity of additional experiments. The calculated spectra, integral curve and δ_{H} values for all lines are displayed. If the predicted spectra of several structures appear to be equally close to the experimental spectrum, the proper choice may be made by using the ΔCH_3 values for the δ_{CH_3} singlets

$$\Delta\text{CH}_3 = |\delta_{\text{CH}_3, \text{exp}} - \delta_{\text{CH}_3, \text{calc}}|$$

and comparing the integrals for all multiplets. In most cases, at $\Delta\text{CH}_3 \geq 0.2$ – 0.3 ppm the structure can be rejected. Resolving of questionable situations requires additional experiments, in particular, using 2D NMR spectroscopy.

Thus, the ACD/Structure Elucidator system differs from other systems in the possibility of using two interacting strategies for solving the problem, each of them being based on corresponding structure generator. If in both operating modes the program cannot automatically find an adequate solution, the possibility is provided of solving the problem in the step-by-step mode under the supervision of a chemist who has considerable opportunities to interfere in the 'reasoning' of the program. Testing of the system on a test set of 220 problems showed that correct solution can be found in 90% of cases.

4. 2D NMR spectroscopy in expert systems

The systems created have progressively been developing. In addition to improving the algorithms and extending the knowledge bases, attempts are made to use 2D NMR spectroscopic data in ES, since methods employed in this area of NMR spectroscopy have received wide acceptance and, actually, became routine.

For instance, instrumental tools for using 2D NMR spectroscopy data were incorporated into the CHEMICS system to extend its capabilities.^{158, 159} Methods of processing the data obtained in 2D-INADEQUATE ($\text{C}-\text{C}$ correlations through one bond) and $^1\text{H}-^{13}\text{C}$ NMR COSY ($\text{C}-\text{H}$ correlations through one bond)/ $^1\text{H}-^1\text{H}$ NMR COSY ($\text{H}-\text{H}$ correlations through three bonds) spectroscopic experiments were developed. Using the data of 2D NMR experiments, it is possible to reveal CH_n groups ($n = 0-3$) bonded by chemical bonds and to correlate this additional information with the library fragments selected by the system, thus testing the possibility of the formation of a bond between the fragments. The data obtained are used for controlling the process of structure generation from the fragments.

A new SESAMI system¹⁶¹ was created as a result of improving the CASE system.¹⁶⁰ The library of ^{13}C NMR spectra containing 5100 ACF with one-layer environment is used as the

database in this system. First, SESAMI generates an exhaustive list of fragments, which then is made more 'sparse' using a special-purpose subprogram. Another subroutine adds extra constraints imposed on the structures. The reduced list of fragments and the constraints are used as input data by the COCOA structure generator.⁷⁹ Preliminary selection of the structures generated is performed on the basis of prediction of their ¹³C NMR spectra and an expert makes the final decision.

Enhancement of potentialities of the SESAMI system is attained by incorporating the software¹⁶² developed for processing the data of 2D NMR experiments. The system receives information on correlations between signals and builds fragments consistent with these data. The structures are generated using the COCOA program. Further improvement of the system is performed to develop a module based on application of ANN and designed to elucidate the fragments in the case of simultaneous use of IR and ¹³C NMR spectra.

In parallel with improving the known ES by incorporating tools for processing 2D NMR data, investigations on creation of computer systems designed to retrieve and efficiently use structural information 'hidden' in 2D NMR spectra for molecular structure generation began in the last decade. The demand for the development of such systems is caused by the necessity of establishing the structures of very large molecules of natural products containing up to 50–60 skeletal atoms. Of interest is a recently developed approach.^{32, 163, 164} The authors started from a rather logical position that if once enormous efforts were made to isolate a natural product, carrying out a number of rather labour-consuming 2D NMR experiments seems to be entirely justified. Fragments designed immediately in the course of experiments are mostly used for structure elucidation. As a result, a CISOC-SES expert system was created whose operation requires the data of 1D (¹H and ¹³C) and 2D DEPT, DQF-COSY, HMQC, HMBC, HETCOR, COLOC and 2D-INADEQUATE NMR experiments. In this approach, structural data obtained from 2D NMR experiments are mostly used (the structure is reconstructed as if by applying 'the first principles'), therefore the authors called this approach 'ab initio'.

Obtaining information from 2D NMR experiments requires a skilful choice of procedures (pulse sequences) and correct use of data. Hence the efficiency of such systems will be to a great extent determined by the success in implementing the man–computer 'symbiosis'. Since the systems based on fragment selection retrieve valuable structural information, one should expect that both approaches will eventually integrate.

VI. Strategy of molecular structure elucidation

Since the requirements for the ES architecture are, on the whole, already formulated, the development of an optimum strategy of the ES application is topical. This problem can hardly be solved

theoretically because it is impossible to imagine the whole versatility of situations that may arise in the course of structure elucidation. Efficient approaches can be found only after analysis of the solution protocols of a rather large number of problems.

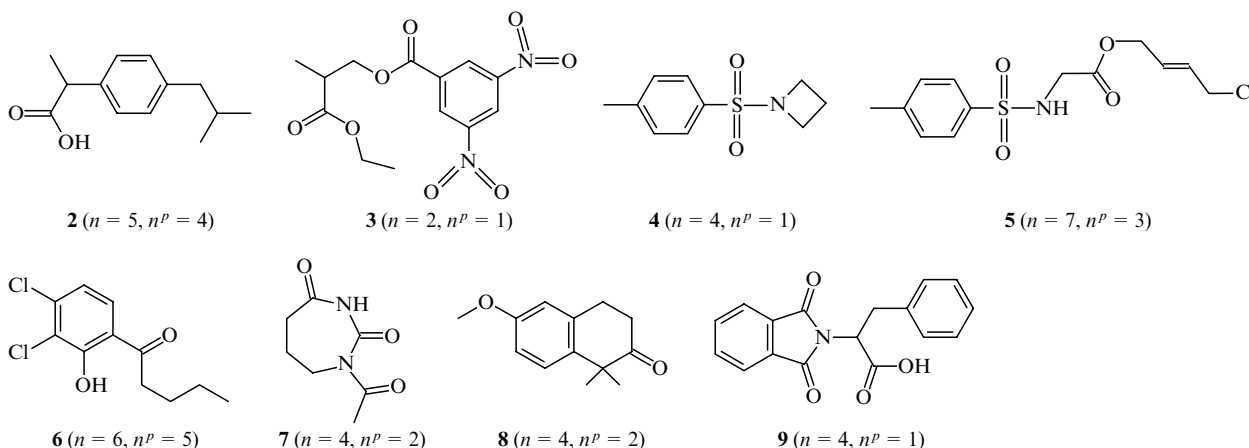
An attempt to develop the methodology of the molecular structure elucidation using ES was made.¹⁴¹ Particular emphasis was placed on the study of difficulties and contradictions that arise when solving the problems and on the development of procedures for overcoming them. The authors carried out a large-scale computational experiment using the X-PERT system.²⁹ About 200 structural problems taken mostly from monographs^{165–168} or spectral databases and analytical practice were solved. The molecules analysed contained from 10 to 23 skeletal atoms, which is characteristic of the compounds commonly used in industrial laboratories. Most of empirical formulae contained hetero-atoms (from 1 to 10). Over 80% of the total number of compounds belonged to the cyclic ones and about 45% of them contained benzene rings.

As a rule, experimental data included IR, ¹H and ¹³C NMR spectra, as well as the empirical formula or the molecular weight of the substance. To find possible ways of solving the problems, each of them was repeatedly solved using different methods and strategies. Particular emphasis was placed on elucidation of the reasons for difficulties and failures. To facilitate the logic-statistical analysis of the data obtained, the system automatically stored the solution protocols as text files incorporated into the active database. Plausible structures were elucidated on the basis of prediction of chemical shifts in the ¹³C NMR spectra using specially developed software.¹⁶⁹ Computational experiments were carried out on an AT 486 personal computer operated at 66 MHz.

Analysis of the protocols has shown that it is possible to find a correct solution in virtually all the cases considered using the interactive mode. The percentage of unambiguous solutions was 40% and the number *n* of candidate structures did not exceed 5 for 70% of the problems. The *n* value exceeded 10 for 15% of the problems. Prediction of ¹³C NMR spectra of ambiguously solved structures increased the total percentage of unambiguous and right answers from 40% to 75%, i.e., the proper structure was ranked 1st and placed at the beginning of the file.

For instance, the answer structures of molecules **2–9** were obtained with indication of *n* values, reduced size of the answer file after prediction of ¹³C NMR spectrum (*n*^p) and the number of the proper structure in the ranked answer file *n*^t. The *n*^p value was defined as the number of structures for which the root-mean-square deviation *s* does not exceed 5.5 ppm (the accuracy of the program¹⁶⁹).

About 60% of problems were solved automatically by using SGA or straightforward structure generation (SSG) from empirical formulae. In those cases where the structure was unambiguously elucidated by means of SSG followed by structure filtration, exhaustive information on the molecular structure was obtained



using characteristic features not observed in the experimental spectra. Moreover, filtration has led to recognition of certain structures containing fragments that were absent in the database.

In essence, the strategy of solving a problem is a set of methods for overcoming various difficulties. The authors¹⁴¹ analysed typical difficulties encountered when using ES.

1. Examples of difficult situations

Mixed-valence atoms. Depending on the valence state, mixed-valence chemical elements can form various functional groups (e.g., SH, >S=O , >SO_2 , >PH , >P=O). Each functional group generates its own family of isomers. Therefore, strictly speaking, structural problems should be repeatedly resolved until all valence states of atoms present in the empirical formula have been searched through. The problem is appreciably simplified if available information on the origin of a specimen or data of independent experiments make it possible to determine the valences of all elements in the empirical formula.

Specific character of IR spectrum. It is known that IR spectrum is extremely sensitive to slight changes in the molecular structure and electron density. This makes it possible to reveal even minor changes in the molecular structure. However, frequencies or intensities can be interpreted only if the structural formula of the molecule is known. This is impossible until the molecular structure has been recognised. For this reason, rearrangements of functional groups in the isomers, which have little effect on the additivity of the molecule, can cause the characteristic frequencies and band intensities to go beyond the limits indicated in the fragment libraries.

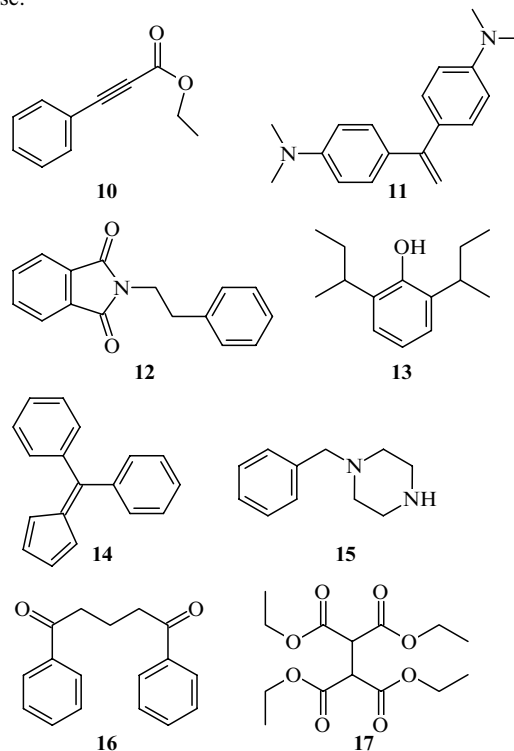
For instance, in some instances the bands at 3000, 1600 and 1500 cm^{-1} characteristic of benzene derivatives appear to be inactive or too weak to be detected in the spectrum. However, if the NMR spectra of such a compound contain signals in the aromatic region, the X-PERT system assesses the situation and prompts the chemist to accept or reject the presence of an aromatic fragment (in other words, to decide between 'yes' and 'no', respectively). Another problem arises if a compound is dissolved in a solvent of the CCl_4 or CHCl_3 type. In this case diagnostically important aromatic bands in the region 700–800 cm^{-1} cannot be used for determination of the types of benzene substitution, which results in increasing the size of the answer file.

The IR spectral pattern in the region of stretching vibrations of the OH group is dependent on many factors (the presence of neighbouring atoms and functional groups, solvent properties, etc.). Because of a very strong effect of the intramolecular $\text{O-H}\cdots\text{X}$ hydrogen bond, the parameters of some IR bands [$\nu_s(\text{OH})$, $\nu_s(\text{C=O})$, etc.] are shifted beyond the limits of characteristic intervals. Therefore, deciding between the presence and absence of the OH group often requires the interference of a chemist (the X-PERT system generates a corresponding message).

It turned out that joint use of IR and NMR spectra often leads to the loss of right fragments whose characteristic features were not confirmed because of unusual IR spectral pattern. Therefore, the IR spectrum should sometimes be 'switched off' during the first program session. Of course, it does not mean that the ES can exclude IR spectra from its 'reasoning', since there is a rather large number of functional groups which contain no C and H atoms (e.g., NO_2 , SO, SO_2 , NO, ONO, P=O , P=S , etc.) and cannot be immediately detected by NMR technique without using the IR spectral bands for confirmation.

The influence of structural peculiarities on the complexity of the problem. At first glance, it may appear that the larger the molecule, the larger the expected n value. Actually, the n value is a very complex function of different structural parameters. Therefore it is quite possible that a large molecule will be identified unambiguously, whereas the answer file created when recognising a relatively small molecule will contain a large number of structures. Let us consider the most important structural factors affecting the problem solution.

If the symmetry of the structure of analysed compound is higher than C_1 , the solution of the problem becomes easier, since a large number of wrong structures are often rejected after comparing the predicted number of signals and their multiplicities in the ^{13}C NMR spectrum with the experimental data. For instance, unique and proper answer structures were found for molecules 10–17. It should be noted that structure 12 containing the O=C-N-C=O fragment was unambiguously recognised despite the fact of the absence of this fragment in the knowledge base.



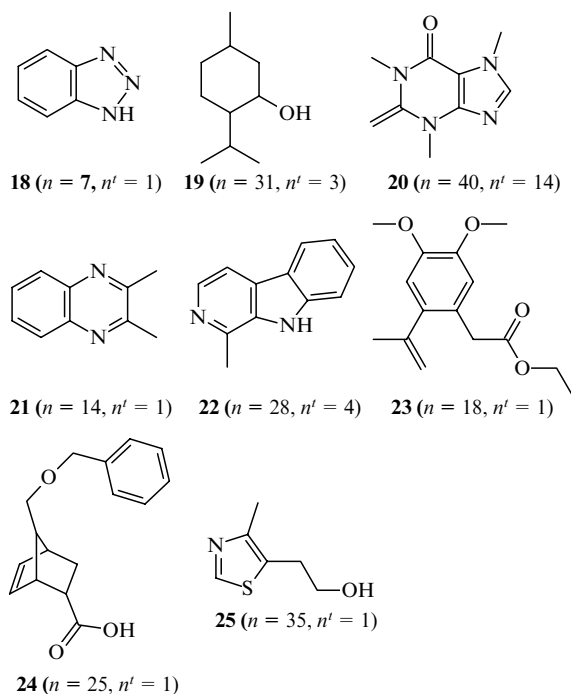
Symmetry of the structure also allows the chemist to use more efficiently the 'Multiple Fragments' procedure²⁹ to generate sets containing admissible (from the viewpoint of the empirical formula) numbers of identical fragments, which makes possible generation of large structures. For instance, a set containing four ester groups and four ethyl groups was created for the empirical formula $\text{C}_{14}\text{H}_{22}\text{O}_8$ and the unique structure 17 was recognised after the filtration procedure.

As is known, the number of signals in a ^{13}C NMR spectrum calculated as the number of groups of topologically equivalent carbon atoms does not always correspond to experimental data. For instance, only three signals are observed in the ^{13}C NMR spectrum of molecule 18 instead of the six expected. In this case the proper structure was unambiguously elucidated using prediction of ^{13}C NMR spectrum.

Accidental degeneracy of signals in the NMR spectrum or splitting of signals of carbon atoms of *gem*-dimethyl, isopropyl and other groups near the stereocentres makes computer-assisted structure recognition more difficult and requires interference by a chemist. If there are several stereocentres in the molecule, the answer file often contains a larger number of structures than usually. This is explained by complexity of ^1H NMR spectra (a small number or even the absence of the first-order signals, different δ_{H} values of geminal protons) and additional splittings of signals in the ^{13}C NMR spectra. For instance, in the case of compound 19 having three stereocentres the program for δ_{C} prediction ranked the proper structure 3rd from the beginning of the answer file containing 31 structures in the structural similarity criterion.

Large number of candidate structures in the answer file is also characteristic of hetero- and carbocyclic compounds, e.g., for 18–25. This is associated with a large number of rearrangements

possible in heterocyclic structures with several substituents. Compound **20** can serve as an example. The set including all fragments of this structure, 3(>N-CH_3), 2(>C=O), >C=C< , >C=N- , was created manually. The program generated 181 structures which were subjected to filtration to select 40 structures containing five- and six-membered rings.



The S value of 11.6 ppm was obtained for the predicted ^{13}C NMR spectrum of the proper structure **20** (the maximum deviation was 25.6 ppm.). As a result, the proper structure was ranked 14th from the beginning of the list of structures in the structural similarity criterion. Thus, we get a 'fuzzy' solution even if the fragment set used is *a priori* suitable for recognition of the proper structure; therefore, elucidation of a proper structure requires additional information (obtained, *e.g.*, from 2D NMR experiments) and application of more reliable methods for spectra prediction.

Analysis of the ways of overcoming difficult situations made it possible to propose methodology resulting in correct solutions of the problems.

2. Strategies of problem solution

To obtain a correct solution of a problem using an ES, *i.e.*, to find a proper structure in the answer file containing a minimum number of possible structures (ideally, one structure), it is necessary (but not sufficient) to provide the possibility of selecting as many fragments constituting the analysed structure as possible. To this end, a large knowledge base should be incorporated into the system and characteristic spectral ranges of the fragments should be rather wide lest the correct fragments be lost.

When these conditions are met, it appears that the number of selected fragments is too large since many superfluous (wrong) fragments are also selected. This requires finding and excluding superfluous fragments. Editing the list of selected fragments is hardly possible without participation of a chemist. This procedure can be excluded only if all logically admissible fragment sets and generation of structural formulae are created automatically. As a result, the number of generated structures will be too large, structure generation and filtration will take a long time and the problem even may appear to be virtually unsolvable. In addition, the answer file can contain the structures that contradict *a priori* information. Hence, in any case checking the list of selected fragments by a chemist seems to be virtually unavoidable rather than desirable.

Thus, meeting the requirement for the presence of the largest possible number of right fragments in the list of selected substructures results in increasing the total number of fragments and, as a consequence, in increasing the size of the answer file. In this case the solution will likely be right, but 'fuzzy'. This should be considered as a pay for correctness.

The selectivity of fragment selection is strongly dependent on the environment descriptors of the fragments. The stiffer the requirements for the fragment environment, the narrower the intervals of characteristic spectral features and, hence, the higher the SGA selectivity. At the same time, the narrowing of the intervals increases the probability of the loss of correct fragments because of the deviation of an experimental feature beyond the bounds of the characteristic interval.

There is also a clear dependence between the size of the structural file and the rigour of definition of descriptors describing the fragment environment. The point is that only those structures which meet all the requirements imposed by the environment descriptors are stored in the course of structure generation. This drastically reduces the number of structures to be checked later. On the one hand, there are problems which cannot be solved at all without descriptor control over structures during the structure generation stage (calculations take too long a time). On the other hand, there is a possibility of losing a proper structure in the case of too rigorous descriptor control. For instance, if the O=C-C=C fragment defined in the library as acyclic (whereas the proper structure contains the C=C bond in the ring) was selected at the SGA stage, all structures containing this fragment in the ring (including the proper structure) are rejected in the course of structure generation. This leads to an incorrect solution. Ideally, it is desired to have an ES characterised by high selectivity at SGA stage and, at the same time, by the capability to generate unambiguous and correct solutions. It is hardly probable to meet both requirements, therefore a compromise should be found.

Since the basic requirement for the solution is that it should be correct, it is possible to put up with its ambiguity. Therefore, the optimum strategy of structure elucidation can be formulated as follows: the problem should be solved in the interactive mode, which is a sequence of iterations followed by increasing the hardness of imposed constraints. For instance, if dimensionality of the problem is not very large, the library of principal functional groups (LPF, see Section V.1) should be used to select the fragments in the first stage. This provides the possibility of using softest structural constraints to generate a maximum number of fragment environments. Recognition of a large molecule requires additional use of the SGA and AROM libraries.

To control the hardness of imposed constraints at the stages of fragment selection and structure generation, the chemist can switch on (or off) the following options: the use of any type of spectra from the available experimental data; the use of signal multiplicities and SSCC in NMR spectra; the use of band intensities and halfwidths in IR spectra; the environment descriptor control over structures in the course of structure generation; the environment descriptor control over structures in the course of structure filtration; setting of various tolerances for the predicted number of signals with different multiplicity in the ^{13}C NMR spectrum; the use of structural constraints at the stages of structure generation and filtration (the limiting size of the ring, the maximum bond multiplicity, satisfying Bredt's rule, GOODLIST, BADLIST, list of unlikely fragments, *etc.*).

If no solution was obtained during the first program run which, as a rule, is carried out automatically, rational use of the above-mentioned switchable parameters in the course of iterative (trial-and-error) procedure usually makes it possible to establish the reasons for contradictions, thus facilitating the search for a correct solution. The search for contradictions is particularly efficient when using the controlled filtration mode (see Section V.1). Storing all intermediate results in the active database allows the user to return to the solution of the problem at any step.

Fast operation of programs for prediction of ^{13}C NMR spectra (0.5–1 s per spectrum) makes possible effective employment of the strategy outlined above. Thus, to attain a correct solution, the initial constraints may sometimes be slacked to such a degree that the answer file will contain thousands of structures. Prediction of the chemical shifts and the maximum likelihood ranking of the structures are carried out automatically; therefore CPU time taken can be considered justified and admissible.

The choice of appropriate strategy of solving a certain problem depends on optimum combination of two basic modes of operation of the system, which can be called the 'Archaeologist' mode and the 'Sculptor' mode. The 'Archaeologist' mode is used to perform SGA and structure generation (to 'glue' fragments and atoms). Then the 'Sculptor' mode should be switched on to carry out structure filtration and reject wrong structures (in this mode, the strategy is to cut off all superfluous structures).

Analysis of a large number of solutions made it possible to divide all problems into the following categories:

(1) problems solved automatically using SSG from molecular formulae followed by application of the 'Sculptor' mode strategy;

(2) problems solved automatically using strategies of the 'Archaeologist' and 'Sculptor' modes;

(3) problems solved using elements of the interactive mode (a chemist edits the 'reasoning' of the program using diversified information easily obtained from experimental data); and

(4) problems which can be solved only in the interactive mode (manual creation of fragment sets, imposing various constraints due to the origin of a specimen, etc.).

Rating a problem in a particular category depends on different factors (e.g., the size of the molecule, the presence of large fragments with characteristic spectral features, symmetry, etc.) and, first of all, on the number of skeletal atoms in the empirical formula. In many instances, SGA can be performed automatically; however, the appearance of at least one contradiction between the axioms of the SGA theory and experimental data makes the interference of an expert virtually inevitable. It should be kept in mind that even coincidence of predicted spectra with experimental ones does not guarantee against incorrect choice of the structure. Additional experiments can appear to be necessary, in particular, an X-ray study or structure confirmation by INADEQUATE 2D NMR technique. Despite carrying out additional labour-consuming procedures, the expenses are incommensurate with the cost of independent synthesis, isolation and purification of the product.

Thus, AI programs must be considered as powerful tools of extending the intellectual potentialities of the investigator rather than those of a method designed to exclude a chemist from the structure elucidation process. This idea was clearly expressed by the authors of monograph:¹⁷⁰ 'Computer-based automated or interactive versions of similar approaches have also been devised for structural elucidation of complex natural products, such as the SESAMI (Systematic Elucidation of Structures by using Artificial Machine Intelligence), but there is no substitute for the hard work, experience and intuition of the chemist.' We cannot but agree with this.

VII. Conclusion

The first studies reported 30 years ago laid the foundations of an independent line of investigation, the development of ES for elucidation of the molecular structure of organic compounds by spectral methods. It is closely related to many branches of chemistry (organic, physical, analytical, quantum chemistry, stereochemistry, molecular spectroscopy, molecular mechanics), mathematics (theory of graphs, combinatorial analysis, mathematical logic, theory of fuzzy sets, mathematical statistics), cybernetics (AI, programming, information theory, pattern recognition, ANN theory, computer graphics, mathematical linguistics), psychology (the man–computer interface) and philosophy of science (the role of the complementarity principle in studying

the structure of matter).¹⁷¹ Therefore rapid progress in the development of ES that absorbs new achievements of interdisciplinary sciences should be expected.

Three major stages of the process of structure recognition, viz., the SGA, structure generation and prediction of the spectra of candidate structures, have been transformed into independently developing investigation lines. It has been possible to computerise the structure generation and prediction of NMR spectra to a greater extent than SGA. Several methods were developed to reveal molecular fragments; however, this stage remains the most vulnerable and dependent on the *a priori* information. Recently, intensive studies on the application of ANN to revealing the fragments have begun.

Up to now, all attempts to develop a fast and reliable method for the prediction of IR spectra have failed. Solving this problem requires investigation of the potentialities of ANN (encouraging results have already been obtained) and development of new approaches. The known methods of calculation of IR spectra must be essentially improved to accelerate calculations. It has been shown^{172–174} that calculations of IR spectra can also be used for quantitative spectral analysis of organic compounds without any calibration. Therefore incorporation of databases (e.g., such as it was made by Gribov and Zinoviyev¹³⁸) into ES will allow one to create systems for both qualitative and quantitative spectral analysis of organic substances.

Taking into account the accumulated experience in solving many structural problems, the general strategy of elucidation of the molecular structure using ES was established. It consists of performing a number of successive iterations followed by a gradual increase in the hardness of constraints imposed. The use of this strategy makes it possible to obtain correct solutions.

Currently, most of ES are capable of recognising small and medium size (up to 20–25 skeletal atoms) molecules; however, this does not mean that ES have limited area of application. Millions of organic structures can correspond to a relatively simple molecular formula (e.g., about 48.5 mln of structures correspond to the empirical formula $\text{C}_9\text{H}_{10}\text{O}_3$); since 'only' ~ 14 mln of compounds are known currently, it is easy to conclude that the area of application of ES is very wide.

Since at present the structures generated by the use of the most sophisticated structure generators contain no more than 10–12 molecular fragments, the ES capable of revealing large fragments are rather promising for recognition of large molecules. Rapid progress of ES in which 2D NMR spectroscopy data are used should also be expected.

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Three-body ion – molecule processes

G V Karachevtsev (deceased), P S Vinogradov

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Abstract. Theoretical models used in the studies of three-body ion – molecule reactions are considered and the experimental methods for the study of these processes are described. The results of experimental studies are presented, including those for gas phase reactions at ultra-low temperatures and for the kinetic isotope effect induced by the symmetry of the species. The bibliography includes 130 references.

I. Introduction

Three-body ion – molecule processes of the type



where A^+ is an atomic or polyatomic ion (in this case, positively charged) and B and M are neutral species, constitute an important class of reactions which can affect substantially the composition and electrophysical properties of the low-temperature plasma.

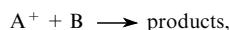
In gas-phase chemical kinetics, the term ‘three-body reactions’ denotes reactions the rates of which depend on the concentrations of the components A^+ , B and M . The rate of a third-order reaction is represented as

$$W = k_t[A^+][B][M],$$

where k_t is the rate constant independent of the component concentrations, these reactions may be regarded as a special case. Such a reaction order is characteristic, for example, of the association reaction at sufficiently low pressure.

The dependence of the reaction rate on the concentrations of the components over a wide pressure range is more complex. This dependence is determined by a combination of several processes: the formation of transition states (with a definite dispersion of lifetimes), decomposition of these states through different channels (into different quantum states with account of the conservation laws), as well as energy exchange between the species and its intramolecular conversion. It should be noted that the rates and

branching ratios between the channels for some exothermic reactions which are formally represented as second-order reactions



can depend on the buffer gas pressure. For some of the ion – molecule processes, this dependence can be noticeable even at a pressure of several Torr.

The majority of studies regarding three-body ion – molecule processes are devoted to the investigation of association reactions. The pressure range in which quantitative measurements of the rate constants have been carried out[†] usually does not exceed 10 Torr. The most reliable values of the rate constants are obtained by the mass spectrometric method where reactions occur in a flow or ion drift in an electrical field at a buffer gas pressure of ~ 1 Torr. Under these conditions, a third order reaction is observed for the majority of systems studied involving a small number of atoms. As the number of atoms is increased (for some systems, starting from seven or eight), a transition mode is established, which corresponds to a change from a third to a second order reaction.

The importance of the association processes is due to the fact that it is the composition of the positive ions that largely determines the loss rate of free electrons, *i.e.*, one of the basic parameters characterising the properties of an ionised gas. The recombination coefficients of various types of positive ions with electrons can differ by several orders of magnitude. This can be seen from two examples.

In the inert gas plasma, three-body association results in the formation of molecular ions such as He_2^+ , Ne_2^+ , Ar_2^+ , which recombine with electrons much more efficiently (in dissociative recombination processes) than the corresponding atomic ions that have different neutralisation mechanisms.

In the atmosphere of Earth, as the altitude decreases, three-body association affects essentially the kinetics of ionic processes starting from the *D*-layer (height range 75–90 km). Rocket-based *in situ* measurements detected complex ions in the *D*-layer.^{1,2} The formation of complex (cluster) positive ions results in a decrease in the concentration of free electrons, as the dissociative recombination coefficients for these ions are about two orders greater than those for non-cluster primary ions. In the Earth stratosphere, where the high-energy intergalactic species are the major ionisa-

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[†] Or rather, effective rate constants, since such processes are not elementary in the strict sense.

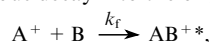
tion source, the ion chemistry is completely determined by transformations of positive and negative cluster ions.^{3,4}

Three-body processes play an important role in high-pressure analytical mass spectrometry,^{5,6} for example, where chemical ionisation and ionisation at atmospheric pressure are used, as well as in plasma chromatography.^{7,8} Termolecular reactions can compete with some slow bimolecular reactions of species exchange^{9–17} and with energy exchange processes.^{11, 18–20}

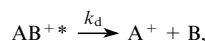
In this review, we discuss the specific features of three-body ion–molecule reactions and the application of the developed theories to processes involving ions; the theories based on statistical approaches occupy a special place among them. The experimental methods for the study of termolecular reactions are described. A separate section deals with the analysis of results of studies of the processes occurring at very low temperatures.

II. Theoretical models for three-body reactions

Three-body reactions involve several steps. The Lindemann scheme of three-body association is rather simplified, however, it gives a qualitative idea of the multistage character of the process. The first step implies the formation of an excited complex in a bimolecular collision; the complex can then undergo a spontaneous decay into the original species

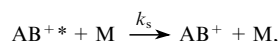


where k_f is the rate constant for the formation of the collisional complex,



where k_d is the rate constant for the spontaneous decay of the collisional complex.

In parallel with the decay, stabilisation of the excited complex can occur upon collision with the third species M



where k_s is the rate constant for the collisional stabilisation of the excited complex. Assuming the concentration of AB^{+*} to be quasi-steady, the rate of, *e.g.*, the association process can be presented as

$$W_a = \frac{d[AB^+]}{dt} = k_s[M][AB^{+*}] = k_f k_s \frac{[A][B][M]}{k_d + k_s[M]}.$$

The rate constant for a three-body reaction k_t (which is of the third order and a dimensionality of $\text{cm}^6 \text{s}^{-1}$) equals

$$k_t = \frac{k_f k_s}{k_d + k_s[M]}. \quad (2)$$

At the low pressure limit, where

$$[M] \ll \frac{k_d}{k_s},$$

k_t does not depend on $[M]$

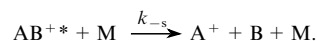
$$k_t = \frac{k_f k_s}{k_d}.$$

If the equality (2) does not hold, the association rate constant is usually represented as an apparent rate constant of a quasi-bimolecular second-order reaction (dimensionality $\text{cm}^3 \text{s}^{-1}$) which depends on $[M]$:

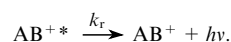
$$k_{\text{ef}} = \frac{k_f k_s [M]}{k_d + k_s [M]}.$$

The dependence on $[M]$ disappears only at the high pressure limit; in this case, $k_{\text{ef}} = k_{\infty} = k_f$.

Some authors supplement the scheme with the formally possible decomposition of the AB^{+*} complex upon collisions with M



Note that the scheme does not take radiative stabilisation into account



This process does not require stabilisation by a third species and can compete with the stabilisation only at very small concentrations of M ($[M] \leq k_r/k_s$).

The Lindemann model is based on formal kinetics concepts. Nevertheless, the model shows the key role of the intermediate excited complex AB^{+*} . It is the formation of this complex with an energy sufficient for its decay that allows one to consider three-body association using various approaches developed in the studies on unimolecular decomposition.^{21–25}

An important role in the transformations of the AB^{+*} complex belongs to energy exchange, including both intramolecular energy conversion of the highly excited species AB^{+*} ('reactive molecule' in terms of the unimolecular decomposition theory) and energy exchange with the buffer gas (collisional relaxation—activation). The contemporary theoretical approaches used for the description of the energy exchange and reactions of highly excited polyatomic molecules, as well as the results of optical experimental studies of these processes, are described in sufficient detail elsewhere.²⁶

1. Association of atomic species

In the simplest case, where A^+ and B are atomic species, the rate constants can be calculated using the method of trajectories. It is also useful to consider other ways of estimating that give a qualitative idea of the magnitudes of the rate constants for this type of reactions.

For ion–atom processes at low energies, the ion–neutral species interactions are determined by the long-range potential and k_f and k_s have a typical value of $10^{-9} \text{cm}^3 \text{s}^{-1}$. The minimum lifetime of a collisional complex $\tau_c = 1/k_d$ can approximately be estimated as the time during which one species is located near another one, *i.e.*, as the ratio of several characteristic sizes of the atoms to the velocity of their relative motion. Such an estimation yields a value of the order of $k_d \simeq 10^{13} \text{s}^{-1}$ and an association rate constant of atomic species of the order of $k_t \simeq 10^{-31} \text{cm}^6 \text{s}^{-1}$ (see Refs 21 and 27).

Let us note an interesting approach to the estimation of the rate constant for ion-atom association based on the data on the mobility of ions and polarisability of atoms. The rate constant for the process can be calculated using the formula²⁸

$$k = 3.27 \times 10^{-27} \frac{Z^{5/2} (\alpha_M m / T m_A)^{3/4}}{\mu_0 (m_A + m_B)} \quad (\text{cm}^6 \text{s}^{-1}), \quad (3)$$

where Z is the ion charge in elementary charge units; m is the reduced mass

$$m = \frac{m_A m_M}{m_A + m_M},$$

m_A , m_B and m_M are the masses of species A, B and M in atomic mass units, respectively; T is the temperature in K; μ_0 is the reduced mobility of the ion in $\text{cm}^2 (\text{V s})^{-1}$ estimated using the Langevin formula (which is valid if the species A and M are different)

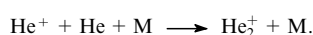
$$\mu_0 = 13.8 \frac{\alpha_B m_A m_B}{m_A + m_B},$$

α_B and α_M are the polarisabilities of B and M in 10^{-23}cm^3 . The experimentally measured mobilities μ_0 are used in the calculations. This approach is based on the fact that the mobility is determined

by the cross-section and kinematics of collisions, *i.e.*, the averaged characteristics of energy transfer in collisions are used.

Formula (3) provides a fairly good description of the experimental data for the association of atomic species and can be used for reliable estimates of the association rate constants at temperatures from 70 K to 300 K. Similar calculated values of rate constants are obtained using an approach suggested elsewhere.²⁹

A quantum-mechanical calculation with account of species tunnelling through a centrifugal barrier (*i.e.*, with account of resonance quasi-bound states) yields a correction (less than 20% at ambient temperature) to the data of a classical calculation even for the reaction of light species,³⁰ for example,



Considerable discrepancies arise at very low temperatures. Experimental results for a flow cooled to 1 K after gas expansion through a nozzle^{31–34} do not correlate with the temperature dependence which follows from formula (3). The reasons for this discrepancy are not known yet. Probably, one has to take the quantum effects in scattering processes into account in order to provide agreement between the experimental results and the calculation.³⁵ The importance of these effects has been noted, *e.g.*, in studies of the ion mobility in a gas at low temperatures.^{36–38} In addition, the dynamics of the collisional complex at very low gas temperatures can be affected by thermal infrared radiation of the relatively ‘hot’ walls.³⁹ This radiation affects the energy redistribution in the system, which affects the lifetime of the intermediate complex.

The approach described above is of interest for the estimation of the association rate constants of electronically excited atomic ions. It is known that the mobility of such ions can differ from the mobility of ions in the ground state.⁴⁰ The difference is due to partial electron density transfer from the neutral species to the ion in collision. The transfer is possible over rather long distances (10 Å). This results in a decrease in the effective polarisability of the neutral species and should affect the collision cross-section and the association rate constant.

An analysis⁴¹ showed that the available experimental results on the association rate constants involving polyatomic species are poorly described by the formula (3). Nevertheless, the following qualitative conclusions may be made from comparison of the experimental results and those of calculations presented in Fig. 1: the points above the straight line, which characterises the equality between the measured rate constants and those calculated using the formula (3), correspond to the formation of complexes with high bond energy (more than 1.5 eV); the points below the straight line correspond to the formation of weakly bound complexes. This correlation is related to the characteristic features of the energy exchange processes in polyatomic systems and may be explained

based on more rigorous theoretical approaches with the use of the statistical theory.

Qualitatively, the divergence between the calculations and experimental results can be explained by the fact that the characteristic lifetime of a complex is longer than that determined by the kinematics of collisions of ‘point’ species having no molecular structure. An increase in the lifetime of the complex in molecular systems virtually does not affect its mobility but results in an increase in the association rate constant.

For weakly bound complexes, the overestimated calculated rate constants for the processes involving molecular species may be explained by a decrease in the efficiency of the complex stabilisation. Upon a collision with the third body, the latter takes away a rather small fraction of the excess internal energy of the complex ($\sim kT$). Therefore, even after collision, the energy in the internal degrees of freedom of the complex is sufficient for its decomposition.

2. Characteristic features of ion–molecule interactions

Close similarities exist between the termolecular reactions involving only neutral species^{42,43} and ion–molecule reactions. On the other hand, there are also differences caused by the specific character of interaction between ions and neutral species. They are characterised by longer-range interactions than colliding neutral species. In addition, there are also certain specific features in the interactions at short distances.

The peculiarity of long-range interactions results in the cross-sections of ion–molecule collisions, and hence the rate constants for collisions, being much greater than the corresponding values for neutral species. The formation of a collisional complex occurs in the first step of three-body processes, and this is one of the reasons why the overall rate for ion–molecule interaction is greater than that for neutral–neutral species.

The typical rate constants for collisions between ions and molecules at room temperature are of the order of $10^{-9} \text{ cm}^3 \text{ s}^{-1}$. Therefore, the rate constants for three-body reactions of ions may be expected to be ~ 2 – 3 orders greater than similar reactions of neutral species at the low pressure limit due to the greater values of $k_{\text{tr}}k_{\text{s}}$.

The dependence of the collision rate constant on the translational energy of species is determined mainly by the polarisation interaction (*i.e.*, the interaction of an ion with an induced dipole) and the ion–permanent dipole interaction if the neutral species has a permanent dipole moment μ_{d} . If one assumes that the dipole is always directed along the radius-vector $\mathbf{r}$ connecting the colliding species regarded as point masses, the corresponding effective potential has the form

$$U_{\text{ef}} = \frac{L^2}{2\mu r^2} - \frac{\alpha q^2}{2r^4} - \frac{\mu_{\text{d}} q}{r^2}, \quad (4)$$

where L is the orbital angular momentum, μ is the reduced mass, α is the polarisability of the neutral species, and q is the ion charge. The first term, *i.e.*, the centrifugal potential, considers the fact that the relative motion occurs in the central ion. If the molecule is non-polar ($\mu_{\text{d}} = 0$, the Langevin model), the collision rate constant is determined by the expression⁴⁴

$$k_{\text{L}} = 2\pi q \sqrt{\frac{\alpha}{\mu}}. \quad (5)$$

If the neutral species has a permanent dipole moment, the dynamics of the collision process becomes much more complex. Formula (4) describes the so-called locked dipole model, while the dipole rotation, which is the closer to the free rotation the greater is r , is not taken into account. One of the coordinates of the potential energy surface of species interacting over long distances, $U(\mathbf{r}, 0)$, is the angle θ between the direction of the dipole axis and the radius-vector

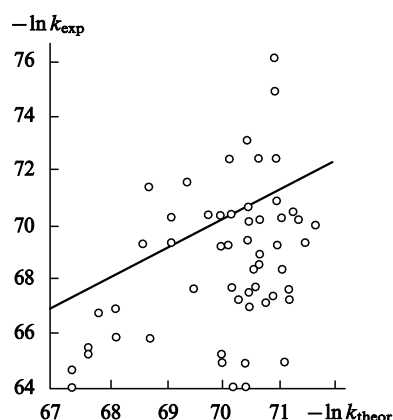


Figure 1. Correlation between the experimental rate constants for molecular ion association and those calculated using the formula (3).⁴¹

$$U(\mathbf{r}, 0) = -\frac{\alpha q^2}{2r^4} - \mu_d \frac{q}{r^2} \cos \theta.$$

The effect of the ion–dipole interaction on the collision rate constants has been studied in sufficient detail^{45–47} and procedures have been developed for the calculation of these constants.^{45, 48}

In spite of the fact that the ion–dipole interaction is long-ranged ($\sim 1/r^2$), its contribution to the overall collision cross-section is not great as compared to the contribution in the case of a locked dipole model. Because of the dipole rotation, the time phases of attraction ($\cos \theta > 0$) and repulsion ($\cos \theta < 0$) are averaged to some extent, and the total effect is comparable with the contribution from the polarisation interaction; however, dependence of the collision rate constant on temperature appears in this case.

For some molecules, the polarisability α can be anisotropic, *i.e.*, it can depend on the molecular orientation in an electrical field. However, taking into account the relationship (5) and the averaging effect described above, it may be noted that the contribution of this anisotropy is insignificant (usually $< 10\%$). If the molecule has a quadrupole moment Q , α is also anisotropic. The corresponding contribution to the interaction potential is determined by the equation

$$U_Q(r, \theta) = \frac{1}{2} \frac{Qq(3 \cos^2 \theta - 1)}{r^3}.$$

Estimates show that the contribution to the collision rate constant due to ion–quadrupole interaction ($\propto Q^{2/3}/\alpha^{1/2}$) is not very large in comparison with the Langevin constant ($\sim 10\%$). The contributions due to other types of interactions proportional to $-1/r^N$ (the exponent N depends on the interaction type) are also relatively small.⁴⁵

To summarise the above considerations, it should be noted that long-range interactions of ions with molecules and atoms are mostly determined by electrostatic forces represented as a sum of terms with different exponents N . The main contribution to the collision rate constant is given by the almost isotropic polarisation interaction ($\propto -1/r^4$). For polar molecules, the rotation of dipoles is not ‘frozen’ at long distances, and the contribution to the collision rate constant due to the ion–dipole interaction can be comparable with the Langevin constant only for a sufficiently large dipole moment (> 3 Debye units).

The Langevin model provides rather precise estimates of actual collision rate constants at translational energies of species from 0.01 to 1 eV. For a typical value of $k_L = 10^{-9} \text{ cm}^3 \text{ s}^{-1}$, the cross-section $\sigma(v) = k_L/v = 3.3 \times 10^{-14} \text{ cm}^2$ at the initial ($r = \infty$) velocity of the relative motion of species $v = 3 \times 10^{-14} \text{ cm s}^{-1}$. In this case, the maximum value of the aiming parameter $b^*(v)$ allowing a collision to occur is

$$b^*(v) = \left[\frac{\sigma(v)}{\pi} \right]^{1/2} = 10.5 \text{ \AA},$$

while the ‘orbiting’ radius $r_c(v)$ defined from a condition where $U_{\text{eff}}(r, v)$ is a maximum (or the top of the ‘centrifugal hump’), is

$$r_c(v) = \sqrt{2}b^*(v) = 7.4 \text{ \AA}.$$

This value is much larger than the characteristic sizes of atoms and small molecules. A criterion for the collision to occur is that the initial translational energy exceeded $U_{\text{eff}}(r_c)$, *i.e.*, the image point passed above the ‘centrifugal hump’ into the region of short distances.

The value of r_c may be regarded as an arbitrary border dividing the regions of interaction at short and long distances. The value of r_c enables an approximate estimate of the position of the ‘critical’ surface (transition state) in the theoretical analysis of the processes with the use of statistical and quasi-equilibrium approaches. The actual position of this surface should be

determined by the more precise variational methods. The corresponding criteria are found, for example, from the condition

$$\frac{\partial [W_{s-1}(E - U(r), r)]}{\partial r} = 0,$$

where $W_{s-1}(E - U(r), r)$ is the sum of the allowed states for all degrees of freedom, except for the reaction coordinate r , in the energy range $E - U(r)$; E is the total energy.

At short distances, the interaction between the species cannot be represented as a sum of electrostatic interactions. In this case, one has to use various quantum-chemical methods (*ab initio* and modifications of the semiempirical methods). Nowadays, it is possible to calculate the optimum geometry of stable ionic complexes, their dissociation energies, frequencies of normal vibrational modes and rotational constants with sufficient precision using computer programmes. In turn, these data allow one to find equilibrium constants and other kinetic characteristics.

When comparing ion–molecule processes with those involving neutral species, it should be noted that the bond energy of the complexes A^+B , *i.e.*, products of association of a molecular ion formed from a stable molecule A and a stable molecule B, is often much higher than the bond energy of neutral van der Waals clusters AB. At short distances, charge delocalisation is typical; distribution of the effective charge between the species can be represented as $A^{+(1-\delta)} - B^{\delta+}$.

It is noteworthy that some stable complex ions, such as $(O_2)_2^+$, $(CO)_2^+$ and $(NO)_2^+$, have a zigzag structure, *i.e.*, the axes of the molecules O_2 , CO and NO are not collinear but are parallel to each other and are coplanar. Let us also note that the multiplicity of the ground state of the $(O_2)_2^+$ complex equals four, which means that this state is formed with parallel spins of the ion (doublet) and the O_2 molecule (triplet).

The reactions of organic molecular ions with the precursor neutral molecules ($A^+ + A$) most commonly result in protonated ions AH^+ as the main products. In the association products of such ions (protonated dimers AH^+A), the species A appear non-equivalent, *i.e.*, they have different structures and effective charges. The structure of the complex ion should be represented as $A-H^+-A$, where one of the bonds is longer than the other by 40%–60%.

Thus, ion–molecule interactions are characterised by greater collision cross-sections than interactions of neutral species and wider ‘potential wells’ in the interactions at short distances. However, despite these features, the fundamental ideas of the theories used for three-body ion–molecule processes and those involving neutral species are alike. Still, the purely technical details can differ essentially in the calculations for particular systems.

3. Statistical methods for the calculation of the rate constants of three-body reactions

The statistical approaches have already been used for theoretical calculations of chemical reaction rates for nearly 70 years. The best known among them are the activated complex theory, the RRKM method (the quasi-equilibrium theory) and the statistical theory (phase space theory) taking the conservation of angular momentum into account. To date, these methods have been described in sufficient detail (see, *e.g.*, Refs 21–26).

The wide application of statistical methods to ionic processes started in the early 1950s after the statistical theory of mass spectra had appeared; this theory was used for the calculation of the energy distribution of fragmentation products (decomposition pathways) in the ionisation of molecules by electrons with different energies. Later, they found use in ion–molecule reactions.

The simplest form of the formula from transition state theory is

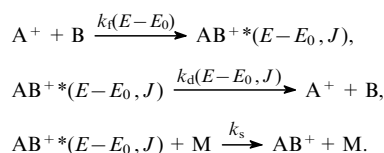
$$k(T) = \frac{k_B T}{h} \frac{Q^\ddagger}{Q} \exp\left(\frac{-E_a}{k_B T}\right),$$

where k_B is the Boltzmann constant, h is the Planck constant, T is the temperature, E_a is the activation energy, $Q^\#$ is the partition function for the transition state, and $Q = Q_A Q_B Q_{tr}$ is the product of the partition functions for the reacting species A and B and the translational statistical sum of their relative motion. The microcanonical equation of the RRKM theory has the form

$$k(E) = \frac{W^\#(E - E_0)}{h\rho},$$

where $W^\#(E - E_0)$ is the number of states (vibrational and rotational) in the energy range $(E - E_0)$, E is the total energy, E_0 is the dissociation energy and ρ is the total density of vibrational-rotational states of the reagents.

The most reliable results are obtained in the calculations of the rate constants with the use of phase space statistical theory that takes conservation of the total angular momentum (J) into account. This approach was used for calculations of the rate constants of three-body ion–molecule reactions (see, *e.g.*, Refs 49–51). An analogue of the Lindemann scheme of the association process is presented by the following scheme within the framework of the statistical model:⁵²



The rate constants of the reactions are presented in a microcanonical form, but a two-dimensional one,

$$k(E - E_0, J) = \frac{W^\#(E - E_0, J)}{h\rho}$$

and then used in this form in the expression for the overall reaction rate. For example, the association rate constant at small pressures is represented as:⁵²

$$k_t = k_f \beta k_c \int_0^\infty dE \int_0^{J^*(E-E_0)} \frac{F(E - E_0, J)}{k_d + k_c \beta [M]} dJ, \quad (6)$$

where β is the stabilisation probability, k_c is the rate constant for the corresponding collision, $F(E - E_0, J)$ is the function of distribution over the states taking the conservation of the angular momentum of the AB^{+*} complex into account, and J^* corresponds to the greatest possible angular momentum for the current value of E .

For the sake of clarity, the stabilisation rate constant in the formula (6) is presented not in the microcanonical, but in a simplified form $k_s = \beta k_c$, *i.e.*, as the product of the stabilisation efficiency per collision of the AB^{+*} complex with the species M by the rate constant for the corresponding collision. The relationships for the calculation of $F(E - E_0, J)$, $k_d(E - E_0, J)$ and the effective constant are reported in Ref. 52. Formula (6) is a stricter analogue of the expression (4).

The statistical approach was used to obtain the temperature dependence of the association rate constant at the low pressures limit. This constant was found to be mainly determined by the difference in the rotational degrees of freedom of the complex and the reagents (S)

$$k_t \simeq T^{-S/2}.$$

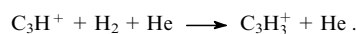
A correction (X) is introduced in order to take the contribution of vibrations into account, which depends on temperature and is estimated from the ratio of the statistical vibrational partition functions

$$k_t \simeq T^{-(S/2+X)}.$$

The effect of X becomes noticeable at rather high temperatures.

The use of the statistical theory requires detailed data on the activated complex and rather complicated calculations. The success of its application for particular systems often depends on how successfully the parameters of the complex are chosen and how meticulously the distribution functions are calculated.

It should be noted that even rather simple approaches can sometimes be used successfully for the interpretation of the experimental results. For example, the simplified statistical approach has been used⁵³ for the reaction



Statistical methods were used to find the boundaries of the area of experimental results processing where the dependences should conform to the behaviour at the low pressure limit for the ion–induced dipole⁵⁴ and ion–dipolar molecule association reactions.⁵⁵

A stricter description of the three-body association process involving complex molecules is based on the solution of the two-dimensional master equation [such as equation (6)]. The corresponding approaches have been considered in detail;⁵⁶ the methods of its solution with account of the specificity of the ion–molecule interaction can be found in Refs 57–59.

The approach with the use of the master equation allows one to take into account the contribution of weak stabilising collisions, where the third body M accepts a relatively small fraction of energy from AB^{+*} . The remaining energy is sufficient for the decomposition of the complex, while complete stabilisation requires several collisions of this kind.^{56–59}

For unimolecular decomposition of the AB^{+*} complex with the characteristics $E - E_0$ and J , the two-dimensional master equation taking into account both the change in the internal state of the complex and its decomposition into the original species, has the following form at any pressure:

$$\begin{aligned} k_{uni}g(\varepsilon, J) = \omega \int \int [P_{2D}(\varepsilon, J \rightarrow \varepsilon_1, J_1)g(\varepsilon_1, J_1) - \\ - P_{2D}(\varepsilon_1, J_1 \rightarrow \varepsilon, J)g(\varepsilon, J)]d\varepsilon_1 dJ_1 - k_d(\varepsilon, J)g(\varepsilon, J), \end{aligned} \quad (7)$$

where k_{uni} is the rate constant of the process, $\varepsilon = E - E_0$, ω is the frequency of collisions between AB^{+*} and the species M, $P_{2D}(\varepsilon, J \rightarrow \varepsilon_1, J_1)$ are the probabilities of transitions between the states $(\varepsilon, J \rightarrow \varepsilon_1, J_1)$ induced by collisions, and $g(\varepsilon, J)$ and $g(\varepsilon_1, J_1)$ are the populations of the states with a given energy and angular momentum. The separation of variables method was used to simplify equation (7):⁵⁷

$$P_{2D}(\varepsilon, J \rightarrow \varepsilon_1, J_1) = P_\varepsilon(\varepsilon, \varepsilon_1)P_J(J, J_1),$$

and present the functions in a form convenient for calculations.

Let us note some features of the use of the statistical theory for ion–molecule association. One of them concerns taking into account rotational freezing if the species B is a dipole. At long distances between A^+ and B, the species B is considered as a rotor, while at a distance shorter than some critical value r_{cr} estimated from the relationship

$$\frac{\mu_d q \cos \theta}{r_{cr}^2} \leq k_B T,$$

where μ_d is the dipole moment, it becomes an oscillator. For example, $r_{cr} = 13$ Å for the HCN molecule, and $r_{cr} = 23$ Å for acetonitrile. The expressions for the partition functions of the oscillator and the rotor are different. There is an approach which takes the ‘hidden rotor’ into account.⁵⁷

Yet another specific feature is the rather large moment of inertia of the transition state (J^*). Many of the methods for the calculation of the association rate constants from approximate solutions of the two-dimensional microcanonical master equation, which are used for the calculation of the association rate

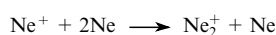
constants of neutral species, can give wrong results when applied to ion–molecule processes. The approaches used for neutral systems are valid if the ratio of the moments of inertia of the transition state and the reagent is $I^*/I < 6$. This inequality usually holds for reactions of neutral species. If the inequality is not valid, the role of weak collisions increases. This factor can be taken into account using the reported procedures.⁵⁷

III. Experimental methods for the study of three-body ion–molecule reactions

Mass spectrometric methods are the most popular and convenient ones for the study of three-body ion–molecule reactions. The ratio of the number of three-body collisions (Z_3) to the number of two-body ones (Z_2) is proportional to the concentration of the species M in the reactor

$$\frac{Z_3}{Z_2} = \frac{k_t[M]}{k_f}.$$

Therefore, one has to increase the pressure in the region where these processes occur to increase the yield of the products. At a pressure of 10^{-8} Torr in the mass spectrometer, the effective time of formation of, e.g., a neon molecular ion in the reaction



is $\sim 10^3$ years.⁶⁰

The contribution of two-body ion–molecule reactions to the mass spectra obtained with mass spectrometers with conventional ion sources becomes appreciable at pressures of $\sim 10^{-6}$ Torr and a characteristic reaction time of *ca.* several microseconds. The study of three-body processes requires much higher pressures, *viz.*, at least 10^{-2} Torr. This implies that the reaction zone and the zone where ion separation according to their masses occurs should be separated, and in the second area the vacuum required for the analysis (no less than 10^{-6} Torr) should be provided.

In ordinary mass spectrometers, small ionisation chambers (with a characteristic size of 1 cm and even smaller) with rather narrow diaphragms (to minimise the gas flow into the high-vacuum zone) are used as a reactor.

Primary ions are usually formed under the action of a fast-electron beam. Diffusion of primary ions to the ionisation chamber walls is accompanied by various reactions. In the vicinity of the diaphragm, the ions are carried away by the gas flow into the high-vacuum zone, separated according to their masses by the mass analyser and detected. The processes occurring in the ionisation chambers at higher pressures have been considered elsewhere.^{7, 61, 62}

The ratio between the current of secondary ions I_2 formed in three-body reactions [see reaction (1)] to the current of primary ions I_1 at low degree of conversion is determined by the expression

$$\frac{I_2}{I_1} = k_t[\text{B}][\text{M}]\tau,$$

where k_t is the reaction rate constant (with the assumption of the low pressure limit) and τ is the lifetime of ions in the ionisation chamber. If $\text{B} = \text{M}$ (it is for such systems that ordinary mass spectrometric methods are most commonly used), then

$$\frac{I_2}{I_1} = k_t[\text{B}]^2\tau.$$

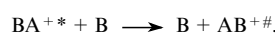
This formula is used to determine the rate constants of three-body reactions from the experimental results. Of greatest difficulty is the determination of τ , as the residence time of ions in the ionisation chamber is determined by many factors: diffusion, drift in the field of the space charge of ions, ‘penetration’ of the extracting field into the chamber, gas flow and geometric parameters of the chamber.

The problem can be simplified by using the pulse method suggested by Tal’roze and Frankevich.⁶³ These methods are

mainly used for the study of ion–molecule reactions at elevated pressures in the ionisation chamber.^{64–67}

Ionisation is carried out by a short pulse of electrons. The time dependences of the intensity of ion currents with different masses (over a sufficiently long time period) are studied with the use of a multichannel pulse analyser.^{64–66} Ionisation pulses are repeated with a certain frequency, and acquisition of data on the time dependence of the current for each type of ions is performed. This is necessary to obtain reliable results as regards the signal-to-noise ratio. Processing of the kinetic dependences of the ion mass spectra obtained in such a way enables one to find the reaction rate constants.

However, the pulse method suffers a number of drawbacks, the main one of which is that a large excess of the buffer gas is not allowed. If $\text{B} = \text{M}$, the mechanism of stabilisation of the complex is much more complicated, as the substitution of the species B, *i.e.*,



can contribute to certain extent.

Instead of the actual reaction time, the kinetic dependences include its analogue which is averaged in a rather complicated way.

The flow and drift mass spectrometry methods are the most reliable. The use of these methods for the study of the ion–molecule reaction kinetics has been reviewed rather thoroughly (see Refs 68 and 69).

The flow method (this is also called the flowing after glow method) makes it possible to study the reactions of ions thermolysed in the excess of a buffer gas (He, Ar, N₂, *etc.*) at temperatures from 80 K to several hundred degrees (Kelvin scale) and pressures from tenths of a Torr to several Torr.^{70–73}

In this method, the region where the primary ions are formed is spatially separated from the reaction zone, which begins where the neutral reagent is added to the flow of the buffer gas containing primary ions that had already been thermolysed. The reaction zone is ended by a nose cone with an orifice in the top, which withdraws a part of the flow for the ionic composition analysis. The time period during which the reactions are studied is determined by the flow rate and the place of injection of the neutral reagent and amounts to several milliseconds.

A useful modification of this method is the injection of ions, which have previously been separated by mass with another mass spectrometer, into the flow [the so-called SIFT (selected ion flow tube) technique]. The main drawback of the SIFT technique is that the conditions of injection from the low pressure zone into the reactor do not allow increasing the pressure in the latter above 1 Torr. Thus, despite the main advantage that only one type of primary ions is considered, the procedure for the processing of the kinetic result is simplified and the reliability is enhanced, the possibility of monitoring the changes in the reaction order occurring at pressures above 1 Torr for many three-body reactions is lost.

A similar principle for studying ion–molecule reactions underlies the drift methods. The motion of ions along the reactor is determined by the rate of the ion drift in an electrical field ($v_d \gg v_T$) generated by a potential difference between the guard rings located along the drift tube rather than by the gas flow rate. The drift methods allow one to study the dependences of the reaction rates on the energy of the relative translational motion of the colliding partners^{74–76} which can vary over a wide range (from the value close to that of ambient-temperature motion to several electron-volts in the centre-of-mass system) by varying the electrical field. At present, drift methods make use of the injection of mass-selected ions into the drift tube. This method is known as selected ion flow-drift tube (SIFDT) method.

In the drift methods, there are nonequilibrium distributions of species according to their energies. These can be characterised as the translational collision temperature of an ion and a molecule, the effective temperature of the internal degrees of freedom of an ion (the relevant formulas can be found in Refs 74 and 77) and the

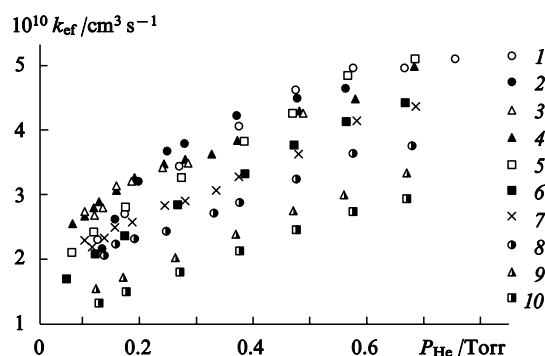


Figure 2. Dependence of the effective rate constant for the process (8) on pressure at different values of E .

E / meV: (1) 41; (2) 42; (3) 47; (4) and (5) 49; (6) 59; (7) 61; (8) 75; (9) 87; (10) 100.

temperature of the neutral reactant, which is equal to the temperature of the reactor walls.

If the translational energy (E) in collisions of rather heavy species (≥ 28 amu) is less than 0.1 eV and helium is used as the buffer gas, the effective temperature of the internal degrees of freedom of an ion does not differ much from the ambient temperature. This allows one to study correctly enough the dependences of the association rate constants on E in the range from 0.04 to 0.1 eV.⁷⁸ Figure 2 can be regarded as an example, it presents the dependences of the effective rate constant for the reaction



on the helium pressure, and Fig. 3 presents the dependence of the ratio of the rate constants for stabilisation in collisions of the complex with helium to the spontaneous reverse decay rate constant of the collisional complex at different E values.

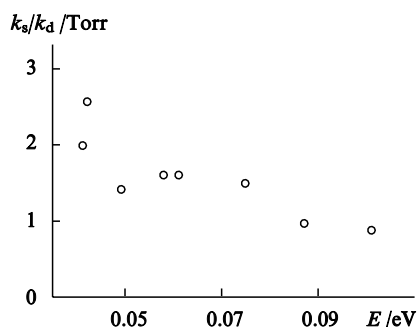


Figure 3. Dependence of the ratio of the rate constant for collisional stabilisation to the rate constant for the collisional complex decay on E for the process (8).

The drift method allows one to study, over a wide energy range, the competition of the association channel with other channels, for example, endothermic charge transfer,⁷⁹ or with reactions accompanied by species rearrangement.⁸⁰

At sufficiently high energy of species relative translational motion in the centre-of-mass system, the SIFDT method is very helpful for the studies of the collision-induced dissociation of stable ionic complexes AB^+ , since the reaction zone contains no neutral reagent B and the reverse process, *viz.*, association, does not occur there. The dissociation of a series of complex ions has been studied in detail.⁷⁷

A procedure with a modified flow reactor has been developed for the measurement of the rate constants for ion–molecule reactions at low temperatures in which the reactions were studied

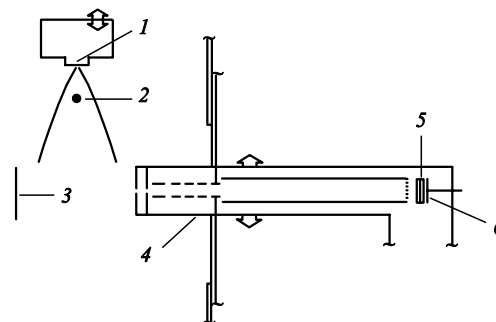


Figure 4. A scheme of an experimental set-up for low-temperature studies of ion-molecule reactions:⁸⁹

(1) gas-dynamic nozzle with a pulse valve for gas flooding; (2) focus of ionising laser irradiation; (3) a plate for the deflection of ions to the input of the mass spectrometer; (4) time-of-flight mass spectrometer; (5) micro-channel plates; (6) collector of secondary electrons.

in a cooled supersonic flow.^{31,81–86} A strongly cooled flow is obtained by adiabatic gas expansion following its discharge through a nozzle or an orifice in a thin wall.

A scheme of this type of experimental set-up is shown in Fig. 4. The gas expands through a pulse nozzle. The ionising laser radiation is focused on the axis of the supersonic flow at a point located sufficiently close to the nozzle. The ions moving together with the supersonic flow react with molecules. When the ions reach the level of the repeller plate, the pulse electrical field directs them into the time-of-flight mass-spectrometer moved along the flow; the mass-spectrometer records the ion composition of the beam.

The yield of secondary ions in reactions can be increased not only by increasing the gas pressure, but also by increasing the time of ion residence in the reactor under low pressure conditions. Various types of ionic traps are widely used for this purpose in mass spectrometry.^{87–93} In the flow and drift methods, the order of characteristic reaction time is 10^{-3} s, while in ionic traps this time can be many orders longer. In ion cyclotron resonance (ICR) spectrometers, the cell retention time for an ion can amount to several hours at a very high vacuum. However, kinetic measurements require higher pressures, but under these conditions the reaction time is usually less than a minute.

In radio frequency traps, such as QISTOR, effective retention of ions requires the presence of a buffer gas (usually, helium) at a pressure of 10^{-3} Torr. However, the ion translational energy in these traps is rather high (> 1 eV), hence, they can be used only for studying the dissociation of complex ions that have been previously injected into them.

Yet more promising are multipole radio-frequency traps (of the ‘ion guide’ type)⁹³ in which the energy of ions is not high. The ionic-trap and ICR methods, like the drift method, allow variation of the translational energy of the reacting ions.

The ICR method is limited to small pressures. Therefore, it can be used for studying the association reactions of relatively complex species, with rather long complex lifetimes (of about a microsecond and more). Only the reagent can act as the stabilising species in this case. However, this method proved to be convenient for radiation stabilisation studies. This can be clearly demonstrated using the Lindemann scheme with allowance for radiative stabilisation with the rate constant

$$k_r = \frac{1}{\tau_r},$$

where τ_r is the radiation lifetime of the species.

The effective rate constant of association (represented as a second-order reaction) has the form

$$k_{\text{ef}} = \frac{k_f k_s [\text{M}]}{k_d + k_r + k_s [\text{M}]} + \frac{k_f k_r}{k_d + k_r + k_s [\text{M}]} \quad (9)$$

and has a nonzero value when $[\text{M}]$ is extrapolated to zero. Experimental studies of the processes taking into account the competition between the collisional and radiative stabilisation are described in Refs 94–100. A more perfect statistical model for data interpretation [in comparison with that used to derive formula (9)] is reported elsewhere.^{101, 102}

The results of the rate constant measurements for three-body ion–molecule reactions using the methods described above are tabulated in reference books.^{103, 104}

IV. Temperature dependences of association rate constants

As noted above, the temperature dependence of the association reaction is a negative power function

$$k \approx T^{-n}. \quad (10)$$

At relatively low temperatures, where the energy difference between the vibrational levels is much greater than the thermal energy ($h\nu \gg k_B T$) for simple molecules, the contribution of the relative vibrational partition functions to the rate constant can be neglected. Under nonequilibrium conditions where the effective temperatures of the internal degrees of freedom for ions (T_i), neutral molecules (T_m) and collisional complexes (T_c) differ (as in the case of ion drift), the temperature dependence of the association rate constant at the low pressure limit has the form⁷⁶

$$k \propto \frac{T_c^{r_c/2}}{T_{\text{tr}}^{3/2} T_i^{r_i/2} T_m^{r_m/2}},$$

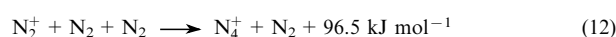
where T_{tr} is the temperature that characterises the energy of the relative motion of the colliding molecules; r_c , r_i and r_m are the numbers of the rotational degrees of freedom of a complex, an ion and a neutral molecule, respectively. It should be noted that the electrical field can affect the translational temperature of ions and their internal energy but not the temperature of neutral species. The validity of this formula was confirmed experimentally in studies of ion drift in an electrostatic field.

In the case of equilibrium temperature, the exponent n is determined by the relationship

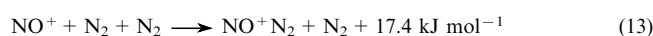
$$n = \frac{3 - r_c + r_i + r_m}{2}. \quad (11)$$

It should be noted that both the statistical theory, which takes conservation of the angular momentum into account, and the simplified theory, which disregards this, give identical expressions for n .¹⁰⁵

It should be noted that the statistical theory is applicable only to the reactions occurring with the formation of an intermediate complex with a sufficiently ‘deep potential well’, which is the reason for its long lifetime necessary for the efficient energy exchange between the degrees of freedom. For example, the temperature dependence of the rate constant for the process



is rather well described by the statistical theory, $n = 2$, whereas for a similar process



$n = 4$.

For complexes with a small bond energy, a transition from statistical to dynamic control of the lifetime of the intermediate complex takes place.^{105, 106} In this case, the lifetime of the complex is given by the effective time of collision, *i.e.*, the time during which the species remain sufficiently close to each other. This value is estimated by numeric calculation of trajectories. The large exponent n for the formation of the intermediate complex

$(\text{NO}^+ \text{N}_2)^*$ is a consequence of dynamic restrictions for the total rotational energy of the colliding species (at fixed energy, collisions are possible only at small values of the total orbital momentum).

As the molecules become more complex and/or the temperature increases, it is necessary to take the contribution of the vibrational partition functions of the colliding species and the intermediate complex into account. Relatively simple models of harmonic oscillators are used for the estimation of this contribution. The corresponding correction of the parameter n in the formula (10) gives results which agree satisfactorily with the experiment.^{107, 108}

The contribution of the aforementioned radiative processes to the stabilisation of complex molecules, *viz.*, association products, can increase considerably. The competition between the channels for complicated hydrocarbon ion–molecule complexes was considered in detail;^{94, 109} it was shown that their ratio evaluated using the approach mentioned above agrees satisfactorily with the experiment. For very complicated systems, the assumption of the uniform energy distribution between the degrees of freedom of a collisional complex may no longer agree with the experimental results.¹¹⁰

V. Some results of studies

A new type of isotope effect related to the involvement of several potential energy surfaces with different symmetry types in one process has been discovered in three-body ion–molecule association processes. The simplest of the processes studied is the association in helium¹¹¹



In a mixture with approximately equal concentrations of ^3He and ^4He , the molecular ions with the isotope composition $^3\text{He}^4\text{He}^+$ are formed with a higher efficiency than the $^3\text{He}^3\text{He}^+$ and $^4\text{He}^4\text{He}^+$ ions. The relative concentration of the mixed molecular helium ions [$^3\text{He}^4\text{He}^+$] exceeded approximately 2.5 times the statistical value, which would be observed if equal association rate constants independent of the isotope composition were assumed.

This isotope effect was rationalised as follows. Only for a half of collisions between the species of identical isotope composition is the interaction potential defined by the term $^2\Sigma_u^+$ of the ion He_2^+ , which corresponds to attraction and passes through a minimum; for the other half of the collisions, the potential interaction energy corresponds only to the repulsive term $^2\Sigma_g^+$, and the species cannot approach for short distances where the formation of a bound state becomes possible (Fig. 5a).

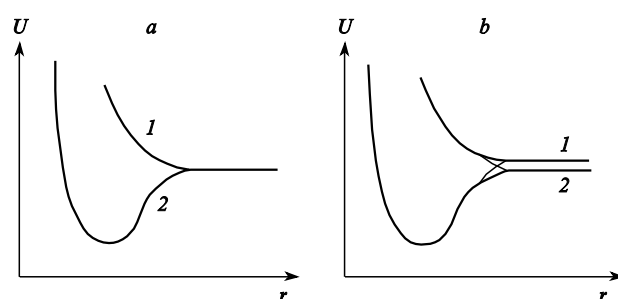


Figure 5. Dependences of the potential energy on the internuclear distance for the system $\text{He}^+ + \text{He}$.¹¹¹ (a) the $^4\text{He}^+ + ^4\text{He}$ system, (1) $^2\Sigma_g^+$, (2) $^2\Sigma_u^+$; (b) the $^3\text{He}^+ + ^4\text{He}$ (1) and $^4\text{He}^+ + ^3\text{He}$ (2) systems.

If the isotopes are different, at sufficiently long distances between the species, along with the term of the original species there is a term with a very small energy difference corresponding

to the charge transfer products, *i.e.*, there is a splitting of terms for the ${}^3\text{He}^+ + {}^4\text{He}$ and ${}^4\text{He}^+ + {}^3\text{He}$ systems (Fig. 5*b*). It is assumed that the binding state of the molecular ion becomes available in every collision, as the transition to the binding term occurs in a nonadiabatic transition in the area indicated in the Figure.

The quantum-mechanical restrictions for symmetry (more exactly, the restrictions due to the identity of species) forbid a transition into the ground state from the ${}^2\Sigma_g^+$ state for identical isotopes. Thus, the isotope effect depends not only on the masses of the species involved in the process, but also on this type of quantum-mechanical restrictions.

Let us compare, for example, the kinetic isotope effect related to the mass difference with the isotope effect due to the symmetry (identity or nonidentity) of the species for the process



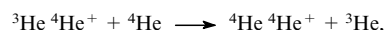
This process has not been studied experimentally yet. The interest in it is due to the fact that the difference between the ionisation potentials of ${}^{20}\text{Ne}$ and ${}^{22}\text{Ne}$, which determines the energy difference of terms, is much smaller than that for helium. In addition, the hyperfine structure for ions is absent (its possible effect has not been discussed) because the nuclei of these isotopes have no magnetic moments.

The magnitude of the isotope effect due to the mass difference only is estimated as $\sim 3\%$. Assuming, as in the case of helium, that upon collision of homonuclear species the potential of interaction between them is determined with equal probability by the terms ${}^2\Sigma_u^+$ and ${}^2\Sigma_g^+$ and that for every collision of heteronuclear species the potential corresponds only to the binding term, we find that the ratio of the association rate constant k_{20-22} , estimated taking into account the mass difference and the nonidentity of the nuclei, to the rate constant k_{st} found ignoring these effects is

$$\frac{k_{20-22}}{k_{\text{st}}} = 2.06.$$

The even greater magnitude of the kinetic isotope effect for the ${}^3\text{He}-{}^4\text{He}$ mixture is due to the fact that the symmetry restrictions manifest themselves not only in the complex formation step but also in its stabilisation step.

Let us note that the isotopes formed in the three-body association can then participate in fast bimolecular switching reactions of the type



There are no symmetry restrictions for these reactions, and they can rapidly result in an equilibrium isotope distribution in the molecular ions. Therefore, the isotope effect described above is observable only at relatively small degrees of conversion determined by the ratio between the association and switching rate constants.

This type of kinetic isotope effect has been also found experimentally in three-body reactions involving molecular species. The theoretical explanation of the effect in this case is much more complicated than in the case of systems involving atomic species.

The enrichment in the ${}^{17}\text{O}$ and ${}^{18}\text{O}$ isotopes upon the formation of the O_4^+ ions in the reaction $\text{O}_4^+ + \text{O}_2 + \text{M}$ was studied.¹¹² It was found that the isotope effect strongly depends on the energy of the ionising electrons used for the formation of the primary O_2^+ ions. The relative enrichment of the dimers in the labelled molecules (in comparison with the statistical enrichment) was found to be ~ 10 at E_i close to the O_2 ionisation threshold (12.077 eV). However, the enrichment at an energy of the electrons above 40 eV decreases to a virtually statistical value.

In addition, the yield of ionic dimers O_4^+ from O_2^+ ions formed by electrons at E_i close to the ionisation threshold is much lower than that from ions obtained at higher electron energies. All this is explained¹¹² by the above-mentioned symmetry restriction upon the formation of a bound electronic state of O_4^+ in a collision of O_2^+

with O_2 (${}^3\Pi_g$). The restriction disappears if O_2^+ (or O_2) is a heteronuclear species.

The efficiency of the $(\text{CO}_2)_2^+$ formation in the $\text{CO}_2^+ + \text{CO}_2 + \text{M}$ reaction also increases as the energy of ionising electrons is increased.¹¹³ The symmetry-induced kinetic isotope effect was also studied for this process with the use of ${}^{13}\text{C}$ and ${}^{18}\text{O}$ labels. If the heavy oxygen label ${}^{18}\text{O}$ is used, an increase in the ionising electron energy from 25 to 100 eV results in a gradual decrease in the heavy isotope enrichment factor from 27 to 8. For ${}^{12}\text{C}$ and ${}^{18}\text{O}$, the heavy isotope enrichment factor is ~ 5 and virtually does not depend on the energy of the ionising electrons.

It is of note that the kinetic isotope effect is also manifested in the clusterisation of ions $(\text{CO}_2)_n^+$ where one of the CO_2 molecules is replaced by another species with a closed electron shell. For example, the isotope effect was observed in the formation of cluster ions in reactions of ArCO_2^+ complexes (see Ref. 114). It was shown that the CO_2 molecules containing heavy isotopes ${}^{17}\text{O}$ and ${}^{18}\text{O}$ are incorporated into the ArCO_2^+ clusters 20 times more efficiently than a statistical combinatorial estimate would predict. The studies of the symmetry-induced kinetic isotope effect in three-body ion–molecule reactions have been reviewed.¹¹⁵

Let us discuss the results of the experiments at ultralow temperatures in a cooled gas-dynamic flow. Figure 6 presents the temperature dependence of the rate constant for the reaction



In a wide range from moderate (~ 300 K) to low temperatures (~ 0.1 K), the rate constant cannot be described by the relationship (10) with an index n which does not depend on T . It was found that $n = 1.8$ at low temperatures, while at moderate temperatures n is much smaller. The average value $\langle n \rangle$ over the entire temperature range studied is equal to 1.2. It should be recalled that the theoretical n value for the association of monatomic species should be equal to 0.75.

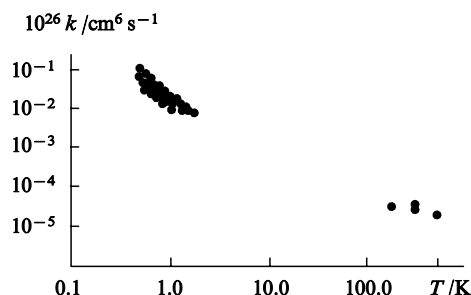
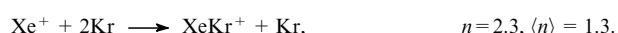
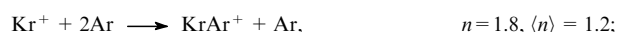
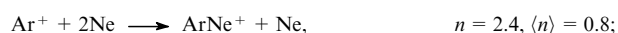


Figure 6. Temperature dependence of the rate constant for reaction (14).¹¹⁶

Similar deviations from the theoretical dependence are also observed for other reactions involving monatomic species:



The values of n are given for $T \simeq 0.1$ K.

For the above process (12) involving molecular nitrogen in the same wide temperature range, the expression (10) at $n = 2$ describes well the experimental temperature dependence of the rate constant (Fig. 7). It would be interesting to study analogous temperature dependences for n at low T for the formation of weakly bound complexes, for example, for the reaction (13) for which n is anomalously high at moderate temperatures.

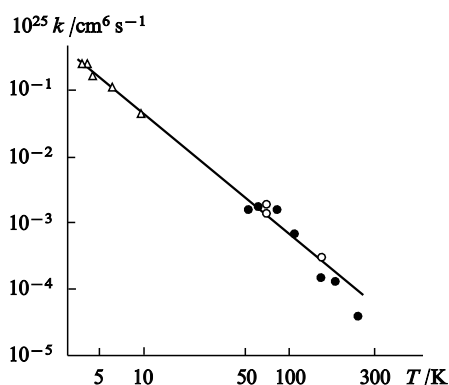
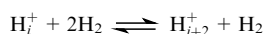


Figure 7. Temperature dependence of the rate constant for reaction (12).¹¹⁶

The points refer to the data from different authors.

The radio frequency ion trap method with cooled walls was used to measure the rate constants for clusterisation and fragmentation



at 10 K for odd i in normal hydrogen $n\text{-H}_2$ with an equilibrium ratio of the *ortho*- and *para*-isomers and in hydrogen enriched in the *para*-component, $p\text{-H}_2$.⁹² The data obtained are presented in Fig. 8. The difference between the curves for $n\text{-H}_2$ and $p\text{-H}_2$ is due to the rotational energy of the molecule with total nuclear momentum $J = 1$ in the *ortho*-modification of molecular hydrogen. The bond energy of the H_2 molecule with the H_i^+ cluster changes from several kcal mol⁻¹ at small i to a value comparable with the heat of evaporation of liquid hydrogen (0.2 kcal mol⁻¹).

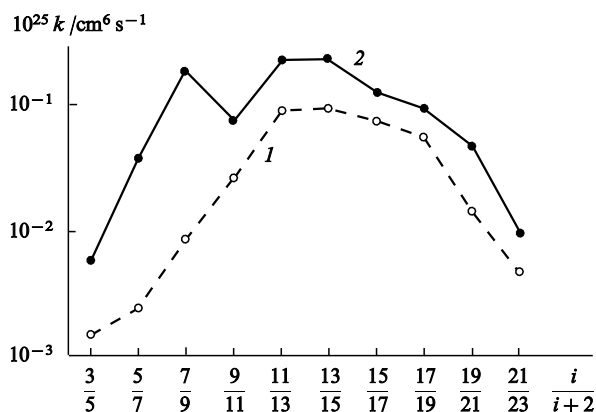


Figure 8. Dependence of the rate constant for the formation of odd hydrogen ionic clusters in the reaction $\text{H}_i^+ + 2\text{H}_2$ on the relative size change $i/(i+2)$ of an ionic cluster H_i^+ at low temperatures.⁹² The points in the curve 1 were obtained in an experiment with an equilibrium concentration of the *para*- and *ortho*-modifications in H_2 , those in the curve 2, in hydrogen enriched with the *para*-component.

This example demonstrates a transition from clusters with sufficiently strong chemical bonds to clusters with van der Waals bonds with an increase in the number of species.

Experiments also give information on the cluster structure. For example, a decrease in the association rate constant with an increase in the cluster size at $i = 9$ is due to the beginning of formation of the second shell around the H_5^+ skeleton. The rate decrease at $i > 15$ is due to a decrease in the efficiency of stabilisation by the third body.^{41, 73}

The effect of the particular features of the complex structure on the association rate constant is demonstrated in Fig. 9, which

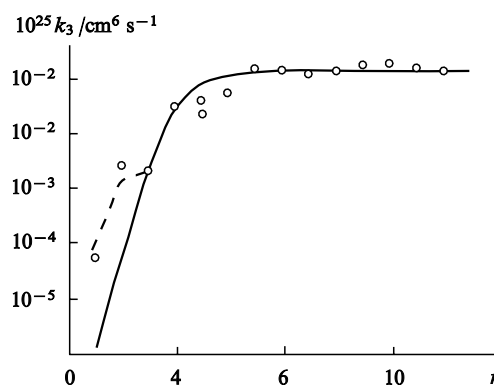
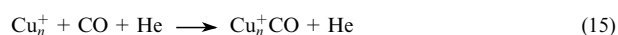


Figure 9. Dependence of the rate constant for reaction (15) on the number of atoms in an ionic copper cluster.⁷³

The points refer to the experiment; the curve gives the calculation in accordance with the RRKM theory under the assumption of a 'soft' transition state. The dotted line connects the calculated points obtained for a 'hard' transition state for $n = 1$ and 2.

shows the experimental dependence of the association rate constant for copper ionic clusters Cu_n^+ with CO molecules

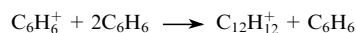


on the magnitude of n .⁷³ On going from the Cu^+ ion to its dimer Cu_2^+ , the rate constant increases by about an order of magnitude. However, the rate constant decreases somewhat on going from Cu_2^+ to Cu_3^+ . This rather unexpected result is related to the specific features of the trimer electronic structure, which are unknown.[‡] The passage from Cu_3^+ to Cu_4^+ again results in an increase in the reaction rate constant by an order of magnitude.

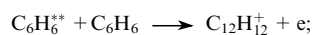
Further increase in the cluster size results in a slower increase in the rate constant, which approaches a steady level at $n = 7$.

The agreement between the calculated and experimental points for the rate constants of the reactions of the Cu_n^+ ions with $n \geq 3$ is good, but the experimental points for Cu^+ and Cu_2^+ 'fall out'. If another type of transition states (so-called hard ones) are assumed for the $\text{Cu}^+ \text{CO}$ and $\text{Cu}_2^+ \text{CO}$ complexes, the agreement for these points with the calculated data is improved considerably.

The rates of three-body association processes usually decrease with an increase in the temperature and translational energy of ions. There is only a single publication¹¹⁷ where the effective rate constant for the reaction



is reported to be independent of the translational energy of the ions over a wide energy range. However, in this case it cannot be ruled out that the $\text{C}_{12}\text{H}_{12}^+$ ions are products of associative ionisation of highly excited benzene molecules¹¹⁸



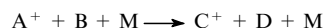
the rate of this process is not affected by electrical fields that accelerate the ions.¹¹⁷

However, some data indicate that the efficiency of association in certain systems is increased with an increase in the translational energy of the colliding species. For example, it was found that collisions of accelerated fullerene ions with inert gas atoms produce long-lived excited complexes with a noble gas atom inside the molecular cage of the fullerene.^{119, 120} These are threshold processes that occur only at sufficiently high collision energies.

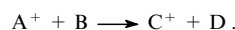
[‡] A semiempirical calculation by one of the authors suggests that for $\text{Cu}_2^+ \text{CO}$ the almost T-shaped structure of the $(\text{Cu}-\text{CO}-\text{Cu})^+$ complex in which the carbon atom is arranged between the two copper atoms has the lowest energy.

The formation of long-lived excited complexes in bimolecular processes also occurs in collisions of ions of large biological molecules with small molecules like NH_3 and CH_4 .¹¹⁸ Probably, association is possible in these systems, and its efficiency increases with an increase in the translational energy of ions.

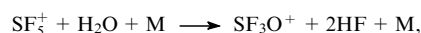
Of the three-body ion–molecule processes, the association processes have been studied most thoroughly to date. However, three-body exchange reactions, which have been little studied thus far, are of considerable interest. There are reasons to believe that at higher gas pressures three-body reactions resulting in the same products as bimolecular ones



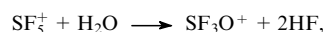
can compete successfully with some slow exothermic bimolecular reactions of the type



The reactions



(rate constant $3 \times 10^{-27} \text{ cm}^6 \text{ s}^{-1}$) and



with a rate constant less than $10^{-11} \text{ cm}^3 \text{ s}^{-1}$ can serve as examples.^{14, 121}

The detailed mechanisms of these processes have not been sufficiently studied yet. Studies of the dependence of the reaction rate on pressure^{122, 123} and temperature¹²⁴ revealed an abnormal behaviour of the $[\text{SF}_5 + \text{H}_2\text{O}]$ complex. This complex can probably exist in different configurations with considerably different reactivities.

VI. Conclusion

Intense studies on ion–molecule reactions in gases have already been continuing for almost half a century after V L Tal'roze discovered these reactions in mixtures of hydrocarbons in the early 1950's. About 15 years later, intense studies of three-body reactions began in parallel with bimolecular reactions; the contribution of the former becomes important upon increasing the pressure in the reaction region. At present, there is a rather extensive experimental data base on the rate constants for such reactions; however, its bulk is about 30 times smaller than that of a similar base for bimolecular ion–molecule reactions.

After the discovery of ion–molecule reactions, it was considered that all of them are fast if this is allowed by their thermochemistry. The main reason in favour of this was the assumption that the activation barriers appearing in the rearrangement of species (characteristic of reactions between neutral species) are already inside the 'potential well' arising due to strong electrostatic ion-dipole or polarisation attraction. In addition, it was shown that the majority of ion–molecule reactions result in an intermediate long-lived complex, and this mechanism is more typical than the 'direct' mechanisms.

It was thus concluded that exothermic ion–molecule reactions are a specific type of process different from similar reactions between neutral species. However, many exceptions from this concept were found later. The presence of energy barriers and the effect of various types of internal excitation on the reaction rates were observed. In view of this, it was concluded that there is no fundamental difference between the mechanisms of ion–molecule reactions and reactions of neutral species.

In fact, the energy barrier exists in the direction of the reaction coordinate, while the potential well originating from electrostatic attraction between an ion and a molecule corresponds to another coordinate describing the distance between the species. The effect of the electrostatic attraction can be demonstrated in a simplified form as a decrease in potential energy relative to the level of dissociation into the original species. The difference between the total energy and the energy barrier level (which, in rare cases, can

even be negative) for ion–molecule system is most commonly different from that for neutral species. However, this is most likely a quantitative parameter, and the theoretical approaches for the consideration of ion–molecule reactions do not differ fundamentally.

It is of note that the role of the ion–molecule attraction should not be overestimated. The electrostatic interactions cannot be extrapolated for the short distance range. When the reacting partners approach each other, considerable redistribution of the effective charge in a system of colliding species occurs, and the character of interaction alters.

However, owing to redistribution of the effective charge, which can occur even at rather long distances between the partners, the properties of the reagents (geometry, bond energies, vibration frequencies) also change. This charge redistribution is more typical of ion–molecule collisions than of collisions involving neutral species (except for the systems with a weakly bonded electron).

Activation is usually non-typical of ion–molecule association reactions. However, specific effects related to the presence of charge in the system manifest themselves in full measure. This corresponds to a deeper global minimum of the potential energy surface for the interaction between the reagents, *i.e.*, an increase in the dissociation energy. The potential well becomes much wider, which results in an increase in the number of internal energy levels. As a result, the rate constants for ion–molecule association appear to be much higher than those for similar systems of neutral species. Upon this is further superimposed the effect of larger collision cross-sections due to long-range interaction.

Despite the similarity of the theoretical approaches for three-body processes involving only neutral and ion-neutral species, the calculation details differ in the practical calculations, where it is necessary to use certain approximations. For ion–molecule association processes, anisotropic effects are essential (an example of their calculation within the framework of the statistical theory was described above). Calculations of potential energy surfaces (which commonly have local minima in addition to global ones in ion–molecule systems) and the corresponding trajectory calculations are also important.

Rather recently, a quasi-classical method has appeared, *viz.*, SACM (statistical adiabatic channel model), for the calculation of ion capture by molecules.¹²⁵ Rather accurate algorithms of trajectory calculations for these processes^{126–129} and three-body collisions¹³⁰ have also been developed. However, a strict theoretical consideration of low-temperature experiments requires the development of purely quantum models.

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High-resolution solid-state NMR spectroscopy in studies of conversions of hydrocarbons and alcohols on zeolites[†]

A G Stepanov

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Abstract. The review surveys advances in high-resolution solid-state ¹H and ¹³C NMR spectroscopy applied to studies of conversions of hydrocarbons and alcohols on zeolite catalysts of an acidic nature. The potential of NMR spectroscopy in studies of mechanisms of chemical reactions and analysis of compounds formed *in situ* is considered. The bibliography includes 134 references.

I. Introduction

NMR spectroscopy has been used for studying solid heterogeneous catalysts and surface chemical reactions over several decades.¹ However, impressive progress in this field has been achieved only with the advent of special techniques for recording NMR spectra and with the development of superconducting magnets producing strong magnetic fields (7–18 T). Thus the application of the magic-angle-spinning (MAS) technique in which the sample is rotated rapidly about an axis subtending a magic angle (57°48'8'')^{2–4} with respect to the external magnetic field (2–35 kHz) leads to substantial narrowing of NMR signals for nuclei of both solid catalysts (¹H, ¹⁷O, ²⁷Al, ²⁹Si and ⁵¹V) and organic molecules adsorbed on the catalyst surface (¹H, ¹³C, ¹⁵N and ³¹P). The implementation of a technique for recording NMR spectra with the use of cross-polarisation simultaneously with high-power proton decoupling^{5–7} enhances the sensitivity of NMR spectroscopy a hundred times and makes possible observations of signals of molecules adsorbed on the catalyst surface.

Presently, high-resolution solid-state NMR spectroscopy is widely used for both characterising structures of heterogeneous catalysts^{1,8–13} and studying conversions of organic molecules on their surfaces.^{13–17} In many cases, NMR spectroscopy appears to be the unique physical method which provides data on reaction mechanisms and enables one to perform reliable analysis of

compounds formed *in situ*, to determine their compositions and structures and to make conclusions about chemical processes that occur on the catalyst surface. Hence, one can go from the hypothetical notion of reaction mechanisms to the understanding of their true mechanisms.

NMR spectroscopy is particularly helpful in studying catalytic conversions at low (as regards traditional organic catalysis) temperatures, for example, in studying low-temperature alkene conversions on zeolites. This field of potentially important low-temperature chemical conversions remains poorly studied due to problems associated with analysis of undesorbable compounds.

Recently, studies of conversions of hydrocarbons and alcohols on zeolites by NMR spectroscopy have attracted growing interest in connection with the solution of the following practical problems:

— a search for ways of enhancing the selectivity of the yields of C₄–C₅ alkenes in the course of catalytic cracking based on zeolite catalysts (HY, USY and HZSM-5);

— synthesis of a motor fuel from methanol on HZSM-5 zeolite.¹⁸

Discussion about the role of various intermediates, *viz.*, alkoxides and carbenium ions, in catalytic hydrocarbon conversions on solid acids (zeolites and amorphous aluminosilicates), which has lasted for the last decade, gave additional impetus to the application of NMR spectroscopy to the studies of hydrocarbon conversions.

The present review surveys the most interesting results of studies of conversions of various hydrocarbons on solid zeolite catalysts of acidic nature which have been performed in the leading world's laboratories with the use of NMR spectroscopy. The first results of studies of hydrocarbon (alkene) conversions are compared with the results obtained by various research groups within the last five years. The possibilities of other methods (primarily, of IR spectroscopy) in studies of hydrocarbon conversions are considered.

In the present review, the discussion is restricted to the results of chemical studies[‡] obtained by NMR spectroscopy.

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[†] Dedicated to the memory of Academician K I Zamaraev.

[‡] Experimental details and discussion of various possibilities of the use of high-resolution solid-state NMR spectroscopy for characterisation of catalysts and processes that occur on their surfaces have been reported in the literature.^{10–13, 16, 19, 20}

II. Alkene oligomerisation

1. Adsorbed products of low-temperature alkene oligomerisation

Until recently, the nature of hydrocarbon products which were formed upon low-temperature oligomerisation of alkenes (ethylene, propene or isobutene) on acidic forms of zeolites (for example, on the HZSM-5 zeolite), remained unclear and was the subject of discussion.^{21–38} It was reasonable to suggest that alkene oligomerisation in the presence of an acidic catalyst should afford a long-chain alkene. However, signals at 1660–1670 [$\nu(\text{C}=\text{C})$] and 3020–3090 cm^{-1} [$\nu(\text{C}=\text{H})$] expected for the double bonds³⁹ were not observed in the IR spectra of adsorbed oligomeric products.^{21–24, 27–29, 31, 33} Signals with the chemical shifts at δ 110–140 typical of alkene double bonds⁴⁰ were absent in the ^{13}C NMR spectra as well.^{24–26, 30, 32, 34–38} The only identified signals were those of saturated hydrocarbon fragments of oligomeric products.^{21–38}

The absence of signals of alkene fragments in the IR and NMR spectra has been explained within the frameworks of two alternative hypotheses. According to the first hypothesis, adsorbed oligomers are hydrocarbon fragments covalently bonded to oxygen atoms of the zeolite lattice, *i.e.*, the hypothesis postulates that oligomeric alkoxides (alkyl silyl ethers), which do not contain double bonds, are formed.^{32–34, 38} According to the second hypothesis, adsorbed oligomers are oligomeric aliphatic carbenium ions,^{27, 28, 37} which do not contain double bonds as well. Unfortunately, both hypotheses are self-contradictory. Actually, if oligomers were alkoxides, the ^{13}C NMR spectra should have signals for the carbon atoms of the C–O–Si fragment at δ 70–90.^{40, 41} However, in a series of studies,^{24–26, 30, 32, 34–38} no mention of these signals was presented, while in other studies^{15, 35, 38, 42–48} these signals were observed only in the case of small hydrocarbon fragments (Me, Prⁱ, Bu^t and Buⁱ) bound to the zeolite framework.

The same is true for carbenium ions containing long-chain hydrocarbon fragments for which signals at δ 300–330 (a carbon atom that carries a positive charge)^{49–51} in the ^{13}C NMR spectra or bands at 1260–1295 cm^{-1} [$\nu(\text{C}^+-\text{C})$ stretching vibration]^{52, 53} in the IR spectra would be expected. However, neither the IR spectra nor the NMR spectra had these signals.

a. Alkoxide nature of the adsorbed oligomers

The ^{13}C CP/MAS NMR spectrum[§] of products of ethylene oligomerisation on the HZSM-5 zeolite at 296 K is shown in Fig. 1.⁵⁴ On the whole, this spectrum is identical with that obtained previously by van den Berg and co-workers for ethylene oligomers.³⁰ The signals at δ 14, 22 and 33 were assigned to the terminal CH_3 groups, to the adjacent CH_2 groups and to internal CH_2 groups of linear hydrocarbon fragments of oligomers, respectively.

The spectrum has no signals with noticeable intensities at δ 110–140 (for alkene fragments)⁴⁰ or at δ 300–330 (for carbenium ions).^{49–51} However, substantial enhancement of the spectrum made it possible to detect a weak broad signal at δ 89, which indicates that adsorbed oligomers contain carbon atoms bound to oxygen atoms of the zeolite framework, *i.e.*, is indicative of the presence of C–O–Si fragments.^{41–45} An analogous signal for C–O–Si fragments at δ 86, while substantially more intense, was observed for isobutene oligomers formed upon dehydration

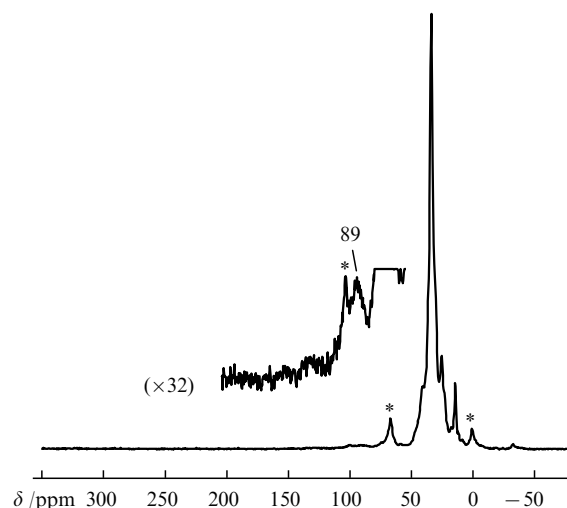


Figure 1. The ^{13}C CP/MAS NMR spectrum of oligomerisation products of ethylene (40% $^{13}\text{CH}_2=\text{CH}_2$) on HZSM-5 zeolite at 296 K. Hereinafter, peaks due to the rotation of the sample are marked with asterisks.

of *tert*-butyl alcohol on HZSM-5 zeolite.^{35, 38} Therefore, evidence for the alkoxide nature of the adsorbed oligomers was obtained.[¶]

b. Carbenium-ion properties of the adsorbed oligomers

An interesting experiment, which gave a deeper insight into the nature of the adsorbed oligomers, was described in Ref. 37. Studies of a possible ethylene oligomerisation product, *viz.*, oct-1-ene containing the selectively ^{13}C -labelled terminal $=\text{CH}_2$ group, adsorbed on the HZSM-5 zeolite demonstrated that the terminal $=^{13}\text{CH}_2$ group of oct-1-ene was converted into the ^{13}C -labelled terminal methyl group immediately after adsorption (Fig. 2). Then the intensity of the signal for the carbon atom of the terminal $^{13}\text{CH}_3$ group at δ 14.3 decreased and the intensities of the signals of internal CH_2 groups of oct-1-ene at δ 30.0 increased with time. This is indicative of the transfer of the selective ^{13}C label from the methyl group of oct-1-ene to its CH_2 groups with the characteristic half-reaction time $\tau_{1/2} \sim 4$ h (at 290 K). The redistribution of the carbon label in the adsorbed oct-1-ene was completed in $t > 20$ h. It is known that the redistribution of

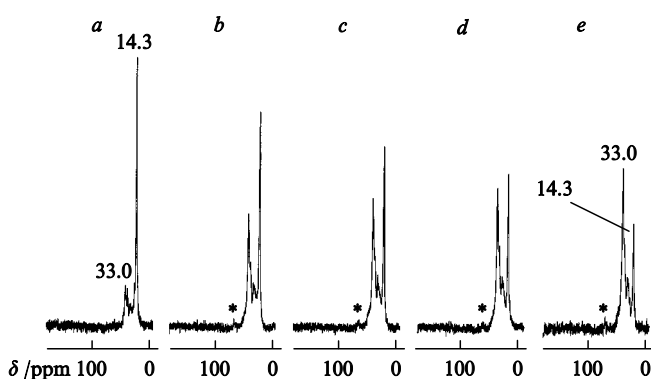
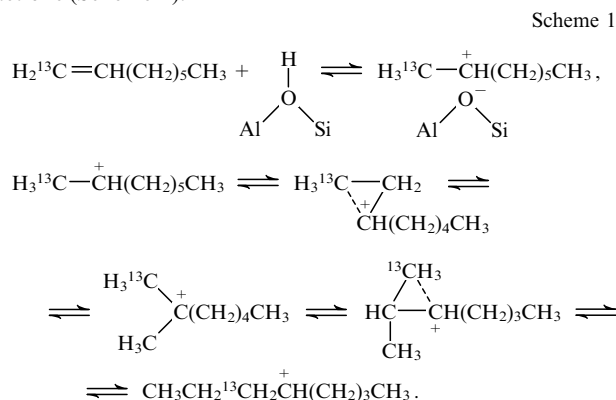


Figure 2. Change in the ^{13}C CP/MAS NMR spectrum of oct-1-ene (containing the ^{13}C -labelled terminal $=\text{CH}_2$ group) adsorbed on HZSM-5 zeolite ($T = 290$ K) with time.³⁷ Time/h: 0.17 (a), 2.83 (b), 6.17 (c), 12.83 (d), 53 (e).

§ The ^{13}C CP/MAS NMR spectrum was recorded with the use of the magic-angle-spinning (MAS) technique at the spinning frequency of 2500–5000 Hz using cross-polarisation (CP).

¶ An explanation of the reasons for the low intensity of the signal for the carbon atom of the COSi fragment in adsorbed ethylene oligomers is offered below, where the interpretation of the spectra is discussed.

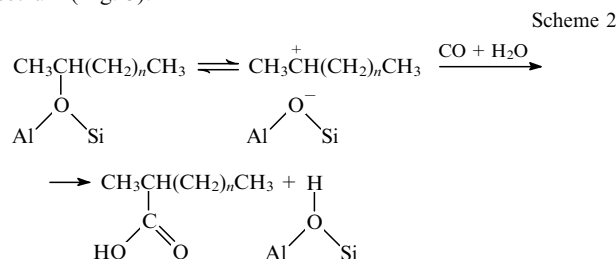
carbon labels is typical only of carbenium ions existing as stable species in solutions of superacids.^{49–51, 55–57} Based on the afore-said, it was concluded that carbenium ions were formed upon adsorption of oct-1-ene on the HZSM-5 zeolite. The changes observed in the NMR spectrum are attributable to the following reactions (Scheme 1):



In the adsorption of oct-1-ene on zeolite, the proton of the acidic OH group of the zeolite is transferred to the oct-1-ene molecule. In this case, the terminal =CH₂ group is converted into the terminal CH₃ group simultaneously with the formation of a carbenium ion. In the cation formed, the ¹³C label is redistributed through the formation of protonated cyclopropane intermediates,^{49, 50, 55–57} which leads to a decrease in the intensity of the signal for the CH₃ group and to an increase in the intensities of the signals for the internal CH₂ groups with time (Fig. 2).

In spite of the label redistribution typical only of carbenium ions, signals at δ 300–330, which are indicative of the presence of carbenium ions in the system, were not observed in the spectrum. It was thus concluded that either the concentration of the cations formed was too low or these cations were short-lived transient species.

Later, the conclusion that carbenium ions exist in small amounts among adsorbed oligomers was confirmed by the chemical reaction at room temperature involving the adsorbed oligomers, which is characteristic of carbenium ions. It is known that carbenium ions readily react with carbon monoxide in solutions of strong acids^{58, 59} to form carboxylic acids. Consequently, carbenium ions formed among oligomeric products would be expected to react with CO and water to form carboxylic acids. Actually, simultaneous adsorption of CO and water on a zeolite specimen containing ethylene oligomers resulted in conversion of oligomers into a mixture of the corresponding oligomeric carboxylic acids (Scheme 2), which is evidenced by the signal of carboxyl groups at δ 189 in the ¹³C CP/MAS NMR spectrum (Fig. 3).^{60, 61}



The formation of carboxylic acids and the redistribution of the selective ¹³C label unambiguously suggest that carbenium ions were present among the adsorbed oligomers. In addition, after completion of the reaction of oligomers with CO and H₂O, signals for oligomeric alkoxides at δ 89 were no longer observed in the ¹³C NMR spectrum (*cf.* Figs 1 and 3), which is indicative of the conversion of alkoxides into acids. These results altogether allowed the conclusion that alkoxides existed in the equilibrium with oligomeric carbenium ions. Though the concentrations of the

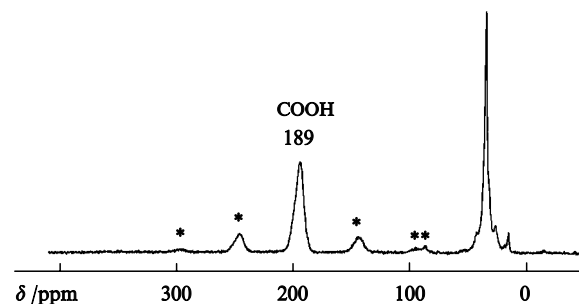


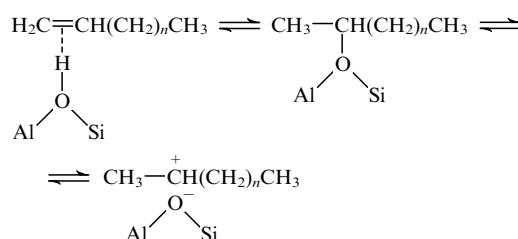
Figure 3. The ¹³C CP/MAS NMR spectrum of products formed after additional adsorption of ¹³CO + H₂O on zeolite containing ethylene oligomers.

latter are too low to be detected by ¹³C CP/MAS NMR spectroscopy, the reactivities of the oligomers are determined by the reactivities of the equilibrium carbenium ions.

Taking into account that conversion of C₂–C₄ alkenes in a flow reactor at $T < 450$ K afforded C₆–C₁₈ alkenes,^{62, 63} *i.e.*, oligomeric products can be desorbed as alkenes under particular conditions,[†] it was concluded that alkenes were present in small amounts among the adsorbed oligomeric products. However, the concentrations of alkenes were so low that these compounds, like carbenium ions, were 'invisible' to NMR spectroscopy.

Hence, the NMR spectral data allow the conclusion that oligomeric products of low-temperature alkene conversions, which are adsorbed on acidic forms of zeolites, exist as three interconvertible forms, *viz.*, as alkoxides, carbenium ions and alkenes (Scheme 3).

Scheme 3



Oligomeric alkoxides present the major adsorbed form.

2. Compositions and structures of products of alkene oligomerisation on HZSM-5 zeolite

In the first studies devoted to oligomerisation of alkenes on HZSM-5 zeolite, qualitative conclusions about the formation of linear oligomers^{25, 26, 30, 34} which contain approximately 16 carbon atoms from alkenes (ethylene, propene or isobutene) were made based on the analysis of the positions of the signals for CH₃ and CH₂ groups in the ¹³C MAS NMR spectra.³⁰ However, signals for the CH₂ groups of linear fragments and signals for the CH₃ groups of branched fragments of oligomers are observed in the same region of the ¹³C NMR spectrum (at δ 20–30).⁴⁰ Consequently, one cannot infer the structures and lengths of hydrocarbon chains of oligomeric products exclusively from the chemical shifts of signals in the ¹³C NMR spectra.

It was suggested that 2D *J*-resolved ¹³C MAS NMR spectroscopy followed by GC-mass spectrometric analysis and traditional high-resolution ¹³C NMR spectroscopy (in solution) of oligomers which have been extracted from zeolite, be used for establishing the compositions and structures of oligomeric products formed from ethylene on HZSM-5 zeolite.⁵⁴

[†] Signals of double bonds are also absent in the NMR spectrum of the adsorbed oligomer.

a. 2D J -resolved ^{13}C MAS NMR spectroscopic data

Two-dimensional J -resolved MAS NMR spectroscopy offers advantages over 1D NMR spectroscopy because not only does it provide data on the chemical shifts of signals for carbon atoms of oligomers but it also allows the determination of the multiplicity of the signals that occurs due to spin-spin coupling between the ^{13}C nuclei and the adjacent protons [the spin-spin coupling constants $J(^{13}\text{C}-^1\text{H})$].^{64,65} In the 2D NMR spectrum, the assignment of the signal with a particular F2-dimension chemical shift to the CH_n group is made based on the calculation of the number of peaks of this signal on the F1 axis.^{36,38,64–66} As a result, the ambiguity of the assignment of the signals for carbon atoms is excluded and the true structure of oligomers in the adsorbed form can be determined.

The contour plot of the 2D J -resolved ^{13}C MAS NMR spectrum of ethylene oligomers on the HZSM-5 zeolite and the corresponding 1D NMR spectrum are shown in Fig. 4b. It can be seen that the signals at δ 30 and δ 34 exist as triplets with the constant $J(^{13}\text{C}-^1\text{H}) = 140 \pm 16$ Hz, which suggests that these signals belong to the CH_2 groups of oligomers. The signal at δ 22 is a singlet characteristic of the quaternary carbon atom. However, it is observed in the region typical of either the terminal CH_3 groups of branched oligomers (in this case, the signal should exist as a quartet on the F1 axis⁶⁶) or the CH_2 group (a triplet on the F1 axis⁶⁶) adjacent to the terminal CH_3 group of the linear fragment of the hydrocarbon chain rather than being located in the region of chemical shifts of the quaternary carbon atom of alkanes (at δ 30–40⁴⁰). The existence of a singlet rather than a doublet at δ 22 suggests that this signal is in fact a triplet for which only the most intense central component is distinct in the spectrum against a background of the noise level.^{35,67} Hence, it was concluded that the signal at δ 22 belongs to the CH_2 groups of oligomers. The existence of four peaks on the F1 axis for the signal at δ 14 indicates that the latter belongs to the terminal CH_3 groups of the oligomer.

To summarise, analysis of the multiplicities of signals of the adsorbed oligomers allowed the conclusion that signals in the

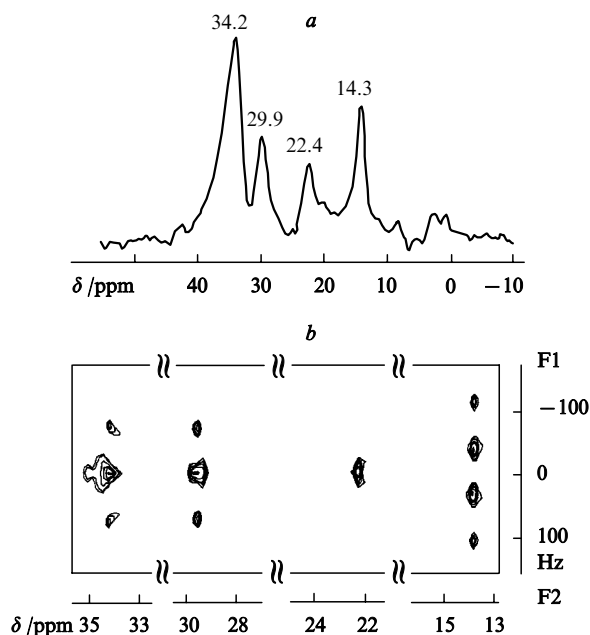


Figure 4. Spin-echo 1D ^{13}C MAS NMR spectrum (a) and the contour plot of the 2D J -resolved ^{13}C MAS NMR spectrum (b) of oligomerisation products of ethylene on HZSM-5 zeolite at 296 K. The observed value of the scalar spin-spin coupling constant $J(^{13}\text{C}-^1\text{H})$ on the F1 axis is half as large as the real value $J(^{13}\text{C}-^1\text{H})$ due to the use of a special technique for recording the 2D spectrum.⁶⁵

region from δ 22 to δ 34 belong to the CH_2 groups, *i.e.*, the oligomers formed are linear hydrocarbon fragments.

b. High-resolution solution ^{13}C NMR spectroscopic data

To confirm the conclusions about the structures of oligomers formed from ethylene, a sample of HZSM-5 zeolite with the adsorbed oligomers was dissolved in 10% NaOH⁶¹ and the liberated hydrocarbon products were extracted with diethyl ether, dissolved in benzene- d_6 and analysed by high-resolution ^{13}C NMR spectroscopy. The major characteristics (chemical shifts, the ratio of the intensities of the signals and the multiplicities of the major, most intense signals) of the spectrum of the products desorbed from the zeolite (Fig. 5) are identical with those of the adsorbed oligomers (see Fig. 1). The most intense signals at δ 22 and 33–34 exist as triplets with $J(^{13}\text{C}-^1\text{H}) = 125$ Hz and the signals at δ 10–14 exist as quartets with $J(^{13}\text{C}-^1\text{H}) = 125$ Hz.

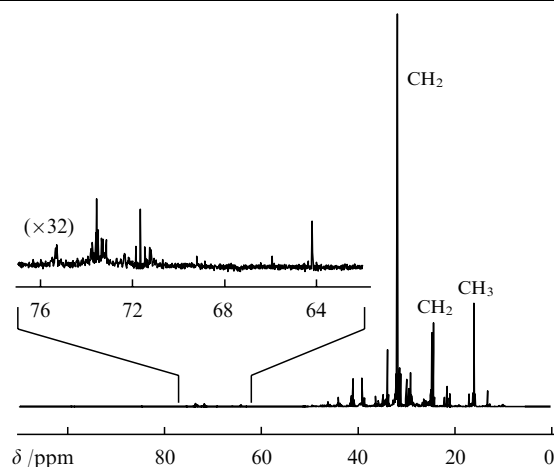


Figure 5. The high-resolution ^{13}C NMR spectrum (in benzene- d_6) of ethylene oligomers extracted from HZSM-5 zeolite after dissolution of the zeolite in NaOH solution.

In the spectra of the extracted products, the intensities of the signals at δ 60–80 are as small as those of the adsorbed oligomers. The fact that the ratio of the signals of the adsorbed products is identical with that of the extracted products as well as the presence of signals for the carbon atoms of the CH_x-OH fragment of alcohols indicate that the oligomers are extracted from the zeolite as alcohols and the structures of the extracted alcohols are analogous to those of the adsorbed alkoxide oligomers. The estimation of the ratio of the signals at δ 14, 22 and 33 (Fig. 5) demonstrated that an average linear oligomeric chain consists of seven carbon atoms [$-(\text{CH}_2)_6\text{CH}_3$] bound to an oxygen atom of the zeolite framework.

From the spectrum shown in Fig. 5 it follows that not only linear but also branched oligomers are formed on the HZSM-5 zeolite, which is evidenced by the signals at δ 35–50 belonging to secondary and tertiary carbon atoms.^{30,68} However, linear oligomers predominate apparently due to the specific structure and the size of the channels in the HZSM-5 zeolite.⁶⁹ The fact that the ^{13}C NMR spectrum (see Fig. 5) has more than 20 signals from alcohols at δ 60–80 indicates that a mixture of no less than 20 oligomeric alkoxides containing predominantly linear fragments is formed upon adsorption of ethylene on the HZSM-5 zeolite. For a mixture of adsorbed oligomers, only one broad low-intensity signal at δ 89 (see Fig. 1) is observed, which is indicative of the alkoxide nature of the adsorbed oligomers.⁵⁴ Previously,^{30,32,34,70,71} attempts to identify this signal have failed for several reasons. First, the adsorbed oligomers exist as a mixture of oligomeric alkoxides (> 50 , according to GC-mass spectrometric analysis⁵³). Second, the signals for oligomeric alkoxides are broad

but their intensities are low. Third, chemical shifts of the signals vary within the range of > 15 ppm.

In some cases, signals at $\delta 87-89$ observed for various alkenes (Pr^i and Bu^i)^{35,45,48,72} were assigned to small hydrocarbon fragments bound to the oxygen atoms of the zeolite framework. However, the fact that the chemical shifts of the signals for alkoxides observed upon propene oligomerisation on HY zeolite^{45,73} or on HZSM-11 zeolite⁴⁸ are identical with those observed upon isobutene oligomerisation on HZSM-5 zeolite³⁵ allows the conclusion that the signals at $\delta 87-89$ (see Refs 35, 45 and 48) should be assigned to oligomeric alkoxides rather than to short hydrocarbon fragments.

c. Data of GC-mass spectrometric analysis

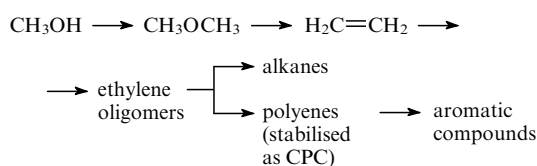
The compositions of ethylene oligomers formed were also determined by GC-mass spectrometric analysis. To do this, the adsorbed oligomers were first converted into a mixture of the corresponding carboxylic acids according to Scheme 2. Then, carboxylic acids were extracted from the zeolite by dissolving the latter in 10% alkali. Subsequent treatment of the mixture of acids with diazomethane⁶¹ made it possible to convert them into the corresponding methyl carboxylates, which were readily separated and analysed by GC-mass spectrometry. It was found that the mixture extracted was comprised of more than 50 different oligomeric products (C_5-C_{14}).

III. Dehydration of alcohols

1. Methyl alcohol

NMR studies of alcohol conversions on zeolites attracted interest immediately after 'Mobil' had discovered conversions of methanol into a motor fuel on HZSM-5 zeolite.^{74,75} The first NMR spectral study devoted to conversions of methanol⁷⁶ had already demonstrated the possibility of the application of ^{13}C MAS NMR spectroscopy in the analysis of intermediates and reaction products. Evidence was obtained for the conversion of methanol first into dimethyl ether and then into a mixture of hydrocarbons *via* intermediate carbenium ions rather than carbenes, as had been suggested previously by Chang and Silvestri.¹⁸ Anderson and Klinowski^{78,79} noted the difference in the composition of the products which were present in the gas phase and in zeolite pores. Thus in no case were C_{10} aromatic products observed among the desorbed products, but these compounds were found *in situ* in zeolite pores. It was thus concluded that products were formed within zeolite pores under conditions of the equilibrium reaction, the composition of the desorbed products being determined by the pore size of the zeolite. Hence, the effect of the internal specific size and the pore structure on the composition of the products desorbed was experimentally demonstrated.

In the study devoted to methanol conversions,⁷⁹ it was noted that ethylene was formed as an important intermediate. It was also reported that the reaction performed under conditions similar to those used in a flow reactor (small contact time) yielded intermediate C_4 alkenes and cyclopentenyl cations (CPC).⁸⁰ Below is given the scheme of conversions of methanol into a mixture of hydrocarbons on the HZSM-5 zeolite.



2. *tert*-Butyl alcohol

Conversions of aliphatic C_3-C_4 alcohols on acidic zeolites were studied with the aim of obtaining more detailed information on the mechanism of dehydration. The molecular sizes of these alcohols are comparable with the pore sizes of zeolites.

Dehydration of C_3-C_4 alcohols starts at substantially lower temperature (300–400 K) than that of methanol (550–700 K). This enables one to obtain more detailed information on the nature of intermediates based on the data of NMR spectroscopy and, consequently, to draw conclusions about the mechanism of these reactions. In addition, it becomes possible to reveal the effect of the pore size of a zeolite on the course of dehydration of isomeric alcohols and to analyse subsequent conversions of the products formed upon primary dehydration. In the present review, the results of studies of dehydration of isomeric butyl alcohols are considered in detail.

Dehydration of *tert*-butyl alcohol on HZSM-5 zeolite occurs at room temperature.⁸¹ NMR spectral studies of this reaction, which is not complicated by secondary processes of cracking of the products formed, are of considerable interest for the understanding of the mechanisms of dehydration and subsequent oligomerisation of isobutene formed upon dehydration.^{35,38,46,70} It was found⁴⁶ that the dehydration of Bu^iOH containing the ^{13}C -labelled tertiary carbon atom on HZSM-5 zeolite ($\text{Si}:\text{Al} = 36$) was accompanied by complete redistribution of the labels in the oligomeric products. It was thus concluded that carbenium-ion intermediates were involved in dehydration of the alcohol and that *tert*-butyl silyl ether (TBSE) was formed as a stable intermediate, *i.e.*, the *tert*-butyl fragment was covalently bound to the oxygen atom of the zeolite framework. The authors⁴⁶ believed that the formation of TBSE is evidenced by the signal at $\delta 77$ corresponding to the carbon atom bound to the oxygen atom of the zeolite[‡] as well as by the unusually large chemical shift of the carbon atom bound to the oxygen atom of the zeolite framework compared to that of the carbon atom in the initial Bu^iOH , which is generally observed in neat alcohol or in neutral solutions.

More recent studies^{33,35} demonstrated that the conclusion about the formation of TBSE as a stable intermediate^{46,70} was erroneous. A special NMR spectral study³⁵ showed that dehydration of Bu^iOH on an HZSM-5 zeolite with $\text{Si}:\text{Al} = 24$ at room temperature proceeded slowly and was completed in > 15 h (Figs 6 and 7). With an HZSM-5 zeolite in which $\text{Si}:\text{Al} = 36$, *i.e.*, the zeolite in which the concentration of reactive acidic OH groups is 1.5 times lower, the dehydration time could only increase. Hence, it was concluded that dehydration of alcohols cannot be completed in 1.5 h (the reaction time in the study⁴⁶) and, consequently, the signal at $\delta 77$ can be assigned only to the initial unconsumed alcohol.³⁵ The difference between the chemical shift of the carbon atom of the $\text{C}-\text{O}$ fragment in the adsorbed alcohol (at $\delta 82$ ^{35,70} or at $\delta 77$ ⁴⁶) and that of this carbon atom in the initial solution (at $\delta 68.97$ ⁴⁰) should be attributed to specific interactions between the alcohol and the centres of its adsorption (Brønsted acidic OH groups) as well as to a possible change in the geometry of the alcohol upon its adsorption in zeolite channels.⁸²

IR spectral studies³³ demonstrated that the rates of oligomerisation and isomerisation of isobutene liberated upon dehydration are substantially higher than that of its dehydration. Hence, the products observed in the NMR spectrum are isobutene oligomers.

The identity of the spectra of isobutene oligomers prepared from Bu^iOH containing selectively ^{13}C -labelled CH_3 or $\text{C}-\text{OH}$ groups suggests the complete redistribution of the selective ^{13}C labels (*cf.* Figs 6 and 7) and confirms the conclusions made by Aronson *et al.*⁴⁶ that carbenium-ion intermediates are involved in dehydration and oligomerisation of Bu^iOH .

The formation of the *tert*-butyl carbenium ion (TBCI) and isobutene as intermediates, which exist in equilibrium with the initial alcohol,³⁵ is evidenced by the experimental data on the incorporation of the deuterium label from D_2O into the methyl group of *tert*-butyl alcohol which had previously been adsorbed on zeolite (Fig. 8, Scheme 4).

‡ It was suggested that dehydration of the alcohol on HZSM-5 zeolite with the $\text{Si}:\text{Al}$ ratio of 36 was completed in 1.5 h.

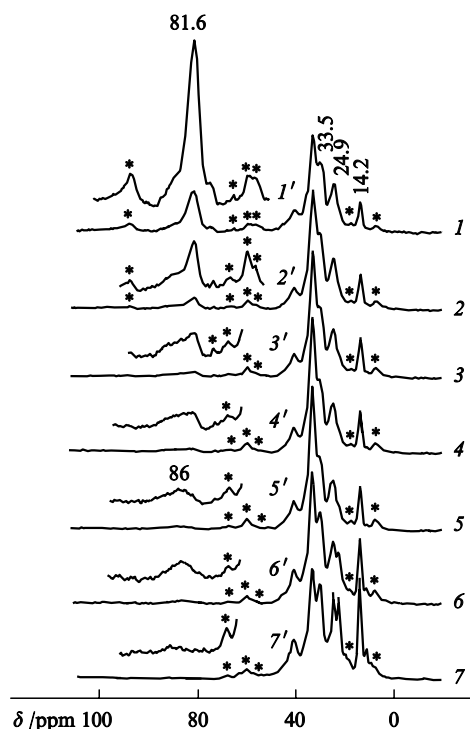


Figure 6. Changes in the ^{13}C CP/MAS NMR spectra of *tert*-butyl alcohol (containing the selectively ^{13}C -labelled C–OH group) with time at 296 K (1–5), 373 K (6) and 448 K (7) after adsorption on HZSM-5 zeolite (Si : Al = 24). Spectra 1'–7' at δ 60–110 are given with a fourfold amplification.

Time /h: (1) 0.33; (2) 2.83; (3) 5.5; (4) 8.0; (5) 15.5; (6) 1; (7) 1. The signal at δ 82 belongs to the ^{13}C –OH group of the unconsumed initial alcohol.

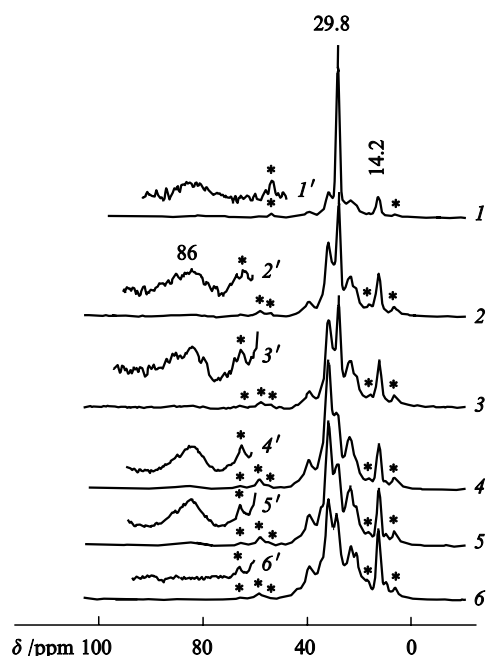


Figure 7. Changes in the ^{13}C CP/MAS NMR spectra of *tert*-butyl alcohol (containing the selectively ^{13}C -labelled CH_3 group) with time at 296 K (1–4), 373 K (5) and 448 K (6) after adsorption on HZSM-5 zeolite (Si : Al = 24). Spectra 1'–6' at δ 60–110 are given with an eightfold amplification.

Time /h: (1) 0.33; (2) 2.83; (3) 5.5; (4) 15; (5) 1; (6) 1. The signal at δ 29.8 belongs to the $^{13}\text{CH}_3$ group of the initial alcohol.

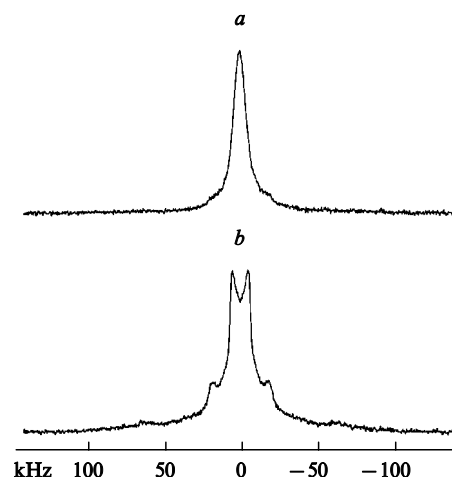
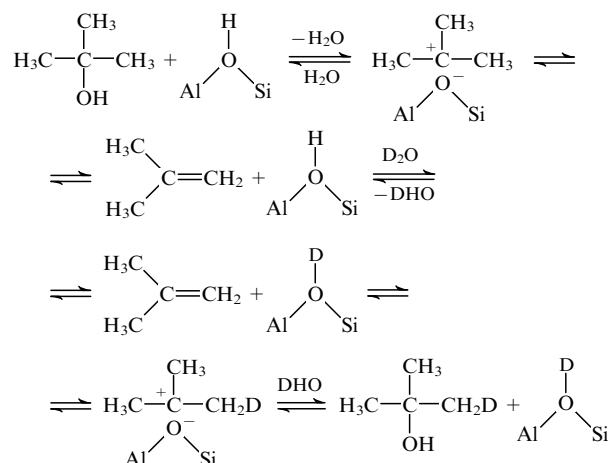


Figure 8. The static ^2H NMR spectra observed after adsorption of D_2O on a HZSM-5 zeolite specimen with the previously adsorbed $\text{Bu}'\text{OH}$ recorded within 5 min (a) and 1 h (b) after adsorption of D_2O ($T = 296\text{ K}$). (a) the shape of the spectral line corresponds to deuterated water; (b) the shape of the spectral line corresponds to superposition of three signals, viz., a signal for the $(\text{CD}_3)_3\text{C}$ fragment of alcohol with the observed quadrupole splitting $Q_3 \approx 10\text{ kHz}$ and signals for the CD_3 and CD_2 groups (weak signals) of oligomers with $Q_2 \approx 38\text{ kHz}$ and $Q_1 \approx 123\text{ kHz}$, respectively.

Scheme 4



It was also demonstrated that if zeolite containing a smaller number of acidic OH groups was used, i.e., in the case of slower dehydration of the alcohol, the selective ^{13}C label from the C–O group of the alcohol was transferred to its CH_3 group (Fig. 9).³⁸ This redistribution of the ^{13}C label confirms that TBCI is formed as an intermediate, which exists in equilibrium with the initial alcohol, in the course of dehydration. An analogous redistribution of the carbon labels was also observed in the case of carbenium ions in superacid solutions (Scheme 5).^{49, 50}

In spite of the above-considered experimental evidence for the formation of TBCI, the signal at δ 330 characteristic of the carbenium ion was not observed.⁵¹ It was thus concluded that the cation formed in zeolite is either transient or present in an amount insufficient for detection by ^{13}C NMR spectroscopy.

The signal at δ 86, which was observed in the ^{13}C NMR spectrum in the course of dehydration of $\text{Bu}'\text{OH}$, was originally assigned to stable *tert*-butyl silyl ether formed in the reaction (see Figs 6 and 7).³⁵ However, it was found that this signal appeared simultaneously with signals of oligomers and persisted after completion of dehydration. This signal disappeared only at a temperature higher than 373 K at which cracking of oligomers

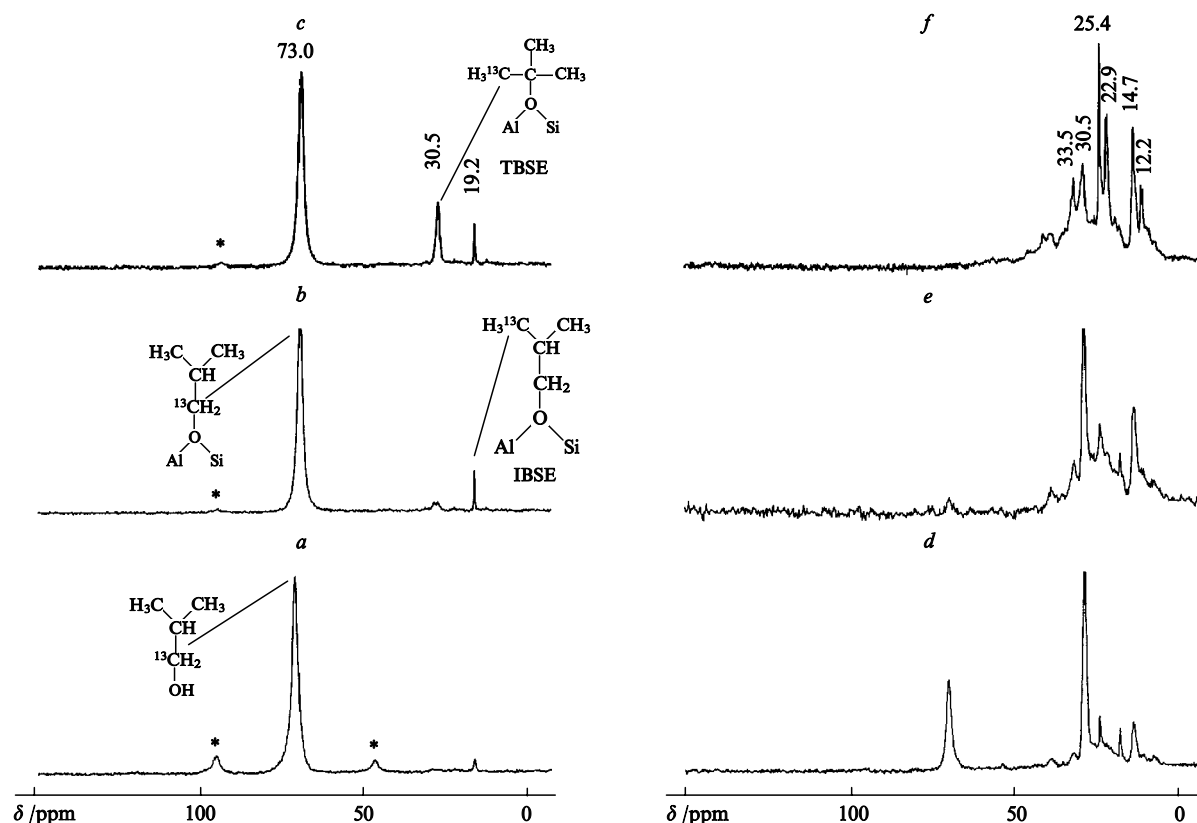


Figure 10. Changes in the ^{13}C NMR spectrum of isobutyl alcohol (containing the selectively ^{13}C -labelled CH_2 group) adsorbed on HZSM-5 zeolite (Si : Al = 24) upon successive heating of the specimen at different temperatures. Temperature /K (duration of heating, min): (a) 296 (without heating); (b) 343 (70); (c) 398 (40); (d) 413 (60); (e) 428 (60); (f) 448 (60).

Further increase in the temperature (Fig. 10 *d–f*) caused subsequent conversions of IBSE and TBSE into a mixture of alkanes (Fig. 10 *f*) and CPC (see Scheme 12 below) *via* butene oligomers.³⁸

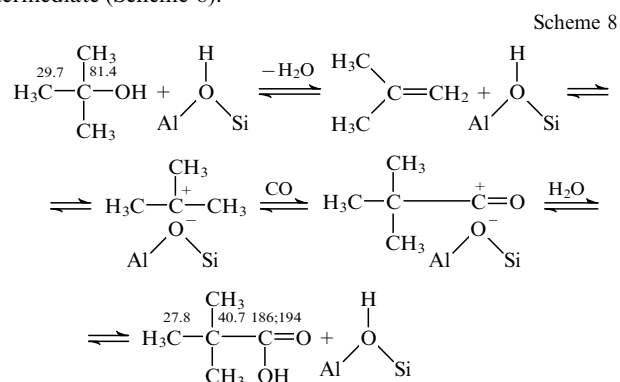
IV. Reactions of alkenes and alcohols with carbon monoxide and acetonitrile

The experimental evidence for the involvement of carbenium ions in conversions of alkenes and alcohols on zeolites obtained in NMR studies was further confirmed by a series of chemical reactions which occurred on zeolites under mild conditions.^{49, 50, 86}

1. The Koch reaction

Selective conversions of isomeric butyl alcohols in the presence of carbon monoxide and of alkenes (ethylene, isobutene and oct-1-ene) in the presence of CO and water on the HZSM-5 zeolite to form carboxylic acids (the Koch reaction^{59, 87}), which were studied with the use of ^{13}C NMR spectroscopy,^{60, 61} were found to occur at lower temperatures (20–100 °C) compared to those (300–500 °C) normally used in catalytic reactions on zeolites. Actually, the use of labelled reagents (alcohols, alkenes and CO) for the analysis of products of their reactions on the HZSM-5 zeolite provided conclusive evidence of selective conversions of alcohols and alkenes into carboxylic acids. Thus the following changes in the ^{13}C NMR spectra (Fig. 11) were observed in the reaction of Bu^tOH with CO at room temperature: when Bu^tOH containing the ^{13}C -labelled tertiary carbon atom was used, a signal at δ 40.7 belonging to the tertiary carbon atom of trimethylacetic acid (TMAA) was observed (Fig. 11 *a*); when Bu^tOH containing the ^{13}C -labelled CH_3 group was used, a signal at δ 27.8 belonging to the methyl group of the acid was observed (Fig. 11 *b*); and when labelled carbon monoxide was used, a signal

at δ 186–194 belonging to the carboxyl group was observed (Fig. 11 *c*). The formation of TMAA from Bu^tOH and CO on a zeolite catalyst at room temperature agrees well with the general concepts of the mechanism of this reaction in solutions of acids and superacids.^{58, 59} In both cases, the carbenium ion is the key intermediate (Scheme 8).



Hereinafter, the chemical shifts for the carbon atoms are given above the corresponding atoms.

The special role of carbon monoxide in this reaction is to capture TBCI formed upon elimination of the water molecule from the alcohol and to hinder its rapid oligomerisation^{35, 38, 46} by converting it into the acylium cation, which reacts with water to form acid.

Trimethylacetic acid is also selectively formed from Bu^tOH and isobutene, which suggests the presence of TBCI. Ethylene is selectively converted into 2-ethyl-2-methylbutyric acid, which is indicative of rapid oligomerisation of ethylene to form the C_6

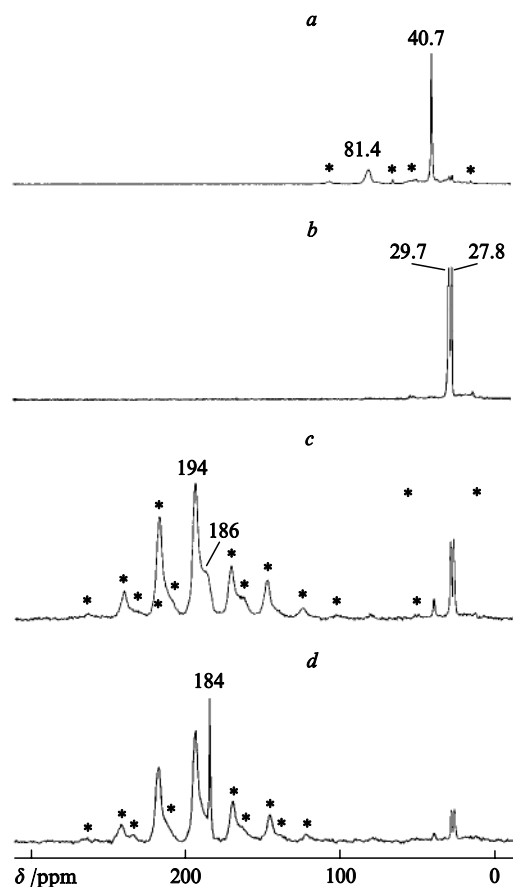


Figure 11. The ^{13}C CP/MAS NMR spectra of the product formed upon adsorption of Bu^tOH and CO on HZSM-5 zeolite at 296 K. Bu^tOH containing the ^{13}C -labelled tertiary carbon atom (a); Bu^tOH containing the ^{13}C -labelled methyl group (b) and labelled CO (c). The spectrum (d) is the spectrum (c) recorded without CP.

carbenium ion followed by termination of the growing oligomeric chain by carbon monoxide.

Subsequent NMR spectral studies demonstrated also that benzene can undergo carbonylation to form benzoic acid on HY zeolite⁸⁸ and sulfatized zirconia.⁸⁹

2. Friedel–Crafts-like acylation of alkenes

In the absence of water adsorbed on zeolite, the alkyl cation which is formed upon adsorption of alkenes on zeolite reacts with CO to give the acylium cation. The latter reacts with another alkene molecule to form unsaturated ketone. This represents the Friedel–Crafts-like acylation of alkenes,^{90–92} the acylating agent being formed *in situ* from the alkene and CO on the zeolite.

Actually, the ^{13}C NMR spectrum of the product formed in the case of simultaneous adsorption of isobutene and ^{13}CO on the HZSM-5 zeolite has two intense signals for the ^{13}C -labelled carbonyl group⁹³ at δ 225 and δ 250 (Fig. 12 a,b). The signal at δ 225 belongs to unsaturated ketones formed in the reaction and the signal at δ 250 belongs to stable cyclic five-membered carboxonium ions (Scheme 9).⁹⁴

The ^{13}C CP/MAS NMR spectra of the products formed after the adsorption of ^{13}C -labelled ethylene and CO on the HZSM-5 zeolite are shown in Fig. 12 c,d.

If a zeolite specimen was kept in air, *i.e.*, was exposed to atmospheric moisture, the signal for the carboxonium ion at δ 250 disappeared, the signal for unsaturated ketones was shifted downfield (to δ 217) and a signal belonging to carboxylic acids appeared at δ 186 (Fig. 12 e). It was thus concluded that carboxonium ions were decomposed in the presence of moisture and the

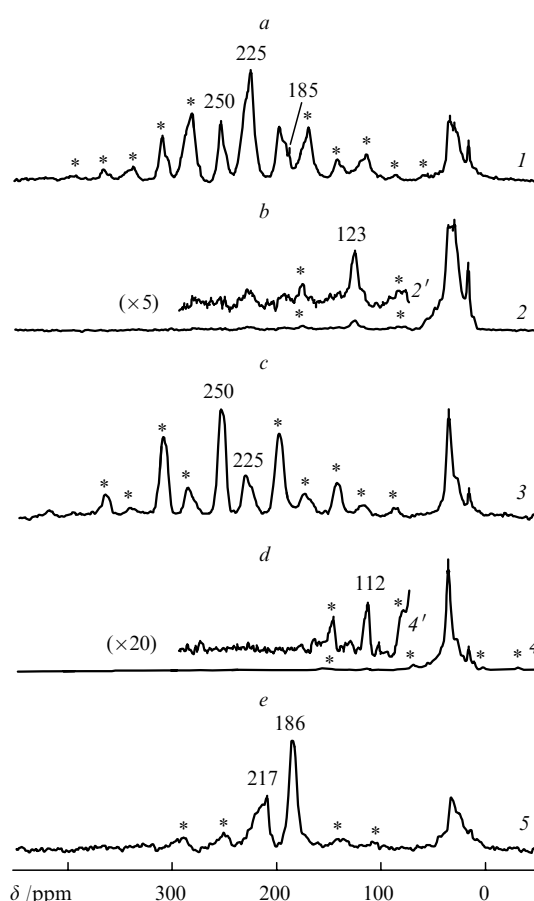
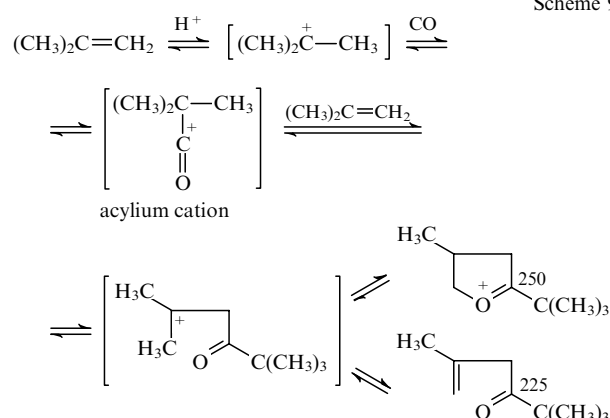
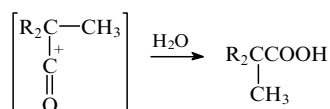


Figure 12. The ^{13}C CP/MAS NMR spectra of the products formed after adsorption of alkenes and CO on HZSM-5 zeolite in the absence of water at 296 K.

(a) $(\text{CH}_3)_2\text{C}=\text{CH}_2 + ^{13}\text{CO}$; (b) $(\text{CH}_3)_2\text{C}=\text{CH}_2 + \text{CO}$; (c) $\text{CH}_2=\text{CH}_2 + ^{13}\text{CO}$; (d) $^{13}\text{CH}_2=\text{CH}_2 + \text{CO}$; (e) $(\text{CH}_3)_2\text{C}=\text{CH}_2 + ^{13}\text{CO} + \text{H}_2\text{O}$. Curves (1–5) without amplification; (2') with a fivefold amplification; (4') with a twenty fold amplification.



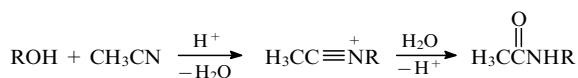
equilibrium shown in Scheme 9 was shifted towards acylium cations, which reacted with water to form carboxylic acids.



Hydroxy ketones, which are the products of the reaction of unsaturated ketones or carboxonium ions with water, were not detected in the reaction under consideration.

3. The Ritter reaction

Since the discovery of the reactions of alcohols and alkenes with nitriles (the Ritter reaction) in 1948,^{95–98} it was believed that the formation of *N*-alkylamides occurs *via* an intermediate *N*-alkylnitrilium cation $\text{CH}_3\text{C}\equiv\text{N}^+\text{R}$.



However, the experimental spectral supporting evidence for the formation of *N*-alkylnitrilium cations was long absent, which has cast doubt on the existence of a cationic intermediate.⁹⁸ It was suggested that this reaction afforded a sulfate $\text{CH}_3\text{C}(\text{OSO}_3\text{H})=\text{NR}$ (the reaction was carried out in sulfuric acid) as an intermediate.^{95,98}

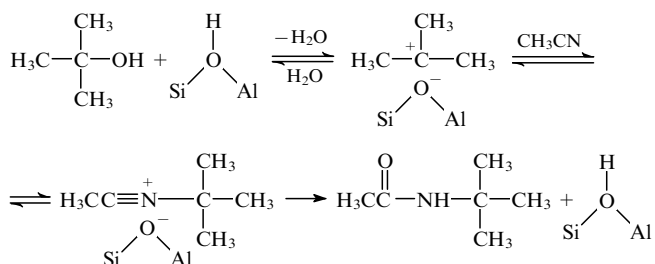
It was demonstrated^{99,100} by ^{13}C and ^{15}N MAS NMR spectroscopy that the Ritter reaction can be performed on zeolite catalysts. These studies provided the first experimental proof for the formation of *N*-alkylnitrilium cations as stable intermediates in the reactions of alkenes (or alcohols) with carbonitriles.

The ^{13}C NMR spectra of the intermediate *N*-*tert*-butylacetonitrilium cation and of the final *N*-*tert*-butylacetamide, which were formed in the reaction of Bu^tOH with CH_3CN on the

HZSM-5 zeolite, are shown in Fig. 13. It was found that *N*-alkylnitrilium cations are long-lived stable species in the absence of moisture.

Hence, the reaction mechanism proposed for the Ritter reaction⁹⁵ was additionally confirmed by the detection of stable *N*-alkylnitrilium cations on zeolites using NMR spectroscopy. The behaviour of the acetonitrile molecule in the Ritter reaction is analogous to that of the CO molecule in the Koch reaction, *i.e.*, acetonitrile acts as a trap for the alkylcarbenium ion thus stabilising the unstable alkyl cation (Scheme 10) and preventing secondary reactions involving highly reactive alkyl cations (oligomerisation and cracking).

Scheme 10



The identification of stable *N*-alkylnitrilium cations confirmed the suggestions made previously that alkylcarbenium cations can be stabilised on zeolite through their interactions with acetonitrile molecules^{101–103} and disproved the suggestion¹⁰⁴ that strong Lewis centres to which acetonitrile molecules are coordinated are formed on the zeolite.

V. Analysis of hydrocarbon products and intermediates formed from alkene oligomers

Adsorbed hydrocarbon products were analysed *in situ* by studying dehydration of Bu^tOH on HZSM-5 zeolite in a wide temperature range (296–637 K) as an example using ^{13}C CP/MAS NMR spectroscopy.³⁸ It was found that heating (448 K) of a zeolite specimen containing adsorbed alcohol resulted in the appearance of two groups of signals at *ca.* δ 10–40 and δ 150–250 in the ^{13}C NMR spectrum (Fig. 14). The signals at δ 10–40 correspond to a mixture of acyclic alkanes (Fig. 14*a*) and those at δ 100–450 correspond to stable cyclopentenyl cations (Fig. 14*d*). The simultaneous formation of alkanes and CPC from oligomers of isobutene, which is formed in the first stage of dehydration of *tert*-butyl alcohol, occurs as a result of cracking of oligomers (for example, of oct-1-ene; Scheme 11). The diene formed upon cracking of the alkene undergoes further dimerisation and cyclisation to form alkyl-substituted cyclopentadienes, which are stabilised within channels of the HZSM-5 zeolite as CPC.

Scheme 11

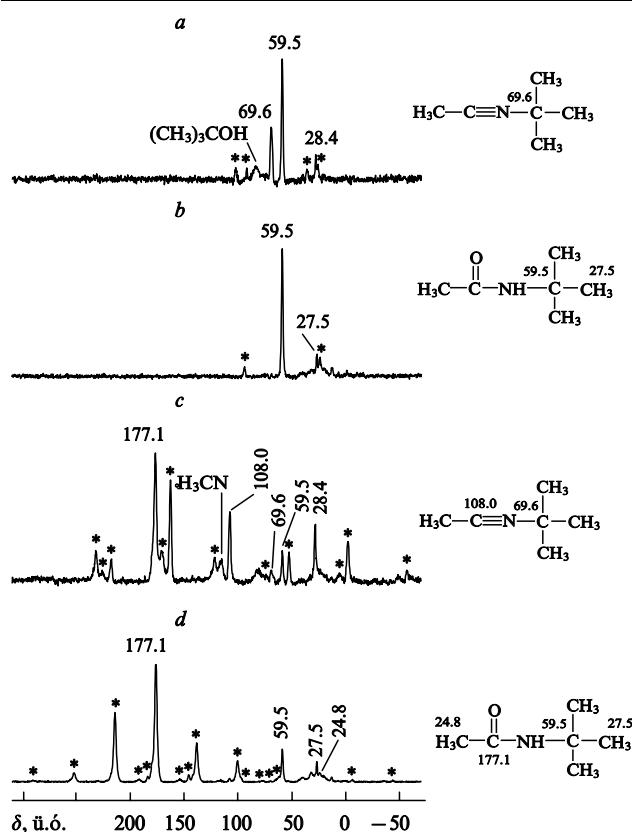
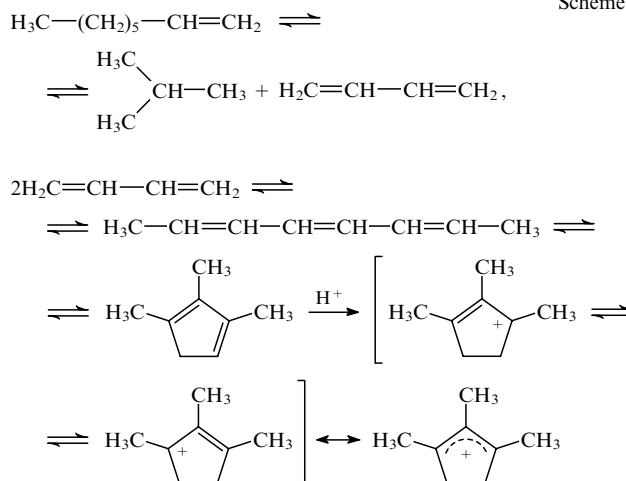


Figure 13. The ^{13}C NMR spectra of the products formed upon simultaneous adsorption of *tert*-butyl alcohol and acetonitrile on HZSM-5 zeolite at 296 K; (a) and (b) simultaneous adsorption of Bu^tOH containing the labelled tertiary carbon atom and CH_3CN ; (c) and (d) adsorption of labelled Bu^tOH (10% enrichment with the ^{13}C isotope) and CH_3CN (80% enrichment with the ^{13}C isotope); (a) and (c) the spectra were recorded within 4 h after the adsorption; (b) and (d) the spectra were recorded within 4 days after the adsorption.

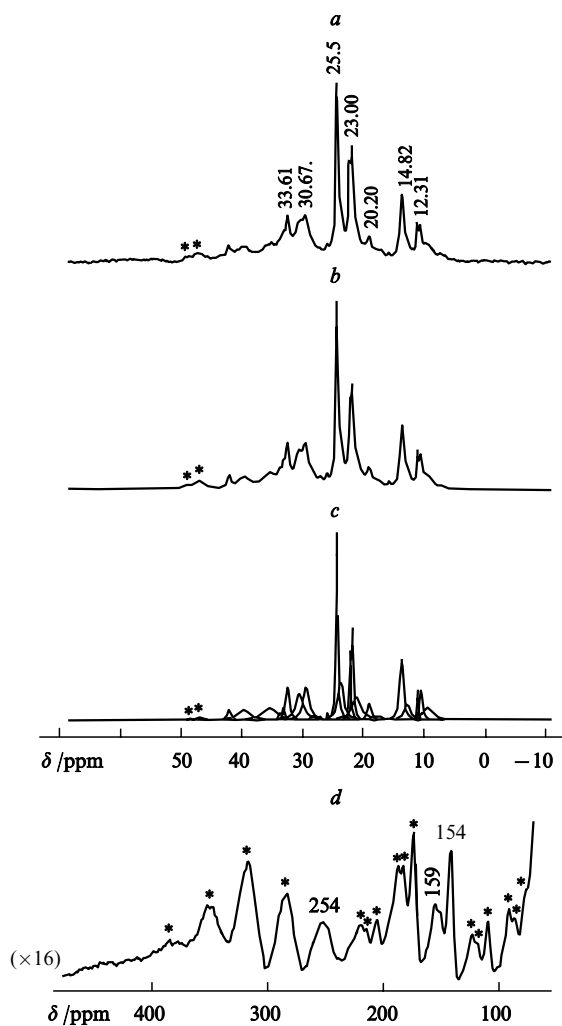


Figure 14. The ^{13}C MAS NMR spectra of the conversion products of Bu'OH on HZSM-5 zeolite at 448 K at δ 10–60 (a–c) and at δ 100–450 (d). (a) experimental data; (b) a model spectrum obtained by superposition of 25 signals of the mixture of 11 hydrocarbons; (c) the spectrum of the cyclopentenyl cation (a 16-fold amplification of the intensities of the signals).

The simultaneous formation of acyclic alkanes and CPC on the HZSM-5 zeolite indicates that the mechanisms of conversions of alkenes on zeolites and in sulfuric acid are similar.

Actually, as early as 1936, Ipatieff and Pines^{105, 106} demonstrated that a mixture of alkanes and cycloalkenes was formed when isobutene was passed through concentrated sulfuric acid at 0 °C. Cycloalkenes, as was demonstrated by Deno and co-workers in the early 1960s using NMR spectroscopy,¹⁰⁷ exist in 96% H_2SO_4 as stable alkyl-substituted CPC.

The use of 2D J -resolved ^{13}C MAS NMR spectroscopy for the analysis of the multiplicities of signals at δ 10–40 corresponding to hydrocarbon products (Fig. 15) allowed the determination of the number of hydrogen atoms attached to the carbon atoms in the CH_n groups ($n = 0–3$).

Based on the analysis of the ^{13}C chemical shifts, the relative intensities of the signals (see Fig. 14) and the multiplicities (see Fig. 15), it was found that a mixture of hydrocarbons was formed

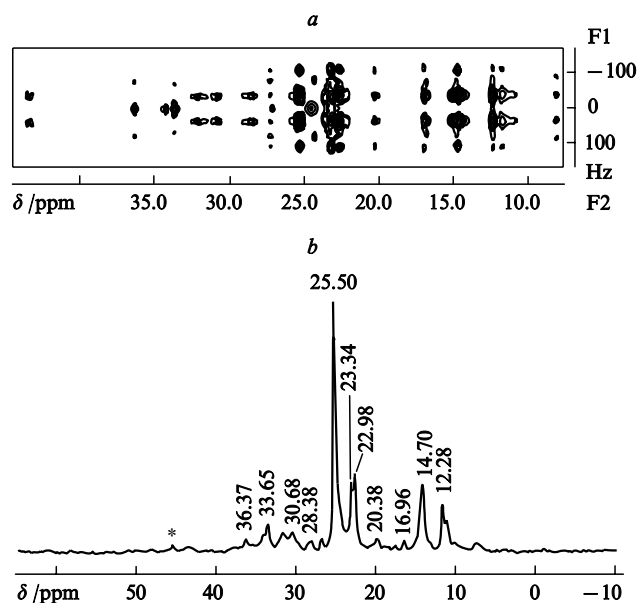


Figure 15. Contour plot of the 2D J -resolved ^{13}C MAS NMR spectrum of the products of Bu'OH conversion on HZSM-5 zeolite at 448 K (a). The 1D spin-echo ^{13}C NMR spectrum (b) corresponding to the spectrum of the standard one-pulse excitation (see Fig. 14a). The observed value of the spin-spin coupling constant $J(^{13}\text{C}–^1\text{H})$ on the F1 axis is half as large as the true value of $J(^{13}\text{C}–^1\text{H})$ due to the use of a special technique for recording the 2D NMR spectrum.^{35, 61, 63}

at 448 K and the relative amount of hydrocarbons that occurred in the adsorbed state (Table 1) was determined.

An increase in the reaction temperature to 573 K led to the redistribution of the intensities of signals for alkanes at δ 10–40 (Fig. 16). In this case, propane and butanes were prevailing

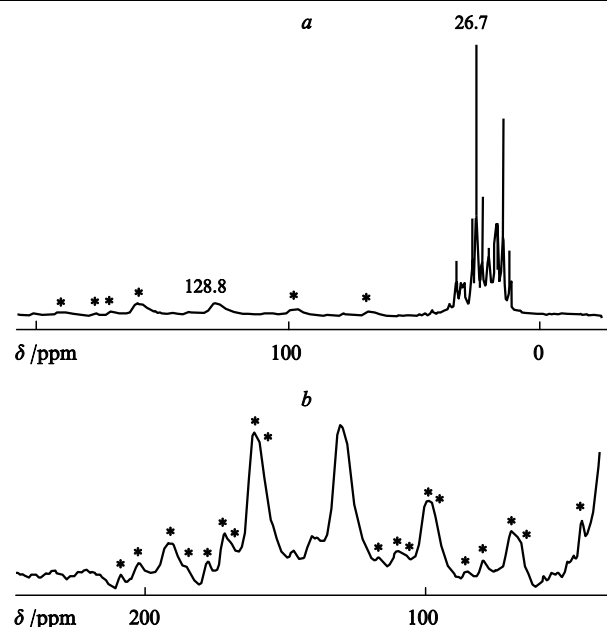


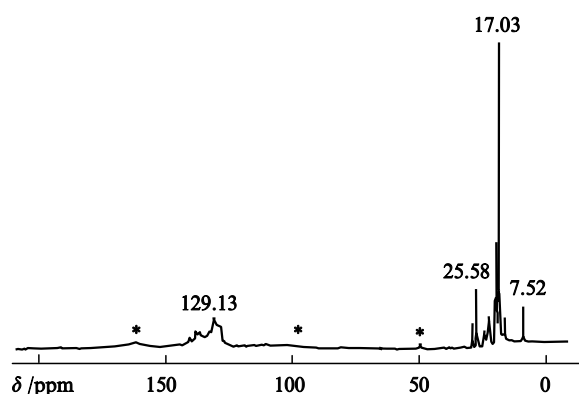
Figure 16. The ^{13}C CP/MAS NMR spectra of the conversion products of Bu'OH on HZSM-5 zeolite at 573 K [spectrum (b) is given with an eightfold amplification of the intensities of the signals at δ 40–240].

Table 1. Assignment of the signals in the ^{13}C NMR spectrum and the relative amounts of alkanes, isobutene oligomers and aromatic hydrocarbons formed upon conversion of Bu^tOH on HZSM-5 zeolite at 373–673 K.

Hydrocarbon	δ /ppm ^a					Relative amount (mol %) at different temperatures (K)			
	$^{13}\text{CH}_3-$	$-^{13}\text{CH}_2-$	$^{13}\text{CH}_3\text{CHCH}_3$ 	$-^{13}\text{CH}<$	$-^{13}\text{C}-$ 	373	448	573	673
Ethane	7.5 (5.7)					—	—	—	8.7
Propane	17.0 (15.4)	18.0 (15.9)				< 1	1.0	29.8	59.2
n-Butane	14.7 (13.1)	27.1 (24.9)				—	< 1.7	18.5	5.3
Isobutane			25.5 (24.3)	25.5 (25.0)		6	17.2	19.6	5.3
n-Pentane	14.7 (13.7)	24.5; 36.6 (22.6; 34.6)				—	17.2	3.7	—
Isopentane	11.8 (11.4)	33.6 (31.7)	23.0 (21.9)	30.7 (29.7)		5	17.9	11.7	—
Neopentane					31.8 (31.4)	—	0.7	—	—
n-Hexane	14.7 (13.7)	24.5; 33.7 (22.8; 31.9)				—	6.9	—	—
2-Methylpentane	14.7 (14.0)	20.2; 40.9 (20.5; 41.6)	23.5 (22.4)	28.4 (27.6)		7	4.1	—	—
2,3-Dimethylbutane			20.2 (19.1)	34.9 (33.9)		—	3.4	—	—
2,2-Dimethylbutane	8.5 (8.5)	36.6 (36.5)			30.7 (30.2)	—	2.1	—	—
Alkanes (C ₇ and above) + isobutene oligomers	10.6 11.8 13.9	22.3; 23.4; 30.7; 34.2; 36.6; 40.9		43.4 30.7		82	27.8	—	—
<i>o</i> - and <i>p</i> -Xylenes	20.7 (19.6; 20.9)					—	—	16.7 ^b	13.4 ^b
Toluene + <i>m</i> -xylene	22.5 (32.3)					—	—	—	8.1 ^b

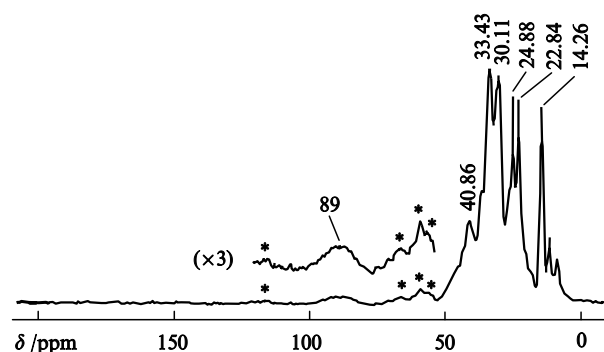
Note. The assignment was made relative to the total amount of hydrocarbons whose CH_n signals are observed at δ 10–40. ^a The chemical shifts of CH_n groups of the adsorbed hydrocarbons were taken from the spectra shown in Figs 14–17 (the accuracy of the determination was ± 0.5 ppm). The chemical shifts of the same hydrocarbons in a solution were taken from the literature⁴⁰ and are given in parentheses. ^b The values were determined only from the intensities of the CH_3 groups without considering the intensities of the carbon atoms of the benzene ring of toluene or xylenes.

alkanes (Table 1), signals for CPC at δ 150 and δ 250 disappeared and a signal at δ 128, which belongs to a mixture of monocyclic and fused aromatic hydrocarbons with the latter predominating, appeared. The changes in the ^{13}C NMR spectrum are indicative of cracking of alkanes formed at 448 K. When the temperature was further increased to 673 K, C₂–C₄ alkanes (with propane predominant) and aromatic hydrocarbons, *viz.*, toluene and xylene, were obtained as the major reaction products (Fig. 17).

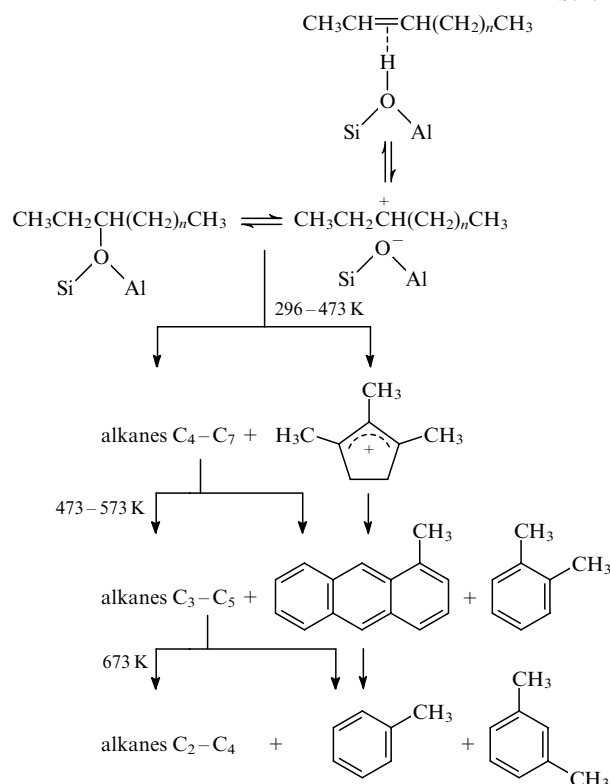
**Figure 17.** The ^{13}C MAS NMR spectrum of the conversion products of Bu^tOH on HZSM-5 zeolite at 673 K.

At 373 and 296 K, alkanes were also formed from isobutene oligomers.³⁸ However, at these temperatures, isobutene oligomers covalently bound to the oxygen atoms of the zeolite framework, *viz.*, alkoxides, were obtained as the major conversion products of Bu^tOH on HZSM-5 zeolite, which is evidenced by the presence of a broad signal for the C–O groups at δ 89 in the spectrum of oligomeric products (Fig. 18).

The sequence of conversions (according to the ^{13}C MAS NMR spectral data) of alkene oligomers adsorbed on acidic zeolite in the temperature range of 296–637 K is shown in Scheme 12.³⁸

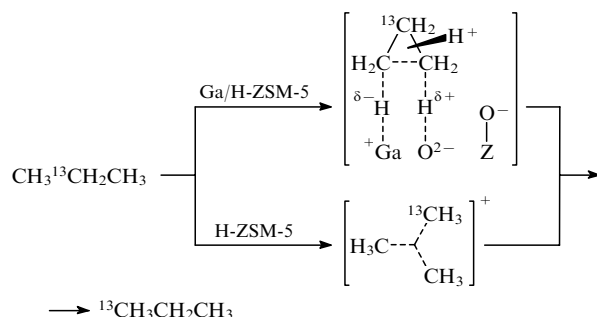
**Figure 18.** The ^{13}C CP/MAS NMR spectrum of the conversion products of Bu^tOH on HZSM-5 zeolite at 373 K.

Scheme 12



VI. Activation of alkanes at low temperatures. Isotope (H/D) exchange between alkanes and acidic OH groups of zeolite

The results of the studies^{108–112} demonstrate that NMR spectroscopy is a particularly informative and unique method for investigating conversions of lower alkanes (propane and isobutane) on acidic zeolites at low (as regards traditional conversions of alkanes on zeolites) temperature (350–550 K). It was found¹⁰⁸ that the selective ¹³C label of the CH₂ group was incorporated into the CH₃ group of propane adsorbed on Ga/HZSM-5 zeolite at 573 K. According to the results of the studies,^{50,55–57} the redistribution of the selective carbon label indicates that the isopropylum ion which is responsible for this redistribution is formed as an intermediate on the zeolite, although Derouane and co-workers¹⁰⁸ believed that the label redistribution observed in the case of Ga/HZSM-5 zeolite proceeds with the participation of a transition complex of propane with the Ga atom,¹⁰⁸ while in the case of pure HZSM-5 zeolite,¹⁰⁹ the redistribution involves the C-ethylmethanum (carbonium) ion.¹¹³



The observed redistribution of the ¹³C label in propane indicates that propane is activated and can undergo subsequent chemical conversions (cracking and alkylation¹¹⁴).

Yet another example of the use of NMR spectroscopy for studying activation of alkanes at low temperature is investigation

of hydrogen isotope exchange^{110,111} and activation of alkanes in the presence of CO and H₂O.¹¹² The H/D isotope exchange between alkanes and acidic OH groups of zeolites proceeds at rather low temperatures (20–200 °C) at which the alkane does not undergo isomerisation and cracking.^{115–121} The isotope exchange involving stages of cleavage and formation of C–H bonds in alkane and O–H bonds in zeolite is indicative of activation of alkane. Hence, it is not surprising that a large number of experimental^{115–124} and theoretical^{121–124} studies were devoted to the elucidation of the mechanism of the hydrogen exchange. Recently, ¹H MAS NMR spectroscopy was used for investigating the kinetics and mechanism of the H/D exchange of alkanes.^{110,111}

1. Propane

In studies of the kinetics of the H/D isotope exchange between deuterated propane and acidic groups of HZSM-5 zeolite (150–250 °C), the simultaneous incorporation of protium from the acidic HO groups into the deuterated methyl and methylene groups of propane was observed. It was found that the intensities of the signals for the CH₃ and CH₂ groups of propane at δ 1.0 and δ 1.45, respectively, in the ¹H MAS NMR spectrum increased with time (Fig. 19). Analysis of the kinetics of the incorporation of protium into the methyl and methylene groups of propane

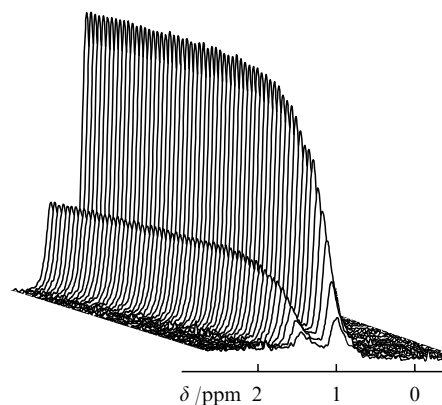


Figure 19. Changes in the intensities of the signals for the methyl (δ 1.0) and methylene (δ 1.45) groups with time at 519 K in the ¹H MAS NMR spectrum of propane C₃D₈ adsorbed on HZSM-5 zeolite. The first spectrum (at the bottom) and the last spectrum were recorded within 3 min and 5 h after the adsorption. The intervals at which the spectra were recorded were 5 min.

revealed a noticeable difference in the rates of hydrogen exchange for these groups (Fig. 20). The corresponding rates, which were

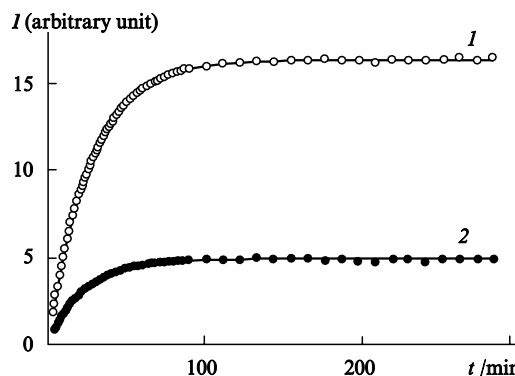


Figure 20. Kinetic curve of the transfer of the proton from acidic OH groups of zeolite to the methyl (curve 1) and methylene (curve 2) groups of propane C₃D₈ at 519 K.

calculated by the kinetic equation $I_t = I_\infty[1 - \exp(-Rt)]$ [I_t and I_∞ are the integral intensities of the signals for the CH_n groups ($n = 2$ or 3) in the ^1H MAS NMR spectrum at times t and $t = \infty$ (equilibrium)] are $R(\text{CH}_3) = 0.03816 \text{ min}^{-1}$ and $R(\text{CH}_2) = 0.0436 \text{ min}^{-1}$. The time $t = 0$ corresponds to the beginning of the experiment when the temperature was increased from room temperature to 519 K. The activation energies of hydrogen exchange for the methyl and methylene groups were determined ($E_{\text{CH}_3} = 118 \pm 2 \text{ kJ mol}^{-1}$ and $E_{\text{CH}_2} = 117 \pm 4 \text{ kJ mol}^{-1}$) from the temperature dependence of the reaction rate of hydrogen exchange (from the Arrhenius parameters; Fig. 21).¹¹⁰

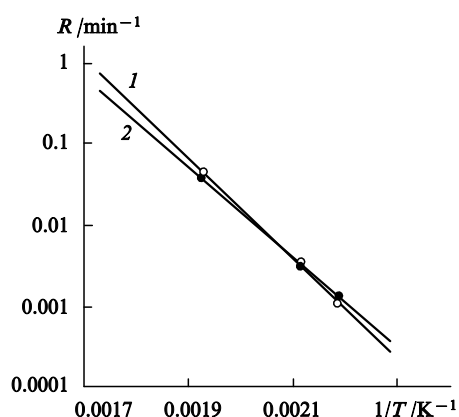
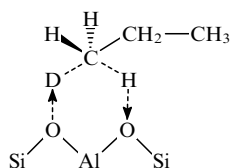


Figure 21. Dependence of the rate of the H/D exchange for the methyl (1) and methylene (2) groups of propane on HZSM-5 zeolite in terms of the Arrhenius parameters.

Taking into account the absence of selective or predominant enrichment of the methyl groups with protium, the fact that the H/D exchange is not inhibited by carbon monoxide and the fact that the experimental activation energies are close to those theoretically calculated for methane and ethane,^{122–124} it was concluded that H/D exchange with the acidic OH protons occurs independently for each group (without the formation of a single carbenium ion intermediate or a transition state) *via* an intermediate pentavalent transition state in which the hydrogen atoms that are exchanged lie halfway between the carbon atom of the methyl (methylene) group and the oxygen atoms of the zeolite.



The data obtained do not also contradict the formation of the carbonium ion as a two-electron three-centre intermediate state involved in the hydrogen exchange in the propane–superacid $\text{DF} - \text{SbF}_5$ system.¹²⁵ The difference in the rate of exchange for the methyl and methylene groups was attributed to the difference in the σ -basicity of the C–H bonds of the primary (CH_3) and secondary (CH_2) groups of the alkane.¹²⁶

2. Isobutane

In the case of the hydrogen exchange in isobutane, the situation is different (Fig. 22). In this case, only methyl groups are subjected to H/D exchange,^{118–120,127} which is manifested in an increase in the intensity of the signal at $\delta 1.0$ (Fig. 22*b*).¹¹¹ The expected increase in the intensity of the signal for the CH group at $\delta 1.85$ (Fig. 22*c*) was not observed. Measurements of the rates of hydrogen exchange in the temperature range of 80–150 °C allowed the determination of the activation energy of the exchange ($50 \pm 2 \text{ kJ mol}^{-1}$) which is half as large as that of

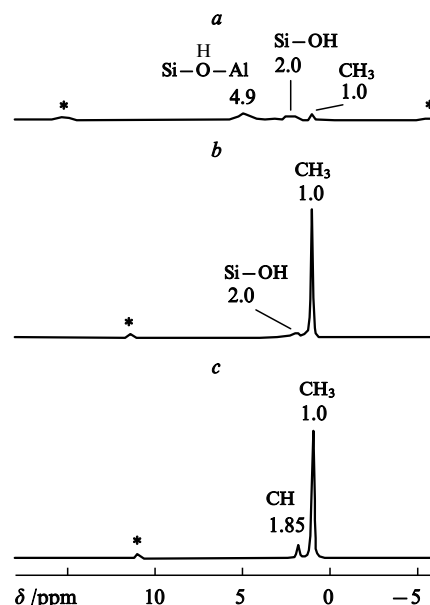
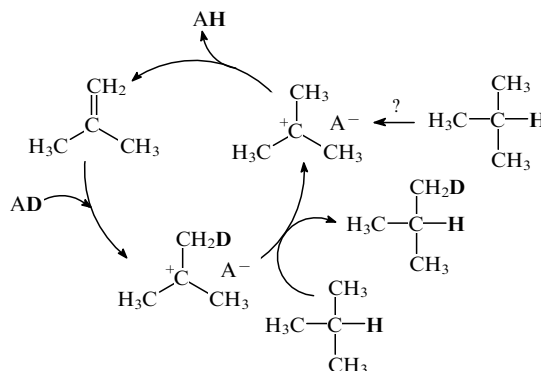


Figure 22. The ^{13}C MAS NMR spectra of isobutane adsorbed on HZSM-5 zeolite at 295 K.

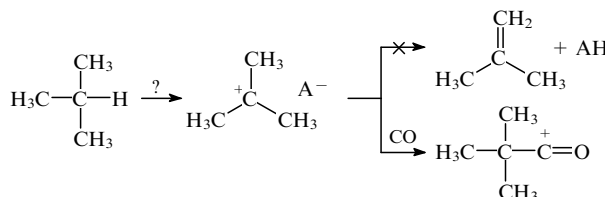
(a) the spectrum of isobutane- d_{10} before the temperature was increased to 425 K or of isobutane- d_{10} in the presence of CO after storage of the sample at 475 K for 10 h; (b) the spectrum of isobutane- d_{10} after storage of the sample at 425 K for 70 min; (c) the spectrum of nondeuterated isobutane.

propane. It was also found that carbon monoxide completely inhibits the regiospecific hydrogen exchange (Fig. 22*a*). The mechanism of the regiospecific hydrogen exchange for isobutane was explained within the framework of the catalytic cycle^{118,120} shown in Scheme 13.

Scheme 13



The regiospecificity of the H/D exchange is achieved due to formation of TBCI and isobutene as intermediates, which exist in equilibrium with each other. Carbon monoxide, which is present in the system, reacts with TBCI to give the oxocarbenium ion. The latter cannot undergo reversible deprotonation to form the alkene, which results in complete inhibition of the hydrogen exchange.



VII. Activation of alkanes at low temperatures. Carbonylation

In addition to the hydrogen exchange in alkanes at 20–200 °C, NMR spectral studies allowed observation of carbonylation at 100–200 °C,¹¹² which is also indicative of the possibility of activation of alkanes on acidic zeolites at low temperatures.

Based on the assumption that alkanes are formed from carbenium ions and alkenes^{118,119,127} as intermediates upon hydrogen exchange at low temperature and taking into account that alkenes (carbenium ions) can react with carbon monoxide and water on zeolites⁶¹ to form carboxylic acids, it was suggested that carboxylic acids can be formed from alkanes at low temperature¹¹² at which hydrogen exchange is observed but alkanes do not undergo cracking.

1. Propane

It was found that heating of a zeolite specimen containing adsorbed propane, CO and water at 373–473 K led to changes in the NMR spectra compared to those of the initial reagents. In the case of simultaneous adsorption of ¹³C-labelled propane, carbon monoxide and water, the ¹³C CP/MAS NMR spectrum has a signal at δ 191 for the carboxy group of isobutyric acid formed along with signals at δ 17.0 and δ 18.2 belonging to the initial propane (Fig. 23a). The ¹H MAS NMR spectrum of the same specimen has a signal for methane at δ 0.25, signals for the initial propane at δ 1.0 and δ 1.45 and a signal for water adsorbed on acidic OH groups of zeolite at δ 6.2 (Fig. 23c). In the case of adsorption of labelled propane-2-¹³C, the ¹³C MAS NMR spectrum has a signal for ethane-1-¹³C at δ 7.3, a signal for the carbon atom of the ¹³CH group of isobutyric acid at δ 36.4 and signals for unconsumed propane-2-¹³C and CO at δ 18.2 and δ 185, respectively (Fig. 23b). These changes agree well with

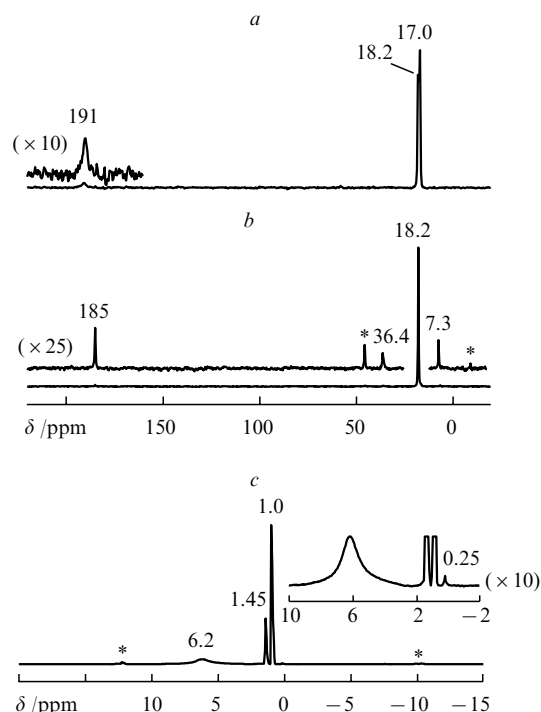
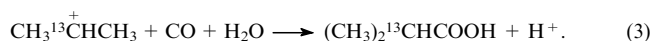
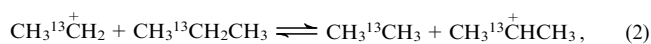
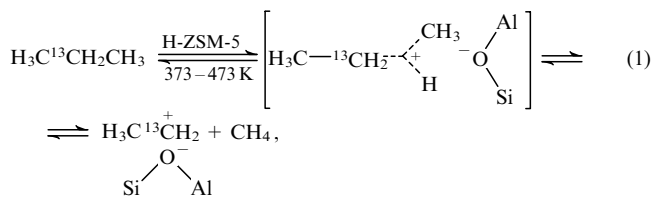


Figure 23. NMR spectra of propane, carbon monoxide and water adsorbed on HZSM-5 zeolite at 473 K. The samples were heated at 473 K for 3 h.

(a) the ¹³C CP/MAS NMR spectrum, simultaneous adsorption of propane, ¹³CO and water; (b) the ¹³C MAS NMR spectrum, simultaneous adsorption of propane-2-¹³C, CO and water; (c) the ¹³C MAS NMR spectrum, simultaneous adsorption of propane, ¹³CO and water.

activation of propane-2-¹³C on zeolite and protolytic cleavage of the C–C bond of propane to form ¹³CH₄, ¹³CH₃CH₃ and (CH₃)₂¹³CHCOOH according to Scheme 14. Actually, in the course of the reaction of ¹³C-labelled propane with CO and H₂O, the selectively ¹³C-labelled CH₂ group of propane was converted into the ¹³CH group of isobutyric acid (δ 36.4). Methane, which is observed only in the ¹H MAS NMR spectrum, is formed in the stage (1) due to the protolytic attack of the acidic group of zeolite on the C–C bond of propane. The ethyl cation formed in the same stage reacts with another molecule of labelled propane to give ethane and the isopropyl cation [stage (2)]. The latter reacts with CO and water to form isobutyric acid [stage (3)].

Scheme 14



2. Isobutane

The reaction of isobutane with carbon monoxide and water on zeolite proceeds analogously.¹¹² After heating of a zeolite specimen containing adsorbed isobutane, ¹³CO and water at 423 K for 3 h, the ¹³C CP/MAS NMR spectrum has four signals, viz., signals for TMAA at δ 193 and δ 27.7, a signal for the initial isobutane at δ 25.5 and a signal for the intermediate Si–C(OOH)–Al at δ 172 (Fig. 24). The ¹H MAS NMR spectrum of the same specimen has signals for the initial isobutane at δ 1.0 and δ 1.8, a signal for H₂O/Si–OH–Al at δ 6.6 and signals for the reaction products, viz., H₂ and TMAA, at δ 4.1 and δ 1.45, respectively (Scheme 15).

No conversion products were detected in a special NMR spectral study of conversions of propane and isobutane on HZSM-5 zeolite in the absence of CO and water in the same temperature range. However, cracking products of these alkanes,

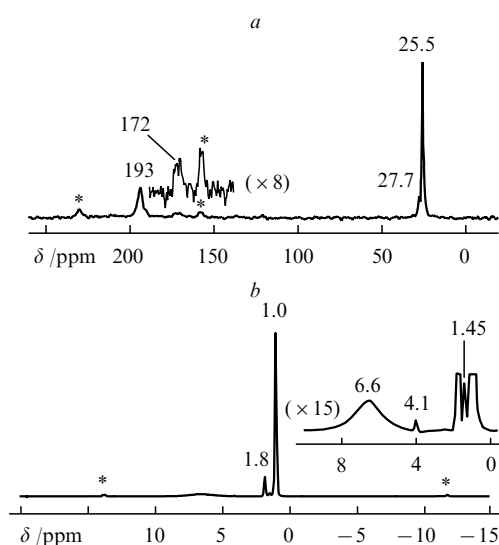
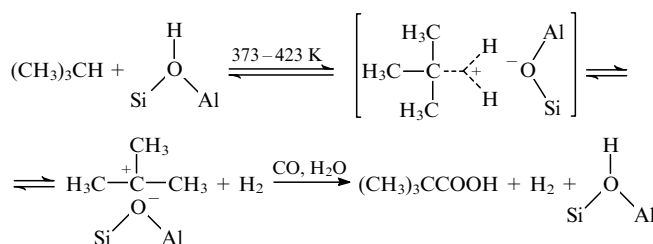


Figure 24. NMR spectra of conversion products of isobutane, ¹³CO and water adsorbed on HZSM-5 zeolite.

(a) the ¹³C CP/MAS NMR spectrum; (b) the ¹³C MAS NMR spectrum.

Scheme 15



such as hydrogen (in the case of isobutane), ethane and methane (in the case of propane), were detected by gas-chromatographic analysis. The amounts of these compounds were so small that they could not be detected by NMR spectroscopy. It was concluded that in the presence of H_2O and CO (a trap of carbenium ions), the cracking equilibrium of alkanes was shifted to the corresponding acids formed from CO and carbenium ions. In this case, the reaction product, *viz.*, a carboxylic acid, was accumulated in amounts detectable by NMR spectroscopy. The low degrees of conversion of propane and isobutane into the corresponding acids at 373–423 K (1%–2%) are attributable to the presence of insignificant amounts of superacidic centres in the zeolite (no more than 1%–2% of the total amount of acidic protonic centres) on which cracking occurs at these low temperatures.

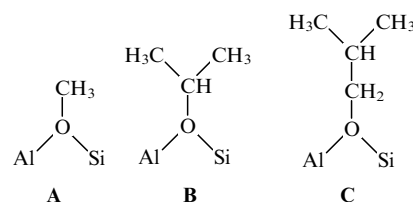
VIII. The nature of intermediates in conversions of alkanes, alkenes and alcohols

The nature of intermediates in the reactions of hydrocarbons and alcohols on heterogeneous catalysts of the acidic nature has long been the subject of discussion. According to the classical concepts of conversions of organic molecules in the presence of acids, alkyl-type carbenium ions represent reactive intermediates in these reactions. However, the absence of direct experimental evidence for the formation of alkyl-type carbenium ions on acidic centres of zeolites has cast doubt on the possibility of their formation as stable species.

The first results of quantum-chemical calculations^{128, 129} demonstrated that carbenium ions are not located in a local minimum on the potential energy surface and these ions can be formed on zeolites only as an unstable transition state. More recent studies^{130–132} demonstrated that alkoxides are key intermediates, while carbenium ions are formed upon thermal excitation of alkoxides where the C–O bond is elongated. Theoretical calculations¹³³ also indicated that acid catalysis on zeolites occurs with the involvement of alkoxide intermediates and without the participation of carbenium ions. Some NMR spectral data (for example, those obtained in studies of oligomerisation products of propene¹³⁴) were interpreted without regard for the participation of carbenium ions in the reaction.

Recently, considerable progress has been achieved in the identification of various intermediates (carbenium ions and alkoxides) by NMR spectroscopy and in the understanding of the role of these intermediates in conversions on solid acids. The reliable evidence was obtained for the formation of alkoxide intermediates in the case of lower hydrocarbons (MeO ,^{42–44} Pr^iO ¹³⁴ and Bu^iO ⁴⁷) and oligomeric alkoxides⁵⁴ and their role as intermediates was revealed. The methoxide (A) and isobutoxide intermediates (C) are stable species at 293–373 K, while the isopropoxide intermediate (B) oligomerises even at 200 K.¹³⁴

Apparently, this fact indicates that isopropoxide rather than the isopropylum ion is a reactive intermediate in the oligomerisation of propene.¹³⁴ However, these conclusions were drawn without considering the characteristic time of the ^{13}C -carbon redistribution in carbenium ions, which should be approximately



39 days at 230 K.¹³⁴ Taking into account that oligomerisation proceeds substantially faster (is completed in several hours), the formation of the carbenium ion, which rapidly undergoes oligomerisation, from isopropoxide must not be ruled out.

The redistribution of the selective ^{13}C label in oct-1-ene at room temperature, which is indicative of the formation of carbenium ions, as well as the alkoxide nature of adsorbed alkene oligomers⁵⁴ allow conclusions to be drawn about the existence of the equilibrium between the alkoxide and carbenium-ion intermediates, the latter being formed in small amounts undetectable by NMR spectroscopy.

The formation of carbenium ions on zeolites is additionally confirmed by the fact that chemical reactions typical of carbenium ions proceed under mild conditions (room temperature). It appeared that unstable carbenium ions undetectable by NMR spectroscopy can be stabilised by introducing these ions into the reaction with CO and CH_3CN to obtain cyclic carboxonium⁹³ and alkynitrilium^{99, 100} cations, respectively, which can be detected by NMR spectroscopy. The hydrogen H/D exchange between D_2O and the methyl groups of Bu^iOH ^{35, 81} and the transfer of the ^{13}C label from the tertiary carbon atom to the methyl group of Bu^iOH ³⁸ are also indicative of the formation of the carbenium ion upon dehydration of Bu^iOH on zeolite. Recent quantum-chemical calculations⁸⁵ of the stability of alkylcarbenium ions adsorbed on zeolite taking into account the stabilising effect of the zeolite lattice (it was believed that 16 oxygen atoms rather than two atoms, as was assumed in all the previous studies,^{128–133} are involved in stabilisation of the intermediate formed) revealed a local minimum for carbenium ions. It was found that the stability of alkyl carbenium ions is 10–20 kJ mol^{-1} lower than that of the corresponding π -complexes of alkenes. Taking into account the experimental data obtained by NMR spectroscopy, it may be concluded that alkylcarbenium ions exist in zeolites as real structures (although they are very unstable and highly reactive) along with more stable alkoxide intermediates.

Alkyl-substituted cyclopentenyl cations belong to another type of carbocationic intermediates that exist in zeolites.⁴⁵ Their formation from alkene oligomers on zeolites simultaneously with alkanes indicates that conversions of alkenes on zeolites and in a solution of concentrated sulfuric acid occur analogously.³⁸ These cations are intermediates, which form aromatic hydrocarbons at higher temperature.

IX. Conclusion

Recently, considerable progress has been made in the understanding of the mechanisms of hydrocarbon conversions on the surface of zeolites of acidic nature. This progress was achieved primarily due to the successful use of high-resolution solid-state NMR spectroscopy for the *in situ* analysis of intermediates and the final products of hydrocarbon conversions. In some cases where the expected intermediate was not observed due to its instability or low concentration (alkyl-type carbenium ions), this was identified from the characteristic reactions, *viz.*, from the redistribution of selective carbon labels or from the reactions with cation traps (CO or CH_3CN). Based on the NMR spectral data, possible pathways of conversions of alkenes and alcohols on zeolites at low temperature were suggested. Carbonylation of alkenes and alcohols (the Koch reaction), Friedel–Crafts-like acylation of alkenes where an acylating agent is formed directly from the alkene and CO on

zeolite and the reactions of alkenes with acetonitrile to form *N*-alkylamides (the Ritter reaction) were studied. Interestingly, the *N*-alkylnitrilium cation as a stable intermediate in the Ritter reaction was first detected and characterised by NMR spectroscopy on zeolite rather than in solution. Hence, presently not only does solid-state NMR spectroscopy confirm or refute the parallels between the mechanisms of conversions of hydrocarbons in solutions and on the surface of solid acidic catalysts, but it also enables one to obtain original data on the mechanisms of chemical conversions. The Friedel–Crafts-like reaction of alkenes with CO adsorbed on zeolite to form unsaturated ketones and carbonylation of alkanes (propane and isobutane) to form carboxylic acids are examples.

The use of NMR spectroscopy for the analysis of products formed *in situ* on zeolites provides a deeper insight into the effect of the internal structure of zeolite pores on the composition of the products, which was clearly exemplified by conversions of methanol on HZSM-5 zeolite. NMR spectroscopy is more informative than IR and UV spectroscopy in the analysis of the structures of adsorbed hydrocarbons. As a result, NMR spectral studies made it possible to identify stable alkyl-substituted cyclopentenyl cations, which were formed in zeolites as intermediates in the conversions of alkenes into aromatic compounds, and to establish their structures. *In situ* studies of the kinetics of the hydrogen exchange of alkanes by NMR spectroscopy allowed conclusions about the nature of intermediates of this exchange to be drawn.

It would be expected that the experimental data on hydrocarbon conversions obtained by NMR spectroscopy and conclusions about the mechanisms of these conversions will be rationally used in the development of new industrially important processes of hydrocarbon conversions, such as alkylation or isomerisation of alkenes and alkanes, and the data on the nature of intermediates will provide the basis for quantum-chemical calculations.

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

^c — *Dokl. Chem. Technol., Dokl. Chem. (Engl. Transl.)*

***N*-Functionally substituted imines of polychlorinated (brominated) aldehydes and ketones**

G G Levkovskaya, T I Drozdova, I B Rozentsveig, A N Mirskova

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Abstract. Published data on the synthesis, structure and chemical transformations of *N*-acyl-, *N*-alkoxy(aryloxy)carbonyl-, *N*-carbamoyl-, *N*-sulfonyl- and *N*-phosphoryl-imines of chlorine-(and bromine)-containing ketones and aldehydes are surveyed and described systematically. The influence of polyhaloalkyl and functional substituents at the azomethine bond on their properties is considered. The bibliography includes 198 references.

I. Introduction

The chemistry of imines presents interest for both theoretical and applied organic chemistry.^{1–21} On the one hand, azomethines are convenient models for the investigation of stereochemistry of organic compounds, tautomerism and isomerism phenomena, molecular rearrangements and mechanisms of radical, electrophilic and nucleophilic addition at the double bond and cycloaddition.^{1–5} On the other hand, imines are used as the starting compounds for organic synthesis,⁶ for the synthesis of biologically active^{7–10} and natural products,⁵ monomers¹ and various nitrogenous heterocycles.^{1–5,11} In addition, compounds containing an azomethine group are known to play an important role in living organisms.^{1,5}

N-Functionally substituted polyhalogenated aldimines and ketimines present special interest due to their enhanced reactivity imparted by electron-withdrawing polyhaloalkyl substituents and by acyl, alkoxy(or aryloxy)carbonyl-, -carbamoyl, sulfonyl or phosphoryl group at the N atom.

The chemistry of polyhalogenated *N*-acyl aldimines and ketimines started to develop in the last two or three decades, because it was not until the early 1960s that preparative methods for their synthesis appeared. Quite a large number of review papers devoted to these interesting compounds have been published. The synthesis and properties of *N*-fluoro-, *N*-acyl-, *N*-sulfonyl- and *N*-phosphoryl-imines of polyfluorinated ketones

and aldehydes have been considered in the literature fairly comprehensively;^{12–17} therefore, they will not be discussed here.

However, known reviews^{18–25} dealing with the corresponding polychloro(bromo)-containing derivatives do not cover adequately the chemistry of *N*-acyl-, *N*-carboxy-, *N*-carbamoyl-, *N*-sulfonyl- and *N*-phosphoryl-imines of polyhalogenated aldehydes and ketones.

Therefore, it appears pertinent to generalise and describe systematically the data concerning the methods of synthesis and chemical transformations of *N*-acyl-, *N*-alkoxy(aryloxy)carbonyl-, *N*-carbamoyl-, *N*-sulfonyl- and *N*-phosphoryl-imines of polychlorinated (brominated) aldehydes and ketones $R^1N=CXCHaI_nR^2$, where $R^1 = \text{Alk}(\text{Ar})\text{CO}$, $\text{Alk}(\text{Ar})\text{OCO}$, Alk_2NCO , NH_2CO , $\text{Alk}(\text{Ar})\text{NHCO}$, $\text{Alk}(\text{Ar})\text{SO}_2$, Alk_2NSO_2 , $(\text{AlkO})_2\text{P}(\text{O})$, $(\text{AlkO})_2\text{P}(\text{S})$, $\text{Ar}_2\text{P}(\text{O})$, $(\text{ArO})_2\text{P}(\text{O})$; $X = \text{H}$, Ar , COOR^3 , CCl_3 , $\text{OAlk}(\text{Ar})$, CN , NR^4R^5 , Cl , *etc.*; $n = 2, 3$; $\text{Hal} = \text{Cl}$, Br ; $R^2 = \text{Alk}$, ArAlk , *etc.*

II. Synthesis of polychlorinated (brominated) aldimines and ketimines *N*-substituted by carboxylic, carbamic, sulfonic and phosphoric acid residues

The known methods for the synthesis of acid *N*-polychloro(bromo)alkylideneamides can be divided into several groups differing in the approach to the formation of the azomethine bond.

1. Preparation of *N*-acylated ketimines and aldimines from carboxamides and polyhalogenated aldehydes and ketones.

2. Syntheses based on amide derivatives — *N*-sulfinylsulfonamides and *N*-sulfonyl isocyanates — and carbonyl compounds.

3. Successive transformation of α,β -polyhaloalkyl isocyanates into amides and azomethines upon reactions with nucleophiles.

4. Creation of an azomethine bond by a free radical reaction of *N,N*-dihaloamides with 1,2-polyhaloethenes and alkynes.

5. Photochemical halogenation of *N*-alkyl(or aryl)amides.

Other methods, which have not found wide application, are also known; they are considered at the end of this Section.

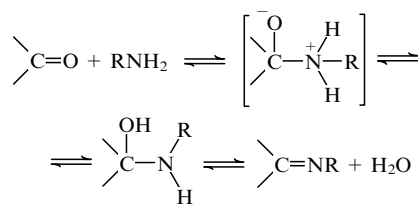
1. Preparation of polychlorinated (or brominated) aldimines and ketimines based on amides and carbonyl compounds

Condensation of carbonyl compounds with amines is a classical method used to introduce an azomethine bond into a molecule. This is a two-stage process involving the intermediate formation of an amino alcohol.

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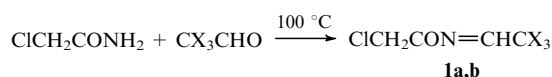
However, in the general case, this reaction cannot be used to prepare imines of polyhalogenated compounds. The presence of electron-withdrawing groups in the molecule enhances the stability of the intermediate amino alcohol. Therefore, the rate of the synthesis of polyhalogenated aldimines and ketimines is limited by the second stage, that is, dehydration of hemiaminals. Thus it is known that condensation of carboxamides with aliphatic and aromatic aldehydes gives *N,N*-alkylidene- or *N,N*-arylidene-bis-amides,¹⁸ whereas polyhalogenated aldehydes and ketones react with amines and amides to give stable 1-hydroxyalkylamines.^{18,26} In the case of aliphatic and aromatic amines and chlorinated aldehydes and ketones, the problem of transformation of amino alcohols into imines was solved by using TiCl_4 .²⁷

For the synthesis of acyl-, alkoxy(or aryloxy)carbonyl- and -carbamoyl-, sulfonyl- and phosphoryl-imines of polyhalocarbonyl compounds, methods based both on dehydration and on other chemical transformations of 1-hydroxypolyhaloalkylamides have been devised.

a. Dehydration of *N*-(1-hydroxypolyhaloalkyl)amides

In the earliest studies^{28–30} devoted to *N*-trichloroethylidene-amides, it was found that treatment of *N*-(1-hydroxy-2,2,2-trichloroethyl)acetamide, *N*-(1-hydroxy-2,2,2-trichloroethyl)chloro-(bromo)benzamides and *N*-(1-methoxy-2,2,2-trichloroethyl)bromobenzamides with dehydrating agents gives bis(1-acylamino-2,2,2-trichloroethyl) ethers instead of the corresponding chloral imines.

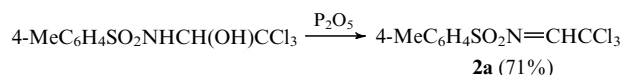
An example of fairly easy thermal dehydration giving rise to the target imines has been reported. Chloroacetamide reacts with chloral and bromal³¹ yielding *N*-(2,2,2-trichloroethylidene)- and *N*-(2,2,2-tribromoethylidene)chloroacetamides **1a,b**.



X = Cl (**a**), Br (**b**).

Subsequently, synthetic expedients have been developed which permit dehydration of some chloral hemiaminals.

N-(2,2,2-Trichloroethylidene)-4-toluenesulfonamide **2a** has been prepared by dehydration of the corresponding *N*-(1-hydroxyalkyl) derivative induced by P_2O_5 at 200 °C in benzene or xylene.³²



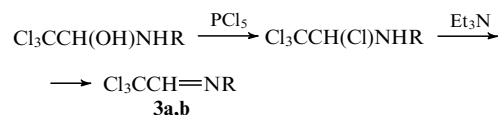
In our opinion, the sulfonamide derivative is esterified in this reaction by phosphoric anhydride and then phosphoric acid splits off. However, phosphorylimines cannot be prepared by dehydration of *N*-(1-hydroxy-2,2,2-trichloroethyl) dialkyl phosphoramidates.³³ An attempt to dehydrate *N*-(1-hydroxy-2,2-dichloroalkyl)amides was also unsuccessful.³⁴

Apparently, the limited scope of the method for the synthesis of imines based on dehydration of hemiaminals of polyhalogenated aldehydes and ketones is due to the fact that these compounds are unstable in the presence of dehydrating agents and decompose to give the initial components or condensation products (esters) under the reaction conditions (see, for example, Refs 28–30).

b. Dehydrochlorination of chloro(bromo)polyhaloalkylamides

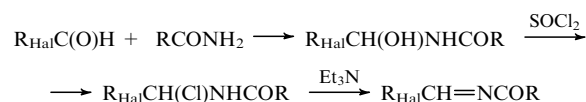
Dehydrochlorination of *N*-(1-haloalkyl)amides, which are prepared by chlorination of the corresponding hydroxy derivatives by SOCl_2 or PCl_5 , is a fairly general method for the synthesis of acyl-, alkoxy- and -carbamoylimines of polyhalogenated carbonyl compounds as well as their sulfonyl and phosphoryl analogues.

This synthetic route was first used³⁵ to prepare *N*-(2,2,2-trichloroethylidene)benzamide **3a** and *N*-(2,2,2-trichloroethylidene)-*N*-benzyloxycarbonylamine **3b**.



R = PhCO (**a**), PhCH₂OCO (**b**).

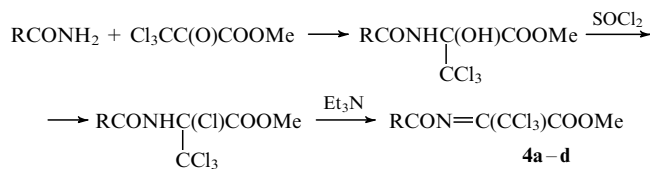
The same method, except that thionyl chloride has been used as the chlorinating agent, has been employed to prepare trichloromethyl- and tribromomethyl-ethylidene-*N*-(alkoxycarbonyl)amines,³⁶ including various acyl- and alkoxy(aryloxy)-carbonylimines of chloral^{37–41} and bromal,⁴² acylimines and alkoxycarbonylimines of bromodichloroacetaldehyde,^{43,44} and *N*-acetyl(benzoyl)imines and *N*-methoxycarbonylimines of 1,1,2-trichloro-2-phenylpropionaldehyde and 1,1,2-trichlorobutyraldehyde,⁴⁵ their yields ranging from 52% to 92%. Several *N*-(2,2,3-trichloropropylidene)amides and *N*-(2,2,3-trichloropropylidene)ethoxycarbonylamine have been prepared in the same way (yields 52%–72%).⁴⁶



$\text{R}_{\text{Hal}} = \text{CCl}_3, \text{CBr}_3, \text{CBrCl}_2, \text{PhCHClCCl}_2, \text{CH}_2\text{ClCCl}_2, \text{MeCHClCCl}_2, \text{AlkCCl}_2$; R = Alk, Ar, PhCH₂, OEt, OMe.

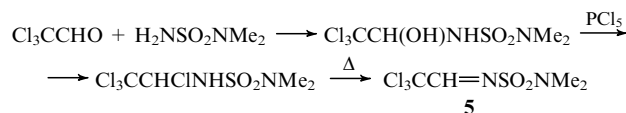
Synthesis of *N*-(2,2-dichloroalkylidene)acetamides by condensation of dichlorinated aldehydes with acetamide followed by chlorination and then dehydrochlorination of the resulting compounds has been reported.³⁴ In the same study,³⁴ dichloroethylidenebenzamide was prepared in a low yield and an attempt to prepare 2,2-dibromoalldimines failed, probably due to the instability of the intermediate hemiaminals formed from 2,2-dihaloaldehydes and amides.

The condensation of carboxamides with methyl trichloropyruvate gave the corresponding *N*-acylhemiaminals, which were then converted into methyl 2-acylimino- and 2-alkoxycarbonylimino-3,3,3-trichloropropionates **4a–d**.⁴⁷



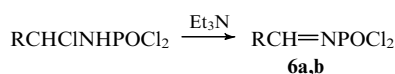
R = Me (**a**), Et (**b**), OMe (**c**), OEt (**d**).

N-(2,2,2-Trichloroethylidene)-*N*',*N*'-dimethylaminosulfonamide has been synthesised by a traditional multistage procedure based on the condensation of chloral with *N,N*-dimethylaminosulfonamide followed by chlorination by PCl_5 . Dehydrochlorination of the intermediate compound was carried out on heating.⁴⁸



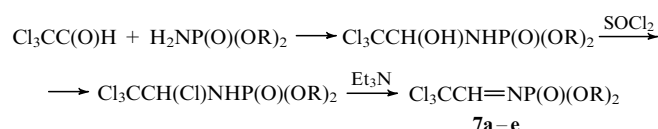
Preparation of the phosphoryl analogues of *N*-acylimines of halogenated aldehydes was first reported in 1965.⁴⁹ It was shown that the products of acidolysis of trichlorophosphazo com-

pounds — *N*-polychloroalkylaminophosphoryl dichlorides containing chlorine atoms at the α -position with respect to nitrogen — readily abstract an HCl molecule on treatment with triethylamine to give *N*-(2-chloro-2-methylpropylideneamino)- and *N*-(2,2-dichloro-3,3-dimethylbutylideneamino)phosphoryl dichlorides.⁴⁹



R = Me₂CCl (**a**), Bu^tCCl₂ (**b**).

Several dialkyl *N*-(2,2,2-trichloroethylidene) phosphoramidates have been prepared in 50%–76% yields from chloral and dialkyl phosphoramidates using chlorination and dehydrochlorination of intermediate products.^{33,50}



R = Me (**a**), Et (**b**), Prⁿ (**c**), Prⁱ (**d**), Buⁱ (**e**).

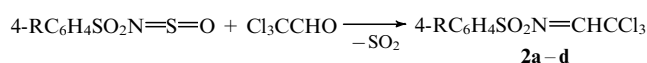
Dimethyl *N*-(2,2,2-trichloroethylidene) phosphoramidothioate has been synthesised in a similar way.⁵¹

It has been shown^{52,53} that some tetrachloroalkanesulfonamides can be dehydrochlorinated thermally without using dehydrochlorinating agents. For instance, *N*-trichloroethylidenemethane- and -propane-sulfonamides were synthesised in 73% and 93% yields on distillation of the corresponding tetrachloroethylalkanesulfonamides.

Thus, this method is fairly versatile and permits the preparation of various *N*-functionally substituted imines of polychlorinated (or brominated) aldehydes and ketones. The drawbacks of this method include the large number of stages, the use of corrosive reagents and also the facts that the intermediate hemiaminals are relatively unstable and haloaldehydes with different halogen atoms are inaccessible.

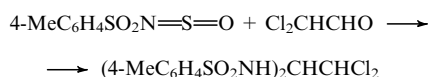
c. Condensation of *N*-sulfinylsulfonamides and *N*-sulfonyl isocyanates with haloaldehydes

Chloral *N*-4-tolylsulfonylimine **2a** has been prepared in 91% yield by the reaction of chloral with unstable *N*-sulfinyl-4-toluenesulfonamide in the presence of AlCl₃.^{32,54,55} The starting amide was synthesised by the reaction of 4-toluene sulfonamide with thionyl chloride in the presence of AlCl₃.⁵⁶ *N*-(Trichloroethylidene)benzenesulfonamide **2b** (yield 40%) and other chloral *N*-arylsulfonylimines (e.g., **2c,d**) were prepared in a similar way.⁵⁷



R = Me (**a**), H (**b**), Cl (**c**), MeO (**d**).

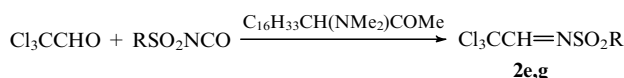
However, an attempt to prepare (*N*-2,2-dichloroethylidene)arenesulfonamides from *N*-sulfinyl-4-toluenesulfonamide and dichloroacetaldehyde³² resulted in the isolation of 1,1-bis-(4-tolylsulfonylamino)-2,2-dichloroethane.



An attempt to synthesise 1-chloroimines by condensation of *N*-sulfinylarenesulfonamides with acid chlorides was also unsuccessful because the condensation products proved to be unstable under the reaction conditions.⁵⁸

Thus, the applicability of this method is quite limited. For example, it is impossible to prepare *N*-trichloroethylidene dialkyl phosphoramidates by the condensation of the corresponding sulfinylamides with chloral.³³

A general method for the synthesis of chloral sulfonylimines consists in the interaction of chloral with sulfonyl isocyanates in the presence of amines and quaternary ammonium bases.⁵⁹



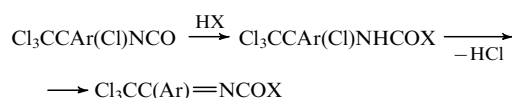
R = Cl (**e**), F (**g**), Alk(C₁–C₂₀), ArAlk(C₇–C₁₂), Ar(C₆–C₁₀).

The method for the synthesis of acyl-, X-carbonyl- and phosphoryl-imines of polyhalogenated aldehydes and ketones based on condensation of *N*-derivatives of amides with carbonyl compounds has not been further developed. However, a large number of sulfonylimines of aromatic and aliphatic aldehydes and ketones⁶⁰ and *N*-*tert*-butyl- and *N*-fluoroalkyl-imines of alkyl, aryl, polyfluoro and chloro aldehydes and ketones have been prepared from sulfinylamines.⁶¹

2. Preparation of imines of polychlorinated aldehydes and ketones from isocyanates

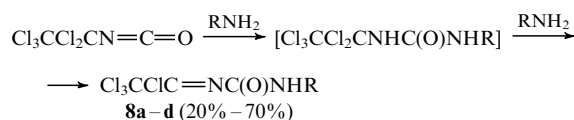
Methods for the synthesis of halo-containing imines based on 1-*R*-1,2,2,2-tetrahaloethyl isocyanates and perchlorinated isocyanates have found wide application.

Thus the reaction of 1-aryl-1,2,2,2-tetrachloroethyl isocyanates with alcohols, phenols, benzenethiols and amines taken in equimolar amounts affords *N*-(1-aryl-1,2,2,2-tetrachloroethyl)amides. These compounds are dehydrogenated on heating or on treatment with bases. *N*-*R*-Oxycarbonyl-, arylthiocarbonyl- and carbamoyl-imines of trichloromethyl phenyl ketone, *N*-*R*-oxycarbonylimines of trichloromethyl 4-methylphenyl ketone and phenoxy carbonylimines of trichloromethyl aryl ketones were prepared in this way.⁶²



Ar = Ph; X = MeO, PhO, 4-MeC₆H₄O, 3,5-Me₂C₆H₃O, 4-BrC₆H₄, O(CH₂CH₂)₂N, Ph₂N, PhNH, 3-CF₃-4-NO₂C₆H₃NH;
Ar = 4-MeC₆H₄; X = MeO, PhO;
X = PhO; Ar = 4-ClC₆H₄, 4-Cl₃CC₆H₄, 4-FC₆H₄.

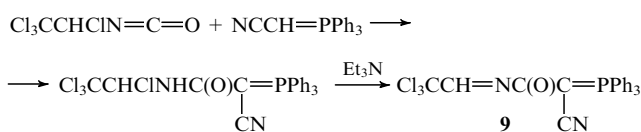
Later,^{63,64} *N*-Alkyl(aryl)-*N'*-(perchloroethylidene)ureas **8a–d** were synthesised by the reaction of perchloroethyl isocyanate with primary amines at –20 °C.



R = Prⁱ (**a**), Bu^t (**b**), Ph (**c**), 2,4,6-Me₃C₆H₂ (**d**).

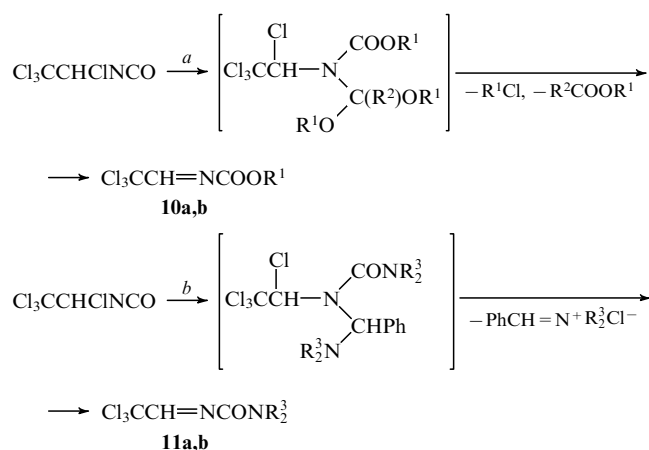
Tetrachloroethyl isocyanate was prepared by treatment of *N*-(1-hydroxy-2,2,2-trichloroethyl)alkoxycarbonylamide with PCl₅³⁹ and pentachloroethyl isocyanate was obtained by its photochemical chlorination.⁶³

The readily available ylide Ph₃P=CHCN easily adds to 1,2,2,2-tetrachloroethyl isocyanate giving rise to a new biphilic reagent, which contains the clearly electrophilic group CCINHCO[–], apart from the nucleophilic centre of the ylide fragment. This new reagent was used to create biphilic phosphonium ylide **9**.⁶⁵



The reactions of 1,2,2,2-tetrachloroethyl isocyanate with orthoesters of carboxylic acids and with benzaldehyde amins

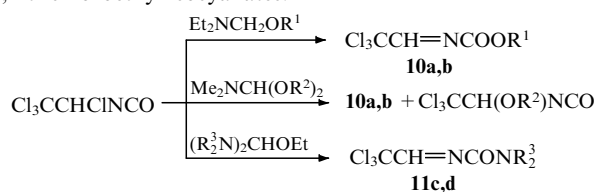
result in the formation of chloral *N*-alkoxycarbonylimines **10a,b** and *N,N'*-substituted dialkoxyureas **11a,b**.⁶⁶



(a) $(\text{R}^1\text{O})_3\text{CR}^2$; (b) $\text{PhCH}(\text{NR}_2^3)_2$; $\text{R}^1 = \text{Me}$ (**10a**), Et (**10b**);
 $\text{R}^2 = \text{H}$, Ph, 4- ClC_6H_4 ; $\text{R}_2^3 = (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$ (**11a**); $(\text{CH}_2)_5$ (**11b**).

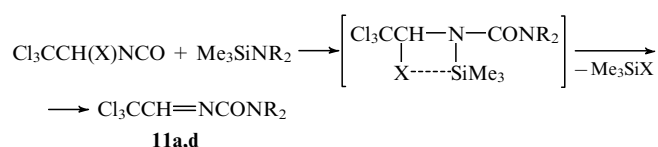
It was found⁶⁶ that acetals do not enter into similar reactions with tetrachloroethyl isocyanate.

1,2,2,2-Tetrachloroethyl isocyanate reacts with (dialkylamino)alkoxymethanes and bis(dialkylamino)ethoxymethanes giving rise to the chloral *N*-alkoxycarbonylimines **10a,b** and the *N,N'*-substituted ureas **11c,d**.⁶⁷ The reactions with dimethylformamide acetals afford a mixture of chloral imines and 1-alkoxy-2,2,2-trichloroethyl isocyanates.



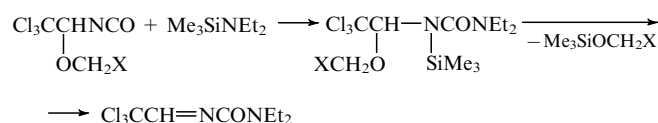
$\text{R}^3 = \text{Me}$ (**11c**), Et (**11d**).

Apart from tetrachloroethyl isocyanate, the products resulting from replacement of one chlorine by an aryloxy or alkoxy group are also employed in the synthesis of imines. Thus the reaction of 1,2,2,2-tetrachloroethyl isocyanate and 1-aryloxy-2,2,2-trichloroethyl isocyanate with trimethylsilylamines gives the *N,N'*-substituted ureas **11a,d**.⁶⁸



$\text{X} = \text{Cl}$, PhO, 4- $\text{ClC}_6\text{H}_4\text{O}$; $\text{R} = \text{Et}$, $\text{R}^2 = (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$.

The compound **11a** was obtained in the reaction of diethyl(trimethylsilyl)amine with 1-alkoxytrichloroethyl isocyanates; the first stage of the reaction yields silylated ureas, which decompose on heating to give the imine **11d** and the corresponding alkoxy silanes.⁶⁹



$\text{X} = \text{Cl}_2\text{CH}$, $\text{H}(\text{CF}_2)_2$, $\text{H}(\text{CF}_2)_4$, COOMe.

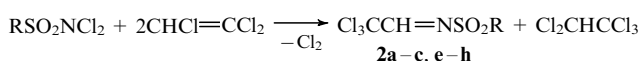
This method was used to synthesise a large number of acyl-, alkoxy(aryloxy)(thio)carbonyl- and *N'*-substituted carbamoylimines of chloral and trichloromethyl aryl ketones.

In conclusion, we would like to note that, despite the fact that these imines are produced from polychloroethyl isocyanates in preparative yields, isocyanates themselves are synthesised from polyhalogenated amides, nitriles, *etc.*, using PCl_5 , COCl_2 and other similar reagents, which restricts the scope of application of this method.

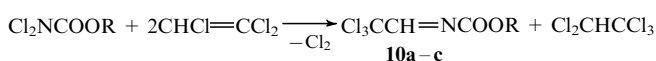
3. Reactions of *N,N*-dihaloamides with 1,2-polyhaloethenes as a new pathway to azomethines

The reactions of 1,2-polyhaloethenes with sulfonic, carboxylic, alkoxy-carboxylic and phosphoric acid *N,N*-dichloroamides have been vigorously studied for about 20 years. These reactions were found to give azomethines rather than saturated adducts. They provide the basis for one-stage procedures for the preparation of polyhaloaldehyde imines and their derivatives. Studies dealing with the synthesis of acyl-, ethoxycarbonyl- and sulfonyl-imines of chloral and other haloaldehydes, *N*-(2-bromo-2,2-dichloroethylidene)benzenesulfonamide, *N*-(2,2-dibromo-2-chloroethylidene)benzenesulfonamide and *N*-(2,2-dichloroethylidene)arenesulfonamides from *N,N*-dichloro- and *N,N*-dibromo-amides and 1,2-polyhaloethenes (trichloro-, tribromo- and dichloro-ethenes) published before 1989 have been surveyed in several reviews.^{23–25} Here we consider the studies that have not been covered in these reviews.

For instance, when *N,N*-dichloronitrobenzenesulfonamide, aminobenzenesulfonamide and *N,N*-dichloroamides of perfluoroalkanesulfonic acids are made to react with trichloroethene (TCE), the chloral sulfonylimines **2a–h** are formed;^{70,71} the reaction of *N,N*-dichlorourethanes with TCE affords chloral *N*-alkoxycarbonylimines **10a–c** in preparative yields.^{72,73}



$\text{R} = 4\text{-MeOC}_6\text{H}_4$ (**a**), Ph (**b**), 4- ClC_6H_4 (**c**), 3- $\text{NO}_2\text{C}_6\text{H}_4$ (**e**), 4- $\text{NO}_2\text{C}_6\text{H}_4$ (**f**), 4- $\text{MeOCONHC}_6\text{H}_4$ (**g**), Alk_F (**h**).



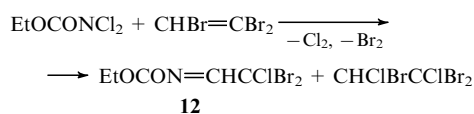
$\text{R} = \text{Me}$ (**a**), Et (**b**), Bu (**c**).

The reactions of TCE with *N,N*-dichloroarenesulfonamides in the presence of Lewis acids (SnCl_4 , AlCl_3) also afford the sulfonylimines **2a–c**, which are formed, however, in lower yields (up to 47%); *N*-(1-arylsulfonylamino-2,2,2-trichloroethyl)arenesulfonamides are formed as side products.⁷⁴

It has been reported previously²³ that TCE reacts with *N,N*-dibromobenzenesulfamide or *N,N*-dibromourethane giving rise to the corresponding imines of 2-bromo-2,2-dichloroacetaldehyde $\text{BrCl}_2\text{CCH}=\text{NSO}_2\text{Ph}$ and $\text{BrCl}_2\text{CCH}=\text{NCOOMe}$.

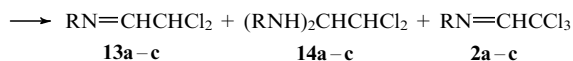
The reaction of TCE with *N*-bromourethane, which is known to disproportionate to give amide and dibromoamide, results in the formation of 2-bromo-2,2-dichloro-1,1-di(ethoxycarbonyl)amino)ethane.⁷⁵

The reactions of *N,N*-dichlorourethane and *N,N*-dichlorobenzenesulfonamide with tribromoethene (TBE) follow a similar route. *N,N*-Dichlorourethane is converted into ethyl *N*-(2,2-dibromo-2-chloroethylidene)carbamate **12**.⁷⁶ The reaction is accompanied by evolution of chlorine, bromine and 1,1,2-tribromo-1,2-dichloroethane.



It has been reported in studies cited in a review²³ that *N,N*-dichloroarenesulfonamides react with 1,2-dichloroethene (DCE) to give *N*-(2,2-dichloroethylidene)arenesulfonamides **13a–c**; the formation of these products was proved by physico-chemical methods and by chemical transformations. In another study,⁷⁷ they were isolated and characterised for the first time. The relative

yields of the compounds **13**, **14** and **2** depend on the reaction conditions.^{76, 77}



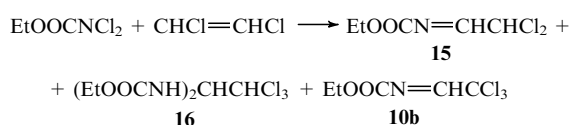
13a–c

14a–c

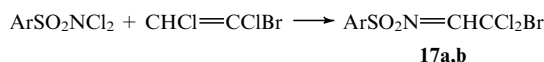
2a–c

R = PhSO₂ (**a**), 4-MeC₆H₄SO₂ (**b**), 4-ClC₆H₄SO₂ (**c**).

The reaction of *N,N*-dichlorourethane with DCE was found⁷⁶ to afford highly reactive ethyl *N*-(2,2-dichloroethylidene)carbamate **15**. However, like the reaction of *N,N*-dichloroarenesulfonamides with DCE, this process yields the imine **10b** and the product of addition of dichlorourethane to the C=N bond of this imine, namely, 2,2,2-trichloro-1,1-bis(ethoxycarbonylamino)ethane **16**, together with the target imine **15**. This is due to the fact that the process is accompanied by the chlorination of DCE giving rise to trichloroethene, tetrachloroethane, tetrachloroethene and urethane.



N,N-Dichloroarenesulfonamides have been found to react readily with 1-bromo-1,2-dichloroethene yielding *N*-(2-bromo-2,2-dichloroethylidene)arenesulfonamides **17a,b**.⁷⁸



17a,b

Ar = Ph (**a**), 4-ClC₆H₄ (**b**).

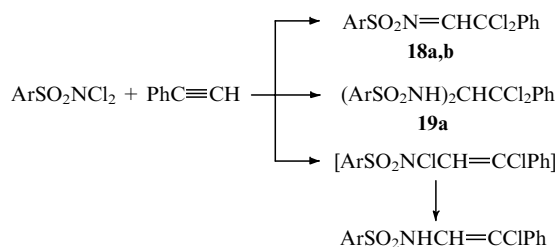
Systematic studies dealing with the influence of the natures of the polyhaloethene and dihaloamide used on the structure of the imine RN=CHCCl_nBr_{3–n} made it possible to refine the scheme proposed previously²³ for this reaction. It was demonstrated that the radical adducts formed either from *N,N*-dibromoamides and polychloroethenes or from *N,N*-dichloroamides and TBE do not undergo 1,2-halotropic rearrangement because these reactions afford neither polychloroaldehyde imines nor bromal imines.^{23, 75–78}

The method for the synthesis of polyhaloaldehyde imines based on the reaction of amidyl radicals with polyhaloethenes permits polychlorinated (or polybrominated) azomethines including those with different halogen atoms to be prepared from available initial compounds and to be used subsequently without isolation for synthetic purposes. However, the process of the preparation of halo-containing acyl- and phosphoryl-imines requires optimisation. The applicability of this method to the preparation of carbamoylimines and fluorinated imines containing residues of various types of acids also has to be studied.

4. Synthesis of *N*-arylsulfonylimines of polyhaloaldehydes by the reaction of *N,N*-dihaloamides with acetylene derivatives

The method for the synthesis of imines from acid dichloroamides and acetylene derivatives was developed in the last decade.

It has been shown^{79, 80} that the reaction of *N,N*-dichloroarenesulfonamides with phenylacetylene occurs by a free radical mechanism and results in the formation of *N*-(2,2-dichloro-2-phenylethylidene)arenesulfonamides **18a,b**. A detailed study of the process⁸⁰ demonstrated that *N,N*-dichlorobenzenesulfonamide reacts with phenylacetylene giving rise to a mixture of compounds, the imine **18a** being the major product (yield up to 75%); adduct **19a**, resulting from the addition of benzenesulfonamide to the C=N bond of **18a**, is also formed in a noticeable amount.

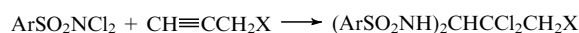


Ar = Ph (**a**), 4-ClC₆H₄ (**b**).

The reaction of phenylacetylene with *N,N*-dibromoarenesulfonamides gives 2,2-dibromo-2-phenyl-1,1-di(phenylsulfonylamino)ethane and benzenesulfonamide.⁸⁰

The reactions of *N,N*-dichlorourethanes and *N,N*-dichloroamides with phenylacetylene have also been studied.^{81, 82} However, the results obtained are contradictory and require more precise determination of the structures and transformations of the reaction products.

The reaction of *N,N*-dichloroarenesulfonamides with propargyl alcohol and 3-chloroprop-1-yne^{83, 84} gave the products of the subsequent addition of arenesulfonamides to the imines formed, namely, 3-chloro- and 3-hydroxy-2,2-dichloro-1,1-di(phenylsulfonylamino)propanes or 1,1-di(4-chlorophenylsulfonylamino)propanes.

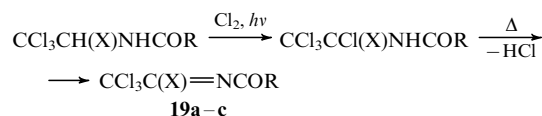


X = Cl, OH; Ar = Ph, 4-ClC₆H₄.

5. Chlorination and bromination of amide derivatives

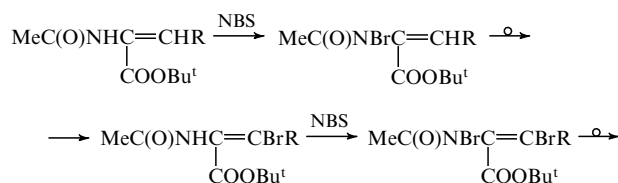
Among the methods for the synthesis of polyhaloaldehyde imines, mention should be made of chlorination of *N*-alkyl(aryl)amides; however, this method has already been considered in several reviews.^{17–21} We would only like to emphasise that chlorination of *N*-acylamides has been shown⁸⁵ to give products resulting from chlorination of both the aldehyde and the amide fragments. Photochemical high-temperature chlorination of isopropylamides of benzoic and 4-chlorobenzoic acids affords the corresponding acylimines of hexachloroacetone.

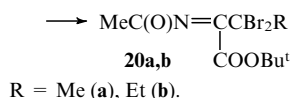
The transformation of *N*-(1-phenyl-2,2,2-trichloroethyl)amides under conditions of photochemical chlorination⁸⁶ and the transformation of *N*-(1-diethoxyphosphoryl-2,2,2-trichloroethyl)benzamide on treatment with the chlorine complex of pyridine⁸⁷ yield *N*-(1-phenyltrichloroethylidene)trichloroacet(or benz)amides **19a,b**⁸⁶ and *N*-(1-diethoxyphosphoryltrichloroethylidene)benzamide **19c** (yield 68%).⁸⁷ It was shown⁸⁷ that the latter product is more convenient to prepare by the chlorination of the silyl derivative CCl₂=C[P(O)(OEt)₂].N(SiMe₃)COPh (yield 84%).



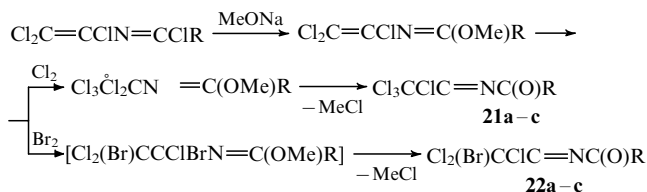
X = Ph, R = CCl₃ (**a**, 58%), Ph (**b**, 62%); X = (EtO)₂P(O), R = Ph (**c**).

Yet another study deserves special attention⁸⁸ in which it was reported that *N*-acetyl-(1-*tert*-butoxycarbonyl-2,2-dibromo)propan- and -butanimines **20a,b** are formed upon successive bromination of the corresponding enamides with *N*-bromosuccinimide (NBS).



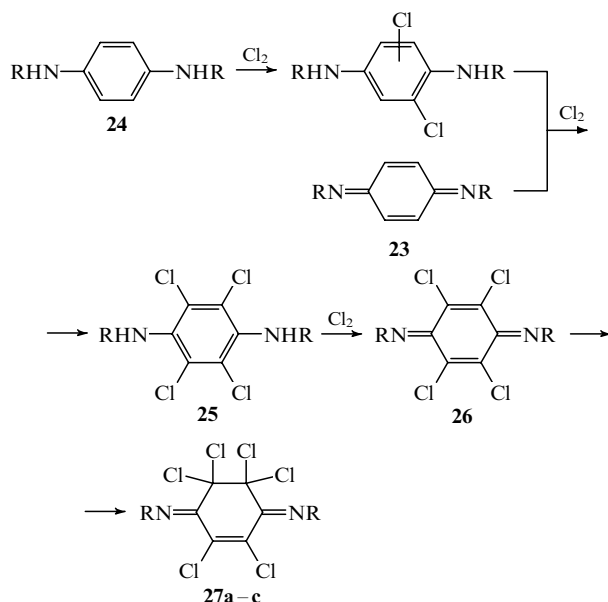


Finally, some polyhalogenated ketimines have been prepared by halogenation of compounds with C=N bonds. Thus *N*-perchlorovinylcarboximidoyl chlorides were used to synthesise *N*-substituted imino esters with a perchlorovinyl group.⁸⁹ When these compounds are subjected to chlorination, the perchlorovinyl group is converted into a perchloroethyl group. Methyl *N*-perchloroethylbenzimidates eliminate chloromethane on heating to give *N*-(tetrachloroethylidene)benzamides **21a–c** in high yields. Bromination of esters of *N*-perchlorovinylimidic acids under mild conditions is accompanied by elimination of MeBr and gives rise to *N*-(2-bromotrichloroethylidene)benzamides **22a–c**.



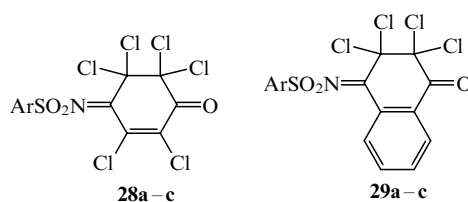
R = 4-XC₆H₄; X = H (a), Cl (b), NO₂ (c).

Chlorination has been employed to prepare imines of cyclic halogen-containing ketones.⁹⁰ Thus chlorination of both *N,N'*-bis(arylsulfonyl)-1,4-benzoquinonediimines **23** and *N*-arylsulfonyl-substituted *p*-phenylenediamines **24** in dimethylformamide results in the isolation of the same products, 2,3,5,6-tetrachloro-*N,N'*-bis(arylsulfonyl)-1,4-phenylenediamines **25**. Further chlorination affords tetrachlorobis(arylsulfonyl)benzoquinonediimines **26**, which, in turn, add a chlorine molecule at a double bond of the quinone ring to give the final products, 1,4-bis(arylsulfonylimino)-2,3,5,6,6-hexachlorocyclohex-2-enes **27a–c**.⁹⁰



R = PhSO₂ (a), 4-MeC₆H₄SO₂ (b), 4-ClC₆H₄SO₂ (c).

Similarly, 4-arylsulfonylimino-2,3,5,5,6,6-hexachlorocyclohex-2-en-1-ones **28a–c**⁹¹ and 4-arylsulfonylimino-2,3,5,5,6,6-hexachloro-1-oxo-1,2,3,4-tetrahydronaphthalenes **29a–c**⁹² were obtained by chlorination of *N*-arylsulfonyl-1,4-aminophenols and *N*-arylsulfonyl-1,4-aminonaphthols.

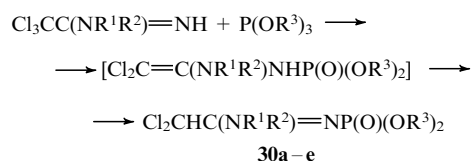


Ar = Ph (a), 4-MeC₆H₄ (b), 4-ClC₆H₄ (c).

6. The use of organophosphorus compounds and PCl₅ for the synthesis of polyhalogenated imines

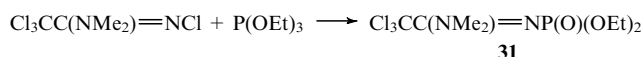
Several methods for the synthesis of *N*-functionally substituted polyhalogenated imines based on organophosphorus compounds and PCl₅ are known.

Dialkyl *N*-(1-amino-2,2-dichloroethylidene) phosphoramidates were prepared by the reaction of trichloroacetylaminides with trialkyl phosphites.⁹³

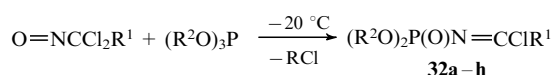


R¹ = H, R² = Me; R³ = Me (a), Et (b), Prⁿ (c), Prⁱ (d);
R¹ = H, R² = Bu^t, R³ = Et (e).

Diethyl *N*-(1-dimethylamino-2,2,2-trichloroethylidene) phosphoramidate **31** was synthesised from *N*-chloro-*N'*,*N'*-dimethyltrichloroacetylaminides and triethyl phosphite.⁹³

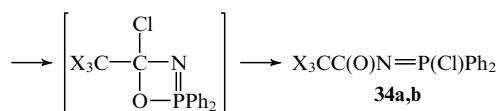
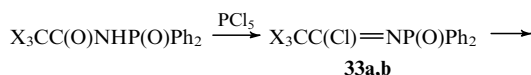


Trialkyl phosphites were shown⁹⁴ to react with polychloronitrosoethanes under mild conditions (–20°C) giving rise to the corresponding dialkyl *N*-chloroalkylidene phosphoramidates **32a–h**.



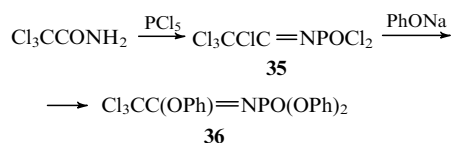
R¹ = CH₂Cl; R² = Prⁿ (a), Buⁿ (b), Buⁱ (c), C₅H₁₁ (d), ClCH₂CH₂ (e);
R¹ = CHCl₂; R² = Prⁿ (f), Buⁿ (g), C₅H₁₁ (h).

The reaction of *N*-trihaloacetyl diphenylphosphinic amide with PCl₅ affords a mixture of *N*-(tetrachloroethylidene) (**33a**) and *N*-(trifluoro-1-chloroethylidene) (**33b**) diphenylphosphinic amides (70%) and phosphazone compounds **34** (30%).⁹⁵ The rearrangement, which occurs presumably *via* a four-centre transition state, is facilitated by the presence of strong electron-withdrawing groups.

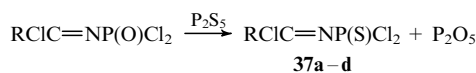


X = Cl (a), F (b).

However, trichloroacetamide reacts with excess PCl₅ to give *N*-dichlorophosphoryltetrachloroethanimine **35**.⁹⁶ This product reacts with sodium phenoxide giving rise to the products of substitution of phenoxyl residues for the halogen atoms — *N*-diphenoxyphosphoryl-2,2,2-trichloro-1-phenoxyethanimine **36**.⁹⁷

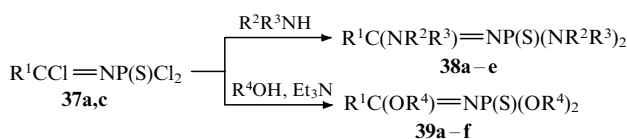


Imines of type **35** have also been used to prepare chlorinated and fluorinated imides of phosphorothioic acids **37a–d**.⁹⁸



R = CCl₃ (**a**), CH₂ClCCl₂ (**b**), MeCCl₂ (**c**), EtCCl₂ (**d**).

When the imines **37a,c** are made to react with alcohols and amines, the chlorine atoms at phosphorus and carbon are substituted to give compounds **38a–e** and **39a–f**.⁹⁸



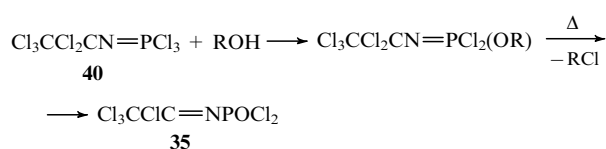
R¹ = Cl₃C: NR²R³ = PhNH (**38a**), 4-ClC₆H₄NH (**38b**), N(CH₂CH₂)₂O (**38c**);

R¹ = Cl₂CMe: NR²R³ = 4-ClC₆H₄NH (**38d**), N(CH₂CH₂)₂O (**38e**);

R¹ = Cl₃C: R⁴ = Me (**39a**), Et (**39b**), Pr (**39c**), Bu (**39d**), Ph (**39e**);

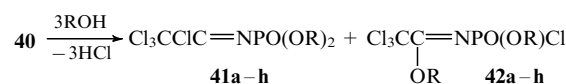
R¹ = Cl₂CMe, R⁴ = Et (**39f**).

Several *N*-phosphorylimines have been synthesised using trichlorophosphorazoperchloroethane **40**,⁹⁹ which reacts with alcohols to yield imides of various structures depending on the reaction temperature and the reactant ratio. When an equimolar amount of an alcohol is employed, one chlorine atom is replaced giving rise to unstable alkyl *N*-(perchloroethyl)dichlorophosphorimidates, which decompose on heating with evolution of an alkyl chloride to give *N*-dichlorophosphoryltetrachloroethanimine **35**.



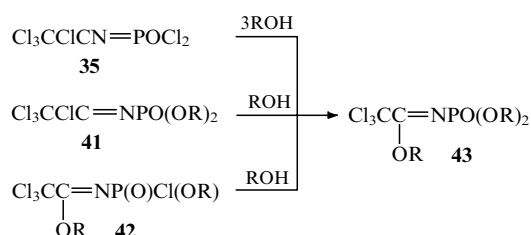
R = Me, Et, Pr, Bu, C₈H₁₇.

When a threefold excess of an alcohol is used, this reaction results in the formation of a mixture of dialkyl phosphoramidates **41a–h** and the corresponding alkoxy chloro derivatives **42a–h** in ~60 : 40 ratio.

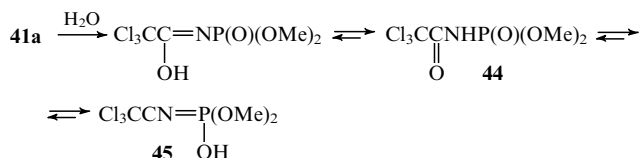


R = Me (**a**), Et (**b**), Prⁿ (**c**), Buⁿ (**d**), Buⁱ (**e**), C₅H₁₁ (**f**), iso-C₅H₁₁ (**g**), C₈H₁₇ (**h**).

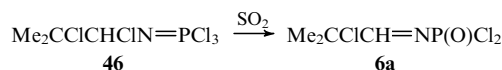
When the alcohol : imine **40** ratio is 4 : 1, dialkyl *N*-(1-alkoxy-2,2,2-trichloroethylidene) phosphoramidates **43** are produced in 65%–85% yields. These compounds can also be obtained by treatment of the compounds **35**, **41** or **42** with an alcohol.



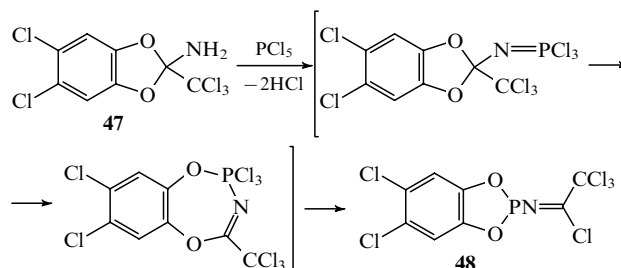
The imine **41a** was converted into dimethyl *N*-trichloroacetyl phosphoramidate **44** using a procedure proposed by Kirsanov *et al.*⁹⁶ The product **44** can exist in solution as the imine tautomer **45**.¹⁰⁰



The compound **6a** can be prepared by treatment of *N*-(1,2-dichloro-2-methylpropylidene)aminophosphorus trichloride with sulfur dioxide.⁴⁹

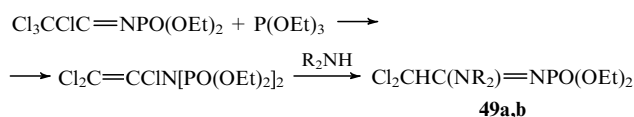


Tetrachloroethylideneaminodioxaphospholane **48** was prepared by the reaction of 2-amino-2-trichloromethyl-5,6-dichlorobenzo-1,3-dioxolane **47** with PCl₅.¹⁰¹ Presumably, a phosphazo compound is formed initially and then it rearranges into the dioxaphospholane *via* a seven-membered intermediate.



7. Other methods of synthesis

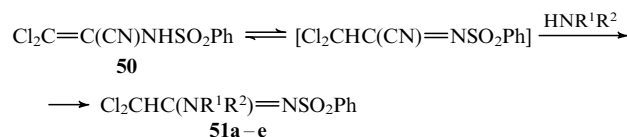
It is worth noting that chlorovinylamides, structural isomers of chloroethylideneimines, can be used in some cases for the synthesis of imines. Thus bis(dialkoxyphosphoryl)trichlorovinylamines react with two equivalents of a dialkylamine to give dialkyl *N*-(1-dialkylamino-2,2-dichloroethylidene) phosphoramidates **49a,b**.¹⁰²



R = Me (**a**), Et (**b**).

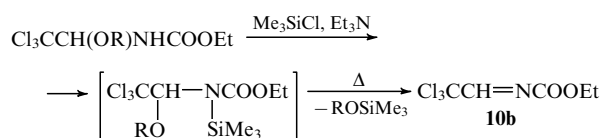
It has been mentioned above that imines with a similar structure have also been prepared from trichloroacetamides.⁹³

(2,2-Dichloro-1-cyanovinyl)benzenesulfonamide **50** reacts with amines, in the opinion of the researchers cited,¹⁰³ in the imine form with replacement of the cyano group by an amino group; *N*-(1-dialkylamino-2,2-dichloroethylidene)arenesulfonamides **51a–e** were isolated in good yields.



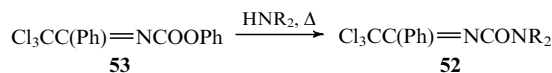
NR¹R² = PhCH₂NH (**a**), PhNH (**b**), 4-MeC₆H₄NH (**c**), Me₂N (**d**), O(CH₂CH₂)₂N (**e**).

A quite promising method for the preparation of imines is that based on ethyl *N*-[trichloro-1-alkoxy(aryloxy)ethyl]carbamates and chlorotrimethylsilane. When ethyl *N*-(1-aryloxy-2,2,2-trichloroethyl)carbamates are silylated with chlorotrimethylsilane in the presence of triethylamine, the intermediate product decomposes to give *N*-(ethoxycarbonyl)chloral imine **10b**.⁶⁹

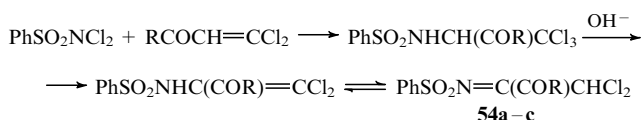


R = Ph, 2,4-Br₂C₆H₃.

It has been shown that 1-phenyl-2,2,2-trichloroethylideneureas **52** can be prepared from phenyl *N*-(1-phenyl-2,2,2-trichloroethylidene)carbamate **53**.⁶² Under rigorous conditions, the phenoxy group is replaced by the amine residue.⁶²



The reaction of *N,N*-dichlorobenzenesulfonamide with dichlorovinyl ketones followed by dechlorination of the resulting *N*-(1-acyl-2,2,2-trichloroethyl)benzenesulfonamides on treatment with alkali resulted in the formation of *N*-(1-acyl-2,2-dichloroethylidene)benzenesulfonamides **54a–c**. They can exist as two tautomers.¹⁰⁴



R = Me (**a**), Pr (**b**), CH₂Cl (**c**).

III. Structure of imines of polyhalogenated aldehydes and ketones: *syn*–*anti* isomerism; enamide–acylimine tautomerism

1. Structure of *N*-trichloroethylidenearenesulfonamides according to the data of ³⁵Cl NQR and NMR spectroscopy. *syn*–*anti* Isomerism of polyhaloaldehyde imines

Despite the considerable attention devoted to the chemistry of carboxylic, sulfonic and phosphoric acid *N*-polyhaloalkylideneamides, their structures certainly have not been adequately studied. Most often, these compounds have been characterised by IR and NMR data; the results of NQR studies of trichloroethylidenearenesulfonamides can be found only in two publications.^{105, 106}

The ³⁵Cl NQR spectra, as well as ¹H and ¹³C NMR spectra,⁷⁰ indicate that chloral arylsulfonylimines **2a–c** occur as one of the two possible isomers. According to quantum-chemical calculations, *anti*-isomer **A** is more favourable than *syn*-isomer **B**; this is confirmed by experimental and theoretical ³⁵Cl NQR data.¹⁰⁵



Ar = 4-MeC₆H₄, Ph, 4-ClC₆H₄.



It has been shown by NMR spectroscopy that the dibromoacetaldehyde imines **12** and **55** exist as mixtures of *syn*- and *anti*-isomers in 3 : 4¹⁰⁷ and 1 : 3⁷⁶ ratios, respectively. Indeed, the ¹H NMR spectrum of the imine **55** exhibits, in addition to the multiplet for the phenyl protons, two singlets at 8.30 and 8.40 ppm due to the protons at the double bond, the ratio of their intensities being 3 : 4. The ¹³C NMR spectrum contains two signals for the carbon atoms of the CH=N group (167.9 and 167.6 ppm) and the CClBr₂ group (135.7 and 135.6 ppm).¹⁰⁷ More evidence supporting the existence of *syn*- and *anti*-isomers of imines is provided by the fact that addition of nucleophiles at the C=N bond affords two enantiomers.¹⁰⁷

It should be noted that *syn*- and *anti*-isomers cannot be detected in the ¹H NMR spectra of chloral sulfonylimines **2a–c** or ethoxycarbonylimines **10b**,^{108, 73} dichloroacetaldehyde sulfonylimines **13a–c** or ethoxycarbonylimines **15**,^{76, 77} or bromodichloroacetaldehyde sulfonylimines **17a,b** or alkoxy carbonylimines.^{23, 78, 109}

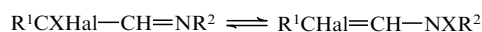
The correlations between the experimental ³⁵Cl NQR frequencies and the C–Cl bond lengths proposed in Ref. 110 were used to calculate the bond lengths in the imines **2a–c**, which were estimated as ranging between 175.8 and 176.3 pm.¹⁰⁵ These values are typical of C–Cl bond lengths in compounds with a trichloromethyl group.

It has been noted that the three chlorine atoms in trichloroethylidene-benzenesulfonamide and -4-toluenesulfonamide **2a,b** are nonequivalent in the ³⁵Cl NQR spectra, whereas the ³⁵Cl NQR spectrum of the corresponding 4-chlorophenylsulfonylimine **2c** exhibits a single signal for the trichloromethyl group,^{105, 106} which is difficult to explain based on its molecular structure. Apparently, the electron environment of all the chlorine atoms in this imine becomes equivalent due to intermolecular contacts.

Unfortunately, no data of ³⁵Cl NQR spectra for imines that are known to exist as both *syn*- and *anti*-isomers can be found in the literature.

2. Enamide–acylimine tautomerism in dichloroethylideneimines

An interesting problem of theoretical chemistry is the question of the existence of enamide–acylimine tautomerism in haloalkylideneimines *N*-substituted by acid residues.



X = H, Hal.

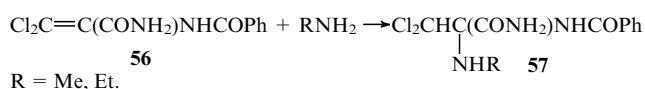
It has been concluded in reviews^{20, 21} that, among *N*-acylimines of chloro(bromo)(fluoro)aldehydes and ketones, stable structures with the imine bond can be found for ald- and ketimines containing no β-hydrogen atoms in the haloalkyl groups.

However, now it is known that arylsulfonylimines of dichloroacetaldehyde ArSO₂N=CHCHCl₂ **13a–c**, Ar = Ph (**a**), 4-MeC₆H₄ (**b**), 4-ClC₆H₄ (**c**), which do have a hydrogen atom in the β-position with respect to the imine group, exist in the stable imine form, as indicated by the presence of characteristic absorption bands of the C=N bond in the IR and NMR spectra (the signal for the azomethine proton at δ 8.35–8.44 ppm and for the carbon atom of the CH=N group at δ 166 ppm).⁷⁷ Similarly, the dichloroethylidenecarbamate **15** (the signal of the azomethine proton at δ 8.06 ppm⁷⁶) and 1-alkylamino-substituted dialkyl 2,2-dichloroethylidene phosphoramidates also exist as stable imine forms.^{93, 102}

According to the data of IR and ¹H NMR spectra, *N*-dichlorovinylamides and *N*-dichlorovinylthioamides exist as stable enamide forms.^{111, 112} Nevertheless, they react with nucleophiles to give stable products of addition at the azomethine bond.^{112–114}

Some functional substituents, for example CN,^{103, 115, 116} CONH₂,¹¹⁷ POPh₂,¹¹⁸ PO(OEt)₂,^{119, 120} and P+Ph₃Cl[–],¹²¹ present in a dichloroalkyl group stabilise the enamide form Cl₂C=C(R¹)NHCOR², where R² = Alk, Ar, OMe, OPh. These amides react with primary and secondary amines in the enamide tautomeric form to give the products of replacement of chlorine atoms.

An exception is provided by *N*-(1-carbamoyl-2,2-dichlorovinyl)benzamide **56**, which reacts with methyl- and ethylamine giving rise to stable addition products **57**.¹¹⁷



R = Me, Et.

It has already been mentioned (see Section II.7) that *N*-(2,2-dichloro-1-cyanovinyl)benzenesulfonamide **50** reacts with amines with substitution of the cyano group to afford stable 1-amino-2,2-dichloroethylidenesulfonamides **51a–e**.¹⁰³

It has also been found that *N*-(1-acyl-2,2-dichloroethylidene)benzenesulfonamides **54a–c** can exist as two tautomers;¹⁰⁴ the amide form predominates in the solid state, whereas in solutions the equilibrium shifts towards the imine form. The facts that the equilibrium is established over a relatively long period and that the tautomers can be observed separately indicate that the energy barrier separating these forms is higher than 107 kJ mol^{−1}.¹⁰⁴

It should be emphasised that bromination of the NH group in *N*-(1-*tert*-butoxycarbonyl-2-methyl- and 2-ethylvinyl)acetamides yields unstable compounds which undergo a 1,3-halotropic rearrangement with migration of the halogen atom giving rise to the imines **20a,b** (see Section II.4). Similarly, *N*-chloro-*N*-(2-chloro-2-phenylvinyl)arenesulfonamides and *N*-bromo-*N*-(2-bromo-2-phenylvinyl)benzenesulfonamide, formed in the reaction of *N,N*-dichloro(bromo)arenesulfonamides with phenylacetylene (see Section II.4), are converted into the corresponding *N*-(2,2-dihalo-2-phenylethylidene)arenesulfonamides of the type **18** as a result of 1,3-halotropic rearrangement.^{79, 80}

Thus, the imine form of dichloroacetaldimines is stable in the case of arylsulfonylimines and alkoxy-carbonylimines and for *N*-dichlorovinyl phosphoric amides if the α -position of the vinyl group has electron-donating substituents. *N*-Dichlorovinyl-substituted dialkyl phosphoramidates, carboxamides and thiocarboxamides containing no substituents at the α -position of the vinyl group are stable in the enamide form; however, they react with nucleophiles in the imine form. The presence of electron-withdrawing substituents at the 1-position of the vinyl group of dichlorovinylamides stabilises the enamide tautomer. The introduction of a halogen atom in the NH group facilitates tautomerisation of enamides to give halogen-containing imines.

IV. Reactivity of *N*-acyl-, *N*-sulfonyl- and *N*-phosphorylimines of polyhalogenated aldehydes and ketones

The reactivity of N-functionally substituted polyhalogenated aldimines and ketimines is due to the presence of the highly electrophilic C=N bond. Electron-withdrawing substituents at this bond increase its reactivity towards nucleophiles and electron-rich species such as dienes, alkenes, alkynes or arenes.

1. Reactions of polychlorinated(brominated) aldimines and ketimines with nucleophiles

Acyl-, alkoxy(aryloxy)(amino)carbonyl-, sulfonyl- and phosphoryl-imines of polyhalogenated aldehydes and ketones have been studied in reactions with O-, N-, S- and P-nucleophiles and bifunctional nucleophiles. To elucidate the relationship between the structure of imines and their reactivity towards nucleophiles, the kinetics have been measured for the addition of ethanethiol and 2,4,6-trichloroaniline to chloral imines with various acyl residues, Cl₃CCH=NCOR, where R = Ph (**3a**), PhCH₂O (**3b**), Me (**3c**), Et (**3d**), Prⁱ (**3e**), Bu^t (**3f**), 4-MeC₆H₄ (**3g**), 4-MeOC₆H₄ (**3h**), 4-ClC₆H₄ (**3i**), 4-O₂NC₆H₄ (**3j**), 3-MeC₆H₄ (**3k**), 3-ClC₆H₄ (**3l**), and to the imines **10a,b**, **2a,b** and **7b**.^{41, 122} It was found that the reactions obey second-order kinetics, the reactivity of imines sharply decreasing in the series **3** > **10** > **7**.

Cl ₃ CCH=NR	3a	3d	10b	7b
R	PhCH ₂ CO	EtCO	EtOCO	(EtO) ₂ PO
<i>k</i> / litre mol ^{−1} h ^{−1}	226.0	77.0	14.6	4.7

The rate constants for the addition of ethanethiol diminish by factors of 20 to 52 on passing from the acylimines **3** and **10** to the phosphorylimine **7**. Evidently, this is due to the decrease in the

electronegativity of the acid residues, resulting in a higher electron density on the carbon atom of the azomethine group. The substantial decrease in the reactivity observed on passing from *N*-ethoxycarbonylchloral imine **10b** to *N*-propionylchloral imine **3d** is due to the decrease in the conjugation of the azomethine group with the carbonyl group involving the alkoxy residue. The considerable influence of conjugation is also supported by the fact that the reactivity of an imino group attached to a phosphonyl residue is even lower because in this case, conjugation is insignificant if at all present.¹²²

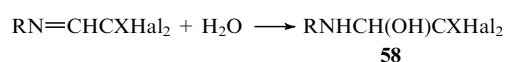
Study of the reactivity of the chloral aroylimines **3i–m** towards 2,4,6-trichloroaniline in benzene, dioxane and acetonitrile demonstrated that the rate of addition of the amine in acetonitrile depends on the substituents in the benzene nucleus.⁴¹ This reaction is accelerated by electron-withdrawing substituents and retarded by electron-donating ones.

Comparison of the reactivity of chloral imines towards 2,4,6-trichloroaniline⁴¹ demonstrated that the influence of the substituent at the nitrogen atom on the capacity of the C=N bond for the addition reactions decreases in the sequence COAr > COAlk > SO₂Ar and also in the sequence COAlk > PO(OAlk)₂ > COOAlk.

Although arylsulfonamide groups possess high electronegativity, they have a lesser influence on the reactivity of the C=N bond towards trichloroaniline. The addition of the amine to phosphoryl- and sulfonylimines is characterised by greater negative values of activation entropy than the addition to acylimines. This was interpreted⁴¹ by assuming that the reactions of the amine with the C=N–C=O, C=N–P=O and C=N–SO₂ systems occur *via* different cyclic transition states. In the case of acylimines, a six-membered transition complex is formed, whereas for phosphoryl- and sulfonylimines a four-membered transition state is involved. This assumption is confirmed by the known fact that acylimines enter into 1,4-cycloaddition reactions, whereas arylsulfonylimines tend to undergo 1,2-cycloaddition.

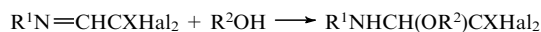
a. Reactions of imines with O-nucleophiles

The reactions of imines with oxygen-containing nucleophiles have been studied most extensively; it was shown that acyl-, alkoxy(aryloxy)carbonyl-, carbamoyl-, sulfonyl- and phosphoryl-imines of polyhaloaldehydes add water and alcohols with heat evolution to give stable hydroxy- **58** and alkoxy-substituted **59** haloalkylamides.

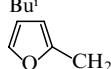


R	X	Hal	Ref.
MeCO	Cl	Cl	37
PhCO	Cl	Cl	35
Ph ₃ P=C(CN)CO	Cl	Cl	65
MeOCO	Cl	Cl	36
EtOCO	Cl	Cl	36, 72
BuOCO	Cl	Cl	72
PhOCO	Cl	Cl	35
Et ₂ NCO	Cl	Cl	68
O(CH ₂ CH ₂) ₂ N	Cl	Cl	68
4-MeC ₆ H ₄ SO ₂	Cl	Cl	32, 74, 123, 124
PhSO ₂	Cl	Cl	74, 123, 124
4-ClC ₆ H ₄ SO ₂	Cl	Cl	74, 123, 124
4-NO ₂ C ₆ H ₄ SO ₂	Cl	Cl	70
3-NO ₂ C ₆ H ₄ SO ₂	Cl	Cl	70
(EtO) ₂ P(O)	Cl	Cl	33, 50
(MeO) ₂ P(O)	Cl	Cl	33
(Pr ⁿ O) ₂ P(O)	Cl	Cl	33
(Pr ⁱ O) ₂ P(O)	Cl	Cl	33
(Bu ^t O) ₂ P(O)	Cl	Cl	33
(MeO) ₂ P(S)	Cl	Cl	51
MeCO	Br	Cl	43
EtCO	Br	Cl	43

R	X	Hal	Ref.
MeOCO	Br	Cl	43, 44
EtOCO	Br	Cl	109
PhSO ₂	Br	Cl	78
4-ClC ₆ H ₄ SO ₂	Br	Cl	125, 78
PhSO ₂	Cl	Br	107
MeOCO	Br	Br	42
EtOCO	Br	Br	36
4-MeC ₆ H ₄ SO ₂	H	Cl	77, 126
PhSO ₂	H	Cl	77, 126
4-ClC ₆ H ₄ SO ₂	H	Cl	77, 126

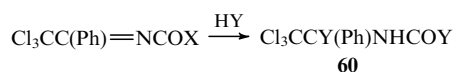


59

R ¹	R ²	X	Hal	Ref.
EtOCO	Me	Cl	Cl	36
Me ₂ NCO	Me	Cl	Cl	68
4-MeC ₆ H ₄ SO ₂	Me	Cl	Cl	32, 72, 124
PhSO ₂	Me	Cl	Cl	8, 124
4-ClC ₆ H ₄ SO ₂	Me	Cl	Cl	8, 124
(MeO) ₂ P(S)	Me	Cl	Cl	51
Ph ₃ P=C(CN)CO	Me	Cl	Cl	65
MeCO	Me	Br	Cl	43
EtCO	Me	Br	Cl	43
MeOCO	Me	Br	Cl	44
EtOCO	Me	Br	Cl	109
EtOCO	Me	Br	Br	36
MeCO	Me	Pr ⁿ	Cl	34
MeCO	Me	Bu ⁿ	Cl	34
PhCO	Et	Cl	Cl	35
PhOCO	Et	Cl	Cl	35
EtOCO	Et	Cl	Cl	36
Et ₂ NCO	Et	Cl	Cl	68
4-MeC ₆ H ₄ SO ₂	Et	Cl	Cl	32, 124
PhSO ₂	Et	Cl	Cl	124
4-ClC ₆ H ₄ SO ₂	Et	Cl	Cl	74
(EtO) ₂ P(O)	Et	Cl	Cl	33
(MeO) ₂ P(S)	Et	Cl	Cl	51
PhSO ₂	Et	Br	Cl	78, 125
4-ClC ₆ H ₄ SO ₂	Et	Br	Cl	78
PhSO ₂	Et	H	Cl	8, 77
PhSO ₂	Et	Br	Cl	107
(Bu ⁱ O) ₂ P(O)	Bu ⁱ	Cl	Cl	33
PhSO ₂		Cl	Cl	127
PhSO ₂	Bu ⁿ	Ph	Cl	128
PhSO ₂	CH ₂ =CHCH ₂	Cl	Cl	129
4-MeC ₆ H ₄ SO ₂	CH ₂ =CHCH ₂	Cl	Cl	129
4-ClC ₆ H ₄ SO ₂	CH ₂ =CHCH ₂	Cl	Cl	129

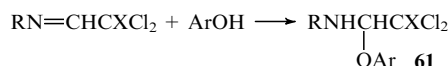
Allyl alcohol adds to chloral arylsulfonylimines under mild conditions without heating.¹²⁹

The addition of alcohols and ammonia at the C=N bond in trichloromethyl phenyl ketimines is accompanied by simultaneous replacement of the fragment X by an alcoholic residue or an amino group to give 1-[alkoxy(amino)carbonylamino]-2,2,2-trichloroethylbenzenes **60**.⁶²



X = OAlk, SAr, NAlk₂; Y = MeO, EtO, NH₂.

Reactions of acyl-, sulfonyl- and dialkoxyphosphoryl-trichloroethylideneamines with phenols and 1-naphthol have been studied. It was shown that phenol^{33, 36, 37, 50, 123, 124, 130} and *p*-chlorophenol^{33, 39, 130} add to almost all types of imines giving rise to aryloxy derivatives **61**.



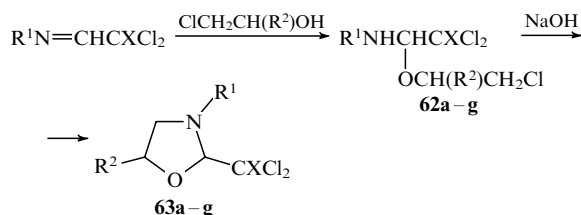
Ar = Ph, 4-ClC₆H₄; X = Cl, CH₂Cl;

R = AlkCO, AlkOCO, (AlkO)₂PO, ArSO₂.

1-Naphthol readily adds to phosphorylimines.^{33, 50} However, these imines give no addition products with 2,6-dimethylphenol, 2,6-dinitrophenol or 2,4,6-trinitrophenol even on heating.³³ This is caused not only by steric reasons but also by the low nucleophilicity of nitrophenols.

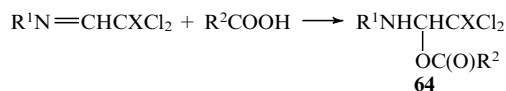
Chloral arylsulfonylimines, which also react with phenol, do not react with chloro-substituted phenols.¹²³

2-Chloroalkanols vigorously react with chloral imines and dichloroacetaldehyde sulfonylimines yielding *N*-[(2,2-dichloro-2-X-1-(2-chloroalkoxy)ethyl)amides **62**, which cyclise on treatment with an alkali giving rise to 1-arylsulfonyl(ethoxycarbonyl)-2-trichloromethyl- and -dichloromethyloxazolidines.^{77, 131}



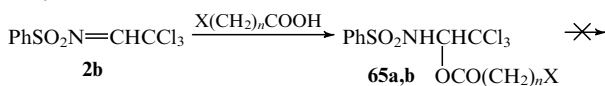
R¹ = PhSO₂ (**a**), 4-ClC₆H₄SO₂ (**b**), 4-MeC₆H₄SO₂ (**c**), EtOCO (**d**), R² = H, X = Cl; R¹ = PhSO₂, R² = CH₂OMe, X = Cl (**e**); R¹ = PhSO₂, R² = CH₂Cl, X = Cl (**f**); R¹ = PhSO₂, R² = H, X = H (**g**).

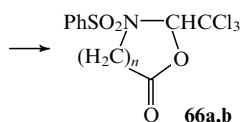
The reactions of imines with carboxylic acids have been studied extensively. Although carboxylic acids are weak nucleophiles, they add at the C=N bond of imines (sometimes on heating) to afford 1-acyloxy-2-polychloroethylalkylamides **64**.



R ¹	X	R ²	Ref.
MeCO	Cl	Me	37
PhSO ₂	Cl	Me	124
(EtO) ₂ PO	Cl	Me	33
(Bu ⁱ O) ₂ PO	Cl	Me	33
PhSO ₂	Ph	CH ₂ Cl	128
MeCO	Bu ⁿ	Me	34
PhSO ₂	Cl	Ph	124
(MeO) ₂ PO	Cl	Ph	33
(Pr ⁿ O) ₂ PO	Cl	Ph	33
(Pr ⁱ O) ₂ PO	Cl	Ph	33
(Bu ⁱ O) ₂ PO	Cl	Ph	33
MeCO	Pr ⁿ	Ph	34
MeCO	CH ₂ Cl	Ph	130
EtCO	CH ₂ Cl	Ph	130
Pr ⁿ CO	CH ₂ Cl	Ph	130
MeCO	CH ₂ Cl	1-naphthyl	130
Pr ⁿ CO	CH ₂ Cl	1-naphthyl	130
PhSO ₂	Cl	2-furyl	127

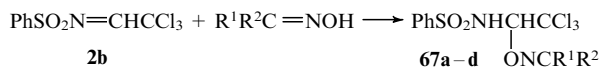
The imine **2b** reacts with halocarboxylic acids to give addition products — sulfonamides **65a,b**. An attempt to dehydrohalogenate these products in order to prepare heterocyclic compounds **66a,b** failed.¹³¹





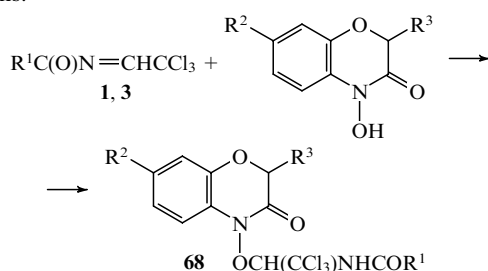
X = Cl, $n = 1$ (a); X = Br, $n = 2$ (b).

The sulfonylimine **2b** vigorously reacts with oximes of aliphatic, cycloaliphatic and aromatic ketones being thus converted into the addition products **67a–d**.^{8, 11, 124}



$\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{Ph}$ (a), Bu^t (b), Me (c); $\text{R}^1-\text{R}^2 = (\text{CH}_2)_5$ (d).

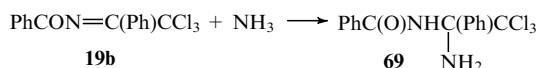
An attempt was made to carry out addition of hydroxylamines to imines. Cyclic hydroxylamines, namely, 4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-ones, were found to add to the acylimines **1** and **3**. Compounds **68** were patented as antimicrobial preparations.¹³²



$\text{R}^1 = \text{Alk}, \text{Ar}, \text{ArO}$; $\text{R}^2, \text{R}^3 = \text{H}, \text{Hal}, \text{AlkO}, \text{Alk}, \text{Ar}, \text{CN}, \text{NO}_2$.

b. Reactions of imines with NH-nucleophiles

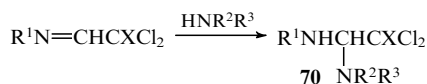
Only two examples of addition of ammonia to the imines in question have been reported. The reaction of the benzoylimine **19b** with ammonia has resulted in the isolation of *N*-(1-amino-2,2,2-trichloro-1-phenylethyl)benzamide **69**.⁸⁶



It was shown⁶⁵ that biphilic phosphonium ylide **9** reacts with ammonia to give the product of addition to the C=N bond, $\text{Ph}_3\text{P}=\text{C}(\text{CN})\text{COCH}(\text{NH}_2)\text{CCl}_3$, in 95% yield, the cyano group and the C=P bond remaining intact. It was also reported that the reaction of ammonia with trichloromethyl phenyl ketimine affords 1-amino-1-phenyl-2,2,2-trichloroethylurea.⁶²

The reactions of N-functionally substituted imines of polyhalogenated aldehydes and ketones with amines, amides and imines have been studied in detail.

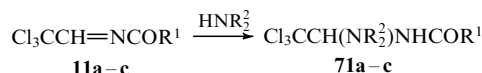
Acyl- and alkoxy(aryloxy)carbonyl-imines of polyhaloaldehydes add primary and secondary amines to give addition products **70** in good yields.^{34–37, 41, 43–45, 65}



$\text{R}^1 = \text{AlkCO}, \text{AlkOCO}, \text{ArCO}, \text{ArOCO}, \text{Ph}_3\text{P}=\text{C}(\text{CN})\text{CO}$;
 $\text{R}^2, \text{R}^3 = \text{H}, \text{Alk}, \text{Ar}$; $\text{R}^2-\text{R}^3 = (\text{CH}_2)_2\text{O}(\text{CH}_2)_2, (\text{CH}_2)_4$;

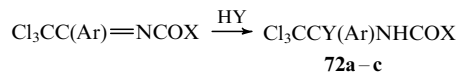
$\text{NR}^2\text{R}^3 =$; X = Cl, MeCHCl, PhCHCl, Br, Pr, Bu.

Trichloroethylideneureas show a similar behaviour in the reactions with amines. Thus the amides **11a–c** add diethylamine, morpholine or piperidine at 20 °C to give diethylamide, morpholide and piperidide, respectively, of 1-diethylamino- (**71a**), 1-morpholino- (**71b**) and 1-piperidino-2,2,2-trichloroethylcarbamic acid **71c**.^{66, 68}



$\text{R}^1 =$, Me_2N ; $\text{R}^2 = \text{Et}$ (a), $(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$ (b), $(\text{CH}_2)_5$ (c).

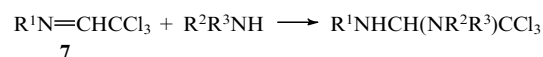
Phenoxy- and methoxycarbonylimines of trichloromethyl aryl ketones also add amines at the C=N bond yielding compounds **72a–c**.⁶²



X = PhO, Ar = 4- $\text{Cl}_3\text{CC}_6\text{H}_4$, Y = PhCH_2NH (a);
X = MeO, Ar = Ph, Y = BuNH (b), PhCH_2NH (c).

However, it was found that the reaction between phenyl phenyltrichloroethylidene carbamate **53** and secondary amines, for example, morpholine or diphenylamine, can occur without participation of the C=N bond. Under rigorous conditions, the phenoxy group is replaced by an amine residue to give the imines **52**.⁶² (see Section II.7).

The reactions of dialkyl *N*-trichloroethylidene phosphoramidates **7** with amines have also been studied in detail. It was shown^{41, 133} that these imines and their sulfur-containing analogues⁵¹ readily react with primary aromatic amines to give stable addition products, *O,O*-dialkyl *N*-(1-amino-2,2,2-trichloroethyl) phosphoramidates and -phosphoramidothioates.



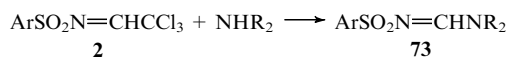
$\text{R}^1 = \text{PO}(\text{OAlk})_2$ (Alk = Me, Et, Prⁿ, Prⁱ, Buⁱ); $\text{PS}(\text{OMe})_2$;
 $\text{R}^2 = \text{H}$; $\text{R}^3 = \text{Ph}, \text{PhCH}_2, 4\text{-ClC}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4, 2,4,5\text{-Cl}_3\text{C}_6\text{H}_2$;
 $\text{R}^2 = \text{R}^3 = \text{Et}$; $\text{R}^2-\text{R}^3 = (\text{CH}_2)_5$.

The imines **7** add aniline, 4-chloroaniline and 4-methylaniline at room temperature; the reaction with 2,4,6-trichloroaniline occurs at ~80 °C and that with the least nucleophilic 2,4,6-trinitroaniline does not occur even at 100 °C.¹³³

Whereas acyl-, phosphoryl-, alkoxy- and carbamoyl-imines of trichloro- and dichloroacetaldehydes, trichloropropionaldehyde and other aldehydes react to give the products of addition to the azomethine bond, the trichloroethylidenearene-sulfonamides **2** can either give the products of addition to the C=N bond or undergo haloform decomposition.

Aniline,^{32, 124} trichloroaniline,⁴¹ morpholine,¹²⁴ *N*-ethylaniline,¹³⁶ *N*-methylaniline¹³⁶ and primary amines (methylamine, *tert*-butylamine, allylamine¹²⁹) yield products of nucleophilic addition. Diphenylamine does not react with chloral arylsulfonylimine.⁷³

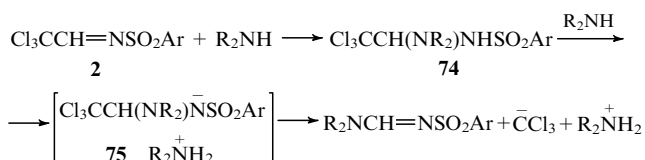
Meanwhile, highly basic dialkylamines induce haloform decomposition; this affords the products of substitution of the CCl_3 group, *N*-arylsulfonyl-*N'*,*N'*-dialkylformamides **73**,^{73, 134–136} in high yields.



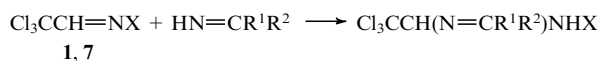
Ar = Ph, 4-MeC₆H₄, 4-ClC₆H₄; R = Me, Et, Pr, Bu, C₆H₁₃;
R–R = (CH₂)₂O(CH₂)₂, (CH₂)₅.

In the case of sulfonylimines, this reaction pathway is explained⁷³ by the fact that the ArSO₂ group, unlike acyl or alkoxy- and carbamoyl groups, cannot participate in conjugation and, hence, it cannot ensure stabilisation of the transition state. Therefore, CHCl₃ is ejected from the intermediate to give the compound **73**.

The reaction scheme proposed in the literature¹³⁶ includes the addition of amine to the double carbon–nitrogen bond and the reaction of the intermediate with a second amine molecule to give ionic species **75**. Fragmentation of this product yields formamide and a trichloromethyl anion.



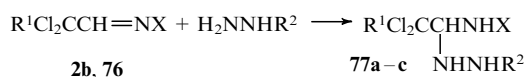
Imines add readily to the azomethine bond of the trichloroethylideneamides **1** and **7** giving rise to azomethines.^{37, 136}



X = MeCO, R¹ = R² = Ph; X = PO(OEt)₂; R¹ = R² = Ph;

R¹ = Ph, R² = 4-MeC₆H₄; R¹ = Me, R² = OEt.

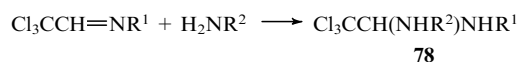
When 2,2-dichloropentanal *N*-acetylamine **76**³⁴ or the phenylsulfonylimine **2b**¹²⁴ are made to react with hydrazines, the addition products, *N*¹-aryl-*N*²-[1-amido-2-(trichloroethyl)- and -(2,2-dichloropentyl)]hydrazines **77a–c**, are produced in good yields.¹²⁴



X = PhSO₂, R¹ = Cl, R² = Ph (**77a**); X = MeCO, R¹ = Pr,

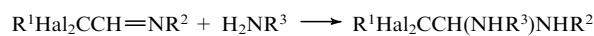
R² = Ph (**77b**), 2,4-(NO₂)₂C₆H₃ (**77c**).

N-2,2,2-Trichloro-, bromodichloro-, dibromochloro- and 2,2-dichloro-ethylideneamides and 2-*R*-2,2-dichloroethylideneamides of carboxylic, carbamic and sulfonic acids and of dialkyl phosphates add acid amides and substituted ureas on moderate heating giving rise to polyhaloalkanedylbisamides **78** and **79** in good yields.



R ¹	R ²	Ref.
MeCO	MeCO	137
MeCO	PhCO	37
MeCO	PhSO ₂	37
MeCO	(EtO) ₂ PO	37
MeCO	(PhO) ₂ PO	37
MeCO	(MeO) ₂ PS	138
MeCO	(Pr ⁱ O) ₂ PO	138
MeCO	(Pr ⁱ O) ₂ PS	138
MeCO	(MeO)(MeS)PO	138
MeOCO	MeOCO	39
MeOCO	(EtO) ₂ PO	39
PhCO	PhCO	137
(EtO) ₂ PO	(EtO) ₂ PO	133
(EtO) ₂ PO	MeCO	133
(EtO) ₂ PO	Cl ₃ CCO	133
(EtO) ₂ PO	Bu ^t CO	133
(EtO) ₂ PO	PhCO	133
(EtO) ₂ PO	4-MeC ₆ H ₄ CO	133
(EtO) ₂ PO	H ₂ NCO	133
(EtO) ₂ PO	Me ₂ NCO	133
(Pr ⁿ O) ₂ PO	MeCO	133
(Pr ⁱ O) ₂ PO	MeCO	133
(Pr ⁱ O) ₂ PO	H ₂ NCO	133
EtOCO	EtOCO	139
PhSO ₂	MeCO	140
PhSO ₂	PhCO	140
PhSO ₂	H ₂ NCO	8
PhSO ₂	—NC(O)(CH ₂) ₃	124
PhSO ₂	PhNHCO	124
PhSO ₂	PhSO ₂	74, 123

R ¹	R ²	Ref.
PhSO ₂	4-MeC ₆ H ₄ SO ₂	123
4-MeC ₆ H ₄ SO ₂	4-MeC ₆ H ₄ SO ₂	74
4-ClC ₆ H ₄ SO ₂	4-ClC ₆ H ₄ SO ₂	74

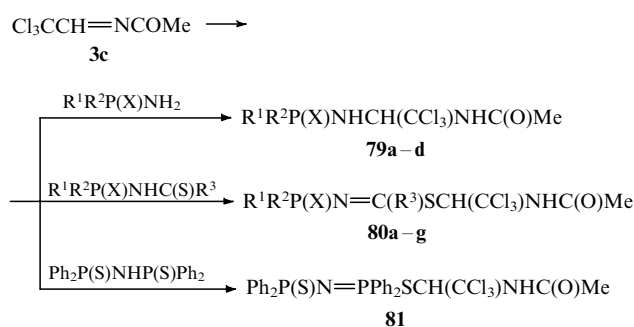


R ¹	Hal	R ²	R ³	Ref.
H	Cl	EtOCO	EtOCO	76
Br	Cl	EtOCO	EtOCO	109
Cl	Br	EtOCO	EtOCO	76
MeCHCl	Cl	MeOCO	MeOCO	45
MeCHCl	Cl	PhCO	MeOCO	45
Br	Cl	PhSO ₂	PhSO ₂	125, 78
Br	Cl	4-ClC ₆ H ₄ SO ₂	4-ClC ₆ H ₄ SO ₂	78
H	Cl	PhSO ₂	PhSO ₂	77, 126
H	Cl	4-MeC ₆ H ₄ SO ₂	4-MeC ₆ H ₄ SO ₂	77, 126
H	Cl	4-ClC ₆ H ₄ SO ₂	4-ClC ₆ H ₄ SO ₂	77, 126
CH ₂ Cl	Cl	MeCO	MeCO	130
CH ₂ Cl	Cl	MeCO	EtCO	130
CH ₂ Cl	Cl	MeCO	Pr ⁿ CO	130
CH ₂ Cl	Cl	MeCO	Me ₂ NCO	130
CH ₂ Cl	Cl	EtCO	EtCO	130
CH ₂ Cl	Cl	EtCO	Pr ⁿ CO	130
CH ₂ Cl	Cl	EtCO	Me ₂ NCO	130
CH ₂ Cl	Cl	ClCH ₂ CO	ClCH ₂ CO	130
CH ₂ Cl	Cl	PhCO	PhCO	130

This reaction can be performed for amides of aliphatic and aromatic carboxylic acids unsubstituted at the nitrogen atom as well as phosphoric and phosphorothioic amides and thioamides; *N*-substituted amides do not react with acetylmines even on refluxing for several hours.^{34, 138}

Detailed investigation of the reactions of the imines **7** with amides has revealed several characteristic features.¹³³ The capacity of amides for the addition sharply changes on variation of the electronegativity in the acyl residue. Comparison of the reactivities of acetamide, trichloroacetamide and the amide of pivalic acid demonstrates that the steric factor is insignificant. When the reaction mixture is heated to ~90 °C, pivalamide and acetamide add quantitatively, whereas trichloroacetamide reacts only at 167 °C.¹³³

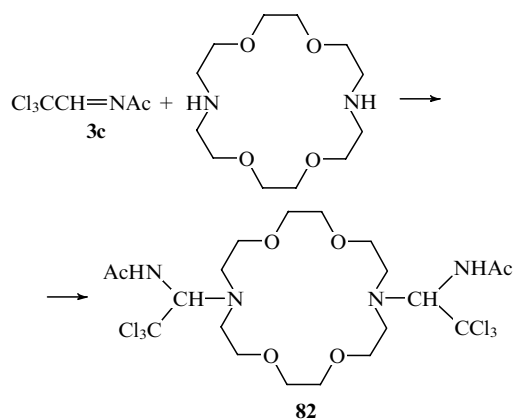
In a study of the addition of amides and thioamides of four-coordinate phosphorus to trichloroethylideneacetamide **3c**, it has been found that amides of phosphorus thioacids add more readily than the oxygen analogues to give the corresponding substituted acetamides **79a–d**.¹³⁸ *N*-Acylated amides and thioamides of phosphorus-containing acids do not enter into this reaction due to steric shielding and low nucleophilicity of the amide nitrogen atom. *N*-Thioacylamides of phosphorus acids, in which the sulfur atom of the C = S group possesses high nucleophilicity, undergo exothermic addition giving rise to carboximidothioates **80a–g**.¹³⁸ Addition at a sulfur atom also occurs in the reaction of the aldimine **3c** with bis(diphenylthiophosphinyl)amine; this affords phosphinimidothioate **81**.¹³⁸



Compound	R ¹	R ²	R ³	X
79a	Pr ⁱ O	Pr ⁱ O		O
79b	Pr ⁱ O	Pr ⁱ O		S
79c	MeO	MeO		S
79d	MeO	MeS		O
80a	Et	Et	Ph	S
80b	Pr ⁱ	Pr ⁱ	Ph	S
80c	Pr ⁱ	Pr ⁱ	4-MeOC ₆ H ₄	S
80d	Pr ⁱ	Pr ⁱ	3-NO ₂ C ₆ H ₄	S
80e	Et	Et	Ph	O
89f	Pr ⁱ	Pr ⁱ	Ph	O
80g	Pr ⁱ	Pr ⁱ	MeO	S

The reactivity of amides and thioamides of phosphorus acids towards chloral acetylamine increases in the sequence $R^1R^2P(X)NHC(O)R^3 < R^1R^2P(O)NH_2 < R^1R^2P(S)NH_2 < R^1R^2P(S)NHP(S)R_2^3 < R^1R^2P(X)NHC(S)R^3$.

Promising complex-forming reagents and biologically active compounds **82** have been prepared by the reaction of diaza-18-crown-6 with two equivalents of the imine **3c**.¹⁴¹



These compounds are smectic liquid crystals with fan texture.¹⁴¹

c. Reactions with S-nucleophiles

Much attention has been devoted to the reactivity of polyhaloaldehyde imines *N*-substituted by functional groups towards sulfur-containing nucleophiles (hydrogen sulfide, thiols, benzene thiols and thioamides), which add to imines very easily.

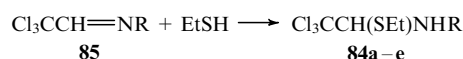
The *N*-acetalimine **3c** and dialkyl phosphoramidates **7d,e** react with hydrogen sulfide at 20 °C (ratio 2 : 1) to give bis(1-amido-2,2,2-trichloroethyl) sulfides **83a–c**.^{33, 37}



R = MeCO (**3c**, **83a**), (PrⁱO)₂PO (**7d**, **83b**), (BuⁱO)₂PO (**7e**, **83c**).

Unlike the reaction of imines with water, which yields stable hydroxy derivatives, in this case, the corresponding product with a thiol group has not been isolated. Evidently, this difference is related to the higher reactivity of *N*-(2,2,2-trichloro-1-sulfanylethyl)amides, formed in the first stage, towards the addition to the C=N bond of the initial imine compared to that of the hydroxy analogue.

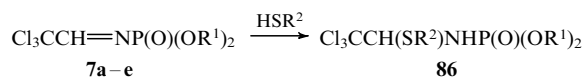
As has already been noted, the rate of the reaction of ethanethiol with chloral imines depends on the nature of the substituent at the nitrogen atom; the reaction gives *N*-(2,2,2-trichloro-1-ethylthioethyl)amides **84**.¹²² Later it has been shown that *O,O*-dimethyl *N*-(2,2,2-trichloroethylidene) phosphoramidothioate **85** also reacts with ethanethiol being thus converted into the compound **84e**.⁵¹



R = PhCH₂CO (**a**), EtCO (**b**), EtOCO (**c**), (EtO)₂PO (**d**), (MeO)₂PS (**e**).

Chloral arylsulfonylimines **2** add butanethiol and prop-2-ene-1-thiol.^{142, 143}

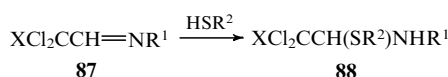
The reactions of the phosphorus-substituted imines of chloral **7** with thiols and diphenylphosphinothioic acid have been studied extensively.^{33, 50} These reactions occur on mixing the reactants without heating, the yields of *N*-(2,2,2-trichloro-1-*R*-thioethyl)amides **86** being quantitative.



R¹ = Me, Et, Prⁿ, Prⁱ, Buⁱ; R² = 4-ClC₆H₄, 4-NO₂C₆H₄, Et, Ph, Ph₂P(S).

The acylimine **3c**,³⁷ the imine **9**, functionally substituted in the acyl fragment,⁶⁵ methoxycarbonylimine **10a**³⁹ and 2,2-dichloroalkylideneacetamides **76**³⁴ also react with ethanethiol,³⁴ 4-nitrobenzenethiol,³⁹ benzenethiol^{34, 39} and 4-chlorobenzenethiol,⁶⁵ with heat evolution.

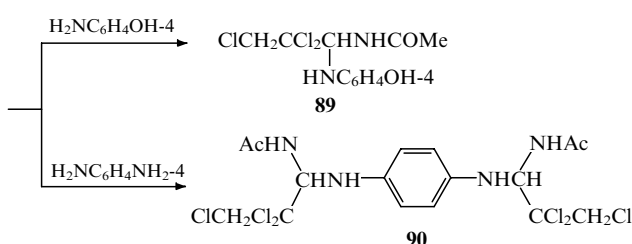
Imines **87** have been introduced *in situ* in the reaction with 4-chlorobenzenethiol; this gave *N*-[polychloroalkyl-1-(4-chlorophenylthio)]amides **88**.⁴⁵



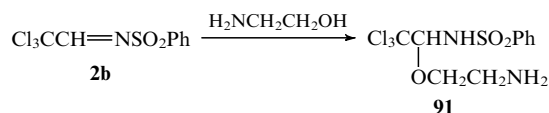
X = MeCHCl, PhCHCl; R¹ = MeOCO, PhCO; R² = 4-ClC₆H₄.

d. Reactions of imines with bifunctional O,O-, O,N-, S,N- and N,N-nucleophiles

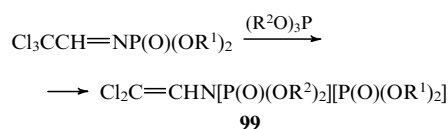
The reactions of trichloropropionaldehyde acetylamine with 4-aminophenol and *para*-phenylenediamine have been studied.¹³⁰ These reactions were found to involve the amino group of the aminophenol or both amino groups of phenylenediamine and to give 4-(1-acetamido-2,2,3-trichloropropyl)aminophenol **89** or bis(*N*-1-acetamido-2,2,3-trichloropropyl)-1,4-phenylenediamine **90**.



The sulfonylimine **2b** reacts with monoethanolamine at –20 °C giving compound **91** in a quantitative yield.¹⁴⁴



Treatment of the sulfonylimines **2** with triethanolamine or dimethylethanolamine induces only haloform decomposition of azomethines.⁷³ However, the ethoxycarbonylimine **10b** reacts with *N,N*-dimethylethanolamine giving rise to a stable addition product **92**.⁷³



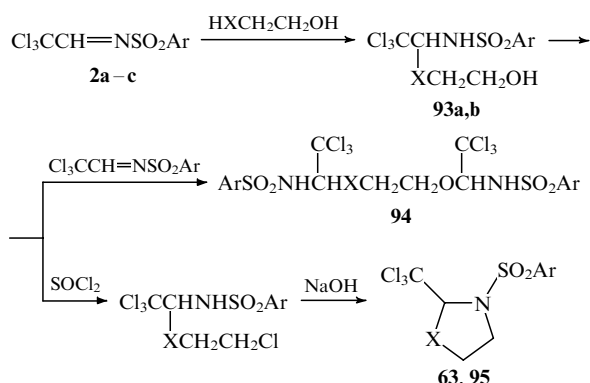
Only decomposition products — sulfamides, chloroform and aminothiol hydrochloride — have been isolated upon the exothermic reaction of the imines **2** with aminoethanethiol.¹⁴⁴

The reaction of ethylene glycol with the imines **3** has given both mono- (**93**) and bis-O-amidoalkylation products, [1,2-bis(1-arylsulfonamido-2,2,2-trichloroethoxy)ethanes **94**.¹⁴⁴

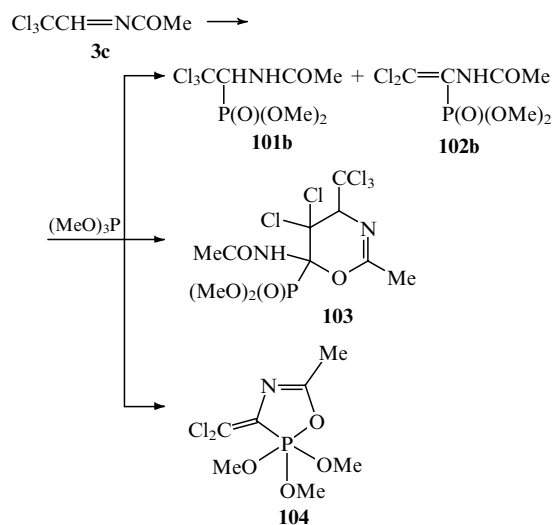
The reactions of dialkyl *N*-tetrachloroethylidene phosphoramidates with trimethyl and triethyl phosphites occur in a similar way and result in the formation of trichlorovinylamides $\text{Cl}_2\text{C}=\text{CClN}[\text{P}(\text{O})(\text{OR}^1)_2]$ ($\text{R}^1 = \text{R}^2 = \text{Me, Et}$; $\text{R}^1 = \text{Me, R}^2 = \text{Et}$).¹⁰²

The reaction of benzoylchloral imine **3a** with triethyl phosphite follows a different pathway yielding a complex mixture of products, in which diethyl 1-benzamido-2,2-dichlorovinylphosphonate **100** and diethyl 1-benzamido-2,2,2-trichloroethylphosphonate **101** have been detected.¹⁴⁷

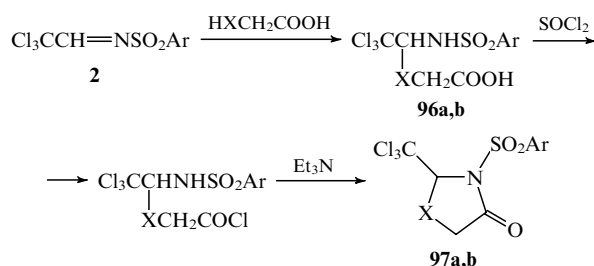
Trimethyl phosphite reacts with the imine **3a** giving only dimethyl 1-benzamido-2,2-dichlorovinylphosphonate **102**; the yield of this product is not given in the study cited.¹⁴⁸


$$\begin{array}{lcl}
 & \xrightarrow{(\text{EtO})_3\text{P}} & \text{Cl}_2\text{C}=\text{C}(\text{NHCOPh})\text{P}(\text{O})(\text{OEt})_2 \\
 & & \mathbf{100} \\
 \text{Cl}_3\text{CCH}=\text{NCOPh} & \xrightarrow{(\text{EtO})_3\text{P}} & \text{Cl}_3\text{CCH}(\text{NHCOPh})\text{P}(\text{O})(\text{OEt})_2 \\
 \mathbf{3a} & & \mathbf{101a} \\
 & \xrightarrow{(\text{MeO})_3\text{P}} & \text{PhCONHCP}(\text{O})(\text{OMe})_2 \\
 & & \text{CCl}_2 \quad \mathbf{102a}
 \end{array}$$

Detailed study of the reaction of the imine **3c** with trimethyl phosphite¹⁴⁸ showed that, depending on the reaction temperature, different products can be obtained.

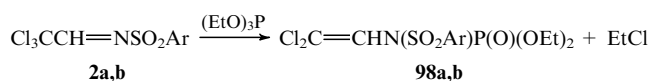


The sulfonylimines **2** react with glycolic and sulfanylacetic acids under mild conditions to give nucleophilic addition products, *O*- or *S*-(2,2,2-trichloro-1-arylsulfonylamino)glycolic **96a** and -thioglycolic **96b** acids, respectively.^{124, 145} When these products are treated with thionyl chloride and then with triethylamine, intramolecular cyclisation occurs giving rise to 3-arylsulfonyl-2-trichloromethyl-1,3-oxazolidin-4-ones **97a** and -1,3-thiazolidin-4-ones **97b**.

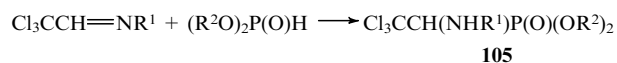


At $-13\text{ }^{\circ}\text{C}$, a mixture of dimethyl α -(*N*-acetyl)amino-2,2,2-trichloroethylphosphonate **101b** and dimethyl α -(*N*-acetyl)amino-2,2-dichlorovinylphosphonate **102b** is formed. The same reaction carried out without cooling ($40\text{--}45\text{ }^{\circ}\text{C}$) affords 1,3-oxazine **103**, and at $-40\text{ }^{\circ}\text{C}$, 1,2,4-oxaphosphazole **104** is obtained.¹⁴⁹

Organophosphorus acids and thioacids react with imines to give addition products.^{36, 37, 150, 151} *N*-Acetyl-,³⁷ *N*-ethoxycarbonyl-³⁶ and perchloroalkylsulfonyl-trichloroacetaldimines⁷¹ readily add various organophosphorus reagents. In the case of dialkyl phosphites, dialkyl 1-acetyl-, 1-ethoxycarbonyl- and perchloroalkylsulfonyl-amino-2,2,2-trichloroethylphosphonates **105** are formed.



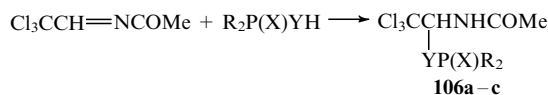
Ar = 4-MeC₆H₄ (**a**), Ph (**b**).



Dialkyl *N*-trichloroethylidene phosphoramidates react with trialkyl phosphites giving rise to bis(phosphorylated) compounds.^{99, 147}

The P-substituted imine **7b** also adds diethyl phosphite being thus converted into diethyl *N*-(1-diethoxyphosphoryl-2,2,2-trichloroethyl) phosphoramidate.⁵⁰

The reaction of diphenylphosphinic acid³⁷ with the acetyl-imine **3c** results in the formation of the O-addition product, 1-acetylaminotrichloroethyl diphenylphosphinate **106a**; in the case of phosphorothioic and -dithioic acids, S-addition products, namely, 1-acetyl-amino-2,2,2-trichloroethyl diphenylphosphino-dithioates and -thioates **106b,c** are produced.^{37, 150, 151}



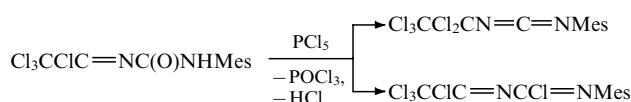
R = Ph, X = Y = O (**a**); R = Ph, MeO, EtO, PrⁿO, PrⁱO, X = Y = S (**b**); R = EtO, PrⁿO, PrⁱO, X = S, Y = O (**c**).

Phosphorus pentachloride is widely used in the reactions with derivatives of alkyl- and alkoxy-carbonylimines of polyhaloaldehydes in order to prepare isocyanates.^{62, 63} However, heating of *N*-perchloroethylideneureas **8**^{63, 64} with PCl₅ yields highly reactive halo-substituted diazadienes **107a,b** in 41%–76% yields.

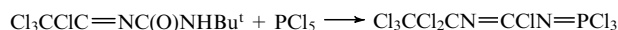


R = Prⁱ (**a**), Ph (**b**).

N-Mesityltrichloroethylideneurea reacts with phosphorus pentachloride to give a mixture of two isomers, carbodiimide and diazadiene.⁶³



An unusual reaction of *N*-*tert*-butyl-*N'*-perchloroethylideneurea with PCl₅ was discovered; in this case, phosphorus pentachloride acts simultaneously as a chlorinating and a phosphorylating agent.⁶⁴

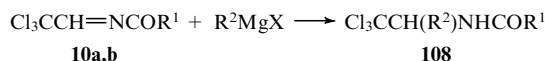


When *N*-dichlorophosphorylimines of polychloroaldehydes are treated with phosphorus pentachloride, (dichlorophosphorylthio)polyhaloethylideneimines **37a–d** are formed (see Section II.6).⁹⁹

3. Reactions of acylimines with organometallic compounds and metals

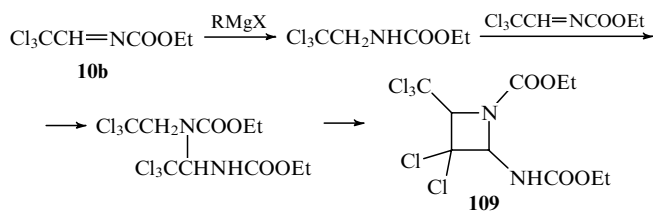
Reactions of polyhaloaldehyde imines with organometallic compounds have been less studied. A review has been published¹⁹ dealing mainly with reactions with organomagnesium and -lithium compounds.

In the general case, alkoxy-carbonylimines of chloral **10a,b** are converted into nucleophilic addition products **108** upon reactions with non-branched Grignard reagents.^{39, 152}



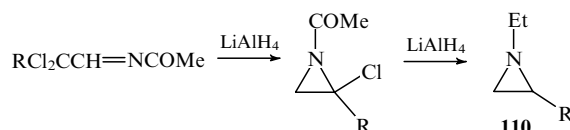
R¹ = MeO, EtO; R² = Me, Et, Pr, Bu, Ph, PhCH₂, CH₂ = CHCH₂.

Branched organometallic compounds reduce the imine **10b** to the corresponding amine, which adds to the initial compound to give the aminal. This product cyclises giving rise to azetidine **109**.¹⁵²



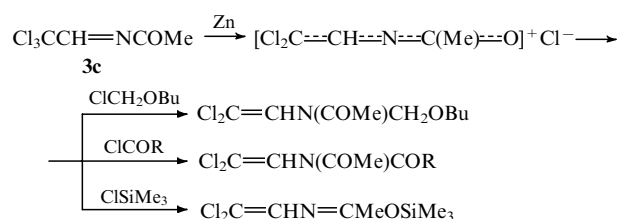
R = Prⁱ, Buⁱ.

Acylimines of halogenated aldehydes, like other halogenated imines, react with lithium aluminium hydride yielding substituted aziridines.^{19, 153, 154} In particular, *N*-acetyl-*R*-2,2-dichloroacetal-dimines are converted into 1,2-substituted aziridines **110**, in which the acyl group has been reduced to an ethyl group.



R = Pr, Bu, C₅H₁₁.

The behaviour of trichloroethylideneacetamide **3c** in reactions with zinc and electrophilic reagents has been studied.¹⁵⁵ The interaction of the imine **3c** with zinc affords a zinc-containing intermediate, which is a polydentate reagent with three nucleophilic centres — the carbon, nitrogen and oxygen atoms. The reaction of this intermediate with α-chlorinated ethers or acyl halides gives *N*-addition products, namely, substituted amides and imides. The reaction with chlorotrimethylsilane affords the O-attack product, *N*-(2,2-dichlorovinyl)-*N*-(1-trimethylsilyloxyethylidene)amine.

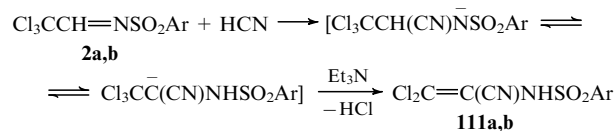


R = Me, Prⁱ, Buⁿ, Bu^t, Ph.

4. Reactions of imines with inorganic acids

The reactions of imines with hydrogen chloride have been studied in the greatest detail; it has been shown that polyhaloalkylidene-amides of dialkylphosphinic, carboxylic and carbamic acids are converted into chloroalkyl derivatives.^{33, 35, 37, 39, 46, 50}

On treatment of the sulfonylimines **2a,b** with hydrogen cyanide in the presence of triethylamine, 1-(arylsulfonylamino)-2,2-dichloroacrylonitriles **111a,b** are readily formed.¹⁵⁶

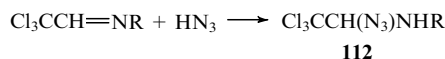


Ar = 4-MeC₆H₄ (**a**), Ph (**b**).

Similarly, when the benzoylimine **3a** is treated *in situ* with hydrogen cyanide, *N*-(2,2-dichloro-1-cyanovinyl)benzamide is produced.³⁸

On the other hand, the methoxycarbonylimine of trichloromethyl phenyl ketone adds hydrogen cyanide to give the amide Ph(CCl₃)C(CN)NHCOOMe.⁶²

The reaction of chloral imines with hydrazoic acid has been carried out; this gave 1-amino-2,2,2-trichloroethyl azides **112**.⁴⁰



R = PO(OEt)₂, COEt, COPr, COCH₂Ph, COOEt.

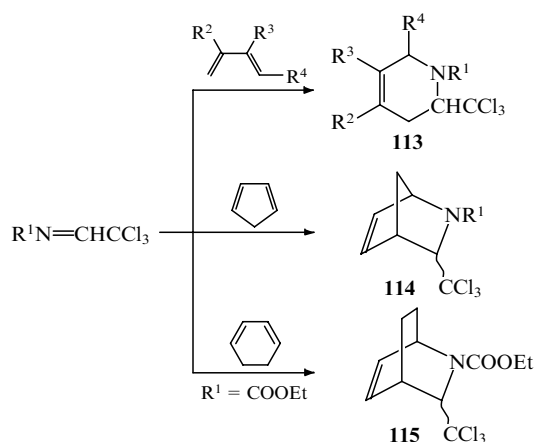
5. Cycloaddition reactions involving alkoxy-carbonyl-, acyl- and sulfonyl-imines of polyhaloaldehydes

The capability of acylimines, including halogenated ones, of exhibiting the properties of both dienophiles and dienes has been discussed in reviews.^{157, 158} Sulfonylimines can act as dienophiles.¹⁵⁸ It should be noted that these reviews^{157, 158} are far from embracing all publications devoted to this topic.

The high reactivity of chloral sulfonylimine **2a** towards dienes (2,3-dimethylbutadiene and cyclopentadiene) was first reported in 1964.¹⁵⁹ Reactions of chloral sulfonylimines with a large number of dienes (piperylene,¹⁶⁰ butadiene,¹⁶¹ cyclopentadiene,^{57, 158–164} dimethylbutadiene^{161, 162, 165} and isoprene^{160, 161}) have been studied much later. The cycloaddition products, 1-arylsulfonyl- and 1-alkoxycarbonyl-2-trichloromethyl-1,2,3,6-tetrahydropyridines **113** and *N*-arylsulfonyl- and *N*-alkoxycarbonyl-2-azabicyclo[2.2.1]hept-5-enes **114** are formed in 50%–94% yields.

N-Ethoxycarbonyl-2-azanorbornenes have been synthesised and some of their reactions, for example, dehydrochlorination and bromination, have been studied.^{161, 162}

N-Ethoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene **115** has been prepared¹⁶³ by the reaction of the imine **10b** with cyclohexadiene. Chloral 4-tolylsulfonylimine **2a** does not enter into the cycloaddition reaction with cyclohexadiene either on heating or under acid catalysis.¹⁶³

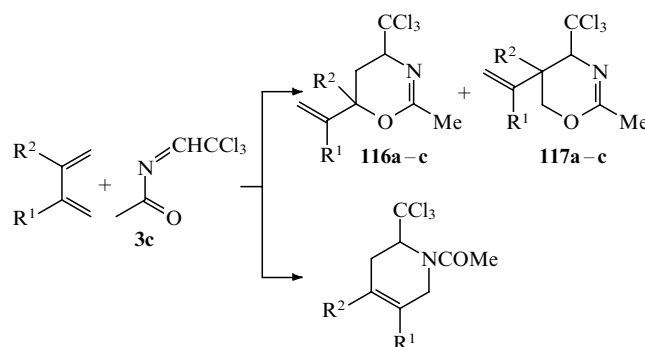


R¹ = MeOCO, EtOCO, MeCO, 4-XC₆H₄SO₂ (X = H, Me, Cl, MeO); R², R³, R⁴ = H, Me.

Cycloaddition of halogenated azomethines to non-symmetrical dienes occurs regiospecifically giving only one of the two possible isomeric heterocycles.¹⁶⁰

Study of the ¹H NMR spectra of 4-tolylsulfonyl-, alkoxy-carbonyl-, and acetyl-substituted 2-azanorbornenes and bicyclooctenes, prepared by the reactions of chloral imines **2a**, **3c**, and **10a,b** with cyclopentadiene and cyclohexadiene, showed that these bicyclic systems are mixtures of two isomers with *exo*- and *endo*-arrangement of the trichloromethyl group, the isomer ratio being dependent on the reaction temperature and on whether or not a Lewis acid is present in the system.^{161–164}

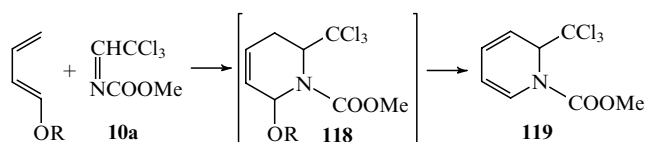
Acylimines of polyhaloaldehydes are able to participate in reactions with dienes not only as dienophiles but as heterodienes.¹⁶²



R¹ = R² = Me (**a**); R¹ = Me, R² = H (**b**); R¹ = OMe, R² = H (**c**).

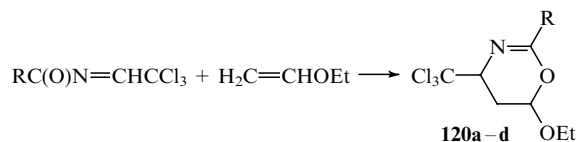
Thus the acetylimine **3c** reacts with 2,3-dimethyl-, 2-methyl- and 2-methoxybuta-1,3-dienes mainly as a diene to give mixtures of 5,6-dihydro-4*H*-1,3-oxazine derivatives **116a–c** and **117a–c**. When the acetylimine reacts with 2,3-dimethylbuta-1,3-diene, it acts as a dienophile; a compound of the type **113** was isolated.¹⁶⁵

The methoxycarbonylimine **10a** reacts with 1-alkoxydienes as a dienophile, the final reaction product, 1-methoxycarbonyl-2-trichloromethyl-1,2-dihydropyridine **119**, being formed in 84% yield upon elimination of an alcohol molecule with simultaneous migration of the double bond in the intermediate **118**.¹⁶⁶



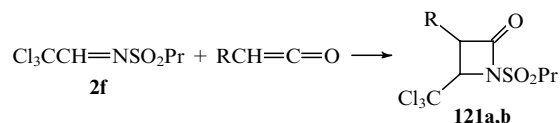
R = Me, Et.

Chloral acylimines introduced in reactions with vinyl ethyl ether act as heterodienes, which leads to 2-alkyl-6-ethoxy-4-trichloromethyl-5,6-dihydro-4*H*-1,3-oxazines **120a–d**.¹⁶⁷



R = Me (**a**), Et (**b**), Pr (**c**), Ph (**d**).

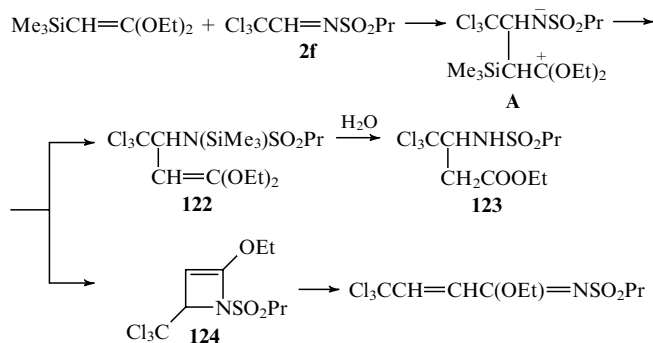
Sulfonylimines are capable of forming [2 + 2]-cycloadducts. Thus the imine **2f** reacts with trimethylsilyl ketene or ketene at room temperature to afford 1-propylsulfonyl-4-trichloromethyl-azetidin-2-ones **121a,b**.^{168, 169}



R = H (**a**), SiMe₃ (**b**).

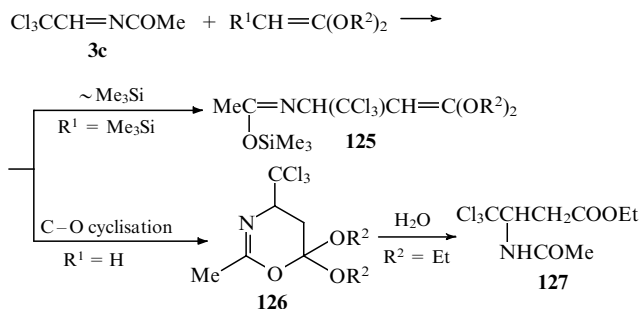
The reaction of the sulfonylimine **2f** with trimethylsilyl ketene diethylacetal gives 3-(*N*-trimethylsilylpropylsulfonylamino)-1,1-diethoxy-4,4,4-trichlorobut-1-ene **122** instead of a cyclic product. The compound **122** undergoes desilylation and hydrolysis yielding ethyl 3-(propylsulfonylamino)-4,4,4-trichlorobutanoate **123**.⁵³

The researchers⁵³ suggested that the reactions with trimethylsilyl ketene acetals occur *via* bipolar intermediate **A**, which is stabilised upon migration of the trimethylsilyl group. An alternative pathway in which the silyl group migrates in [2 + 2]-cycloadduct **124** formed from the intermediate **A** is also possible.



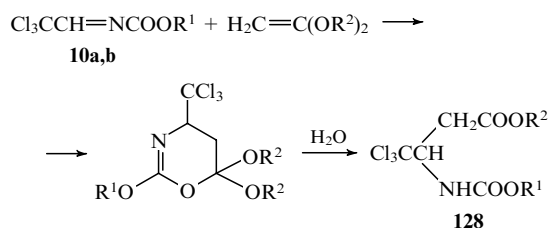
O-Silylated analogues of the compound **122**, 1 : 1 adducts **125**, have been isolated upon reactions of trimethylsilyl ketene dialkylacetals with the acetylimine **3c**. No desilylation was observed in this case.^{169, 170}

It is noteworthy that the reaction of the imine **3c** with ketene acetals occurs without heating and gives [2 + 4]-cycloadducts, 6,6-dialkoxy-2-methyl-4-trichloromethyl-5,6-dihydro-4*H*-1,3-oxazines **126**. Under hydrolysis conditions, they are converted into alkyl 3-(methylcarbonylamino)-4,4,4-trichlorobutanoates, for example, compound **127**.¹⁷⁰



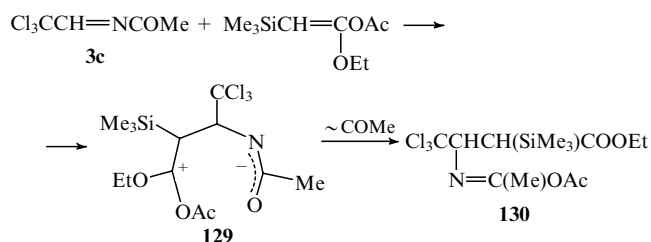
$\text{R}^1 = \text{H}, \text{Me}_3\text{Si}; \text{R}^2 = \text{Me}, \text{Et}, \text{Pr}^i$.

No cyclic products have been isolated after the reactions of the imines **10a, b** with ketene diethyl- and dimethylacetals. However, the formation of these products was proved by spectroscopy and by isolation of esters **128**, resulting from their transformations, in quantitative yields.¹⁷¹

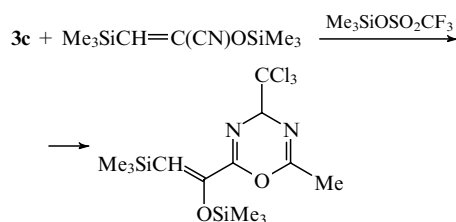


$\text{R}^1, \text{R}^2 = \text{Me}, \text{Et}$.

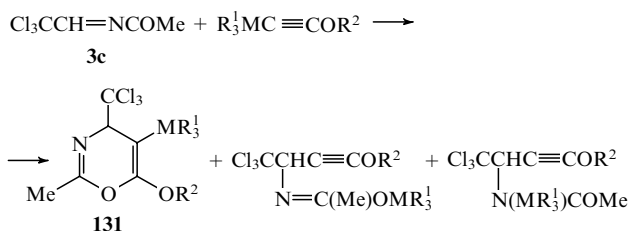
The reaction of chloral acetylimine **3c** with *O*-acetyl-*O*-ethyl-trimethylsilyl ketene acetal gives a 1 : 1 product **130**, which is an ester of substituted butyric acid containing a trimethylsilyl group at the α -position. Presumably, this product results from migration of the acetyl group in the intermediate **129**.¹⁷²



Meanwhile, 2-trimethylsilyloxy-3-trimethylsilylacrylonitrile reacts with the imine **3c** only in the presence of a catalyst, trimethylsilyl trifluoromethanesulfonate. The reaction involves the activated cyano group and results in [4 + 2]-cycloadduct, 4*H*-1,3,5-oxadiazine.¹⁷³



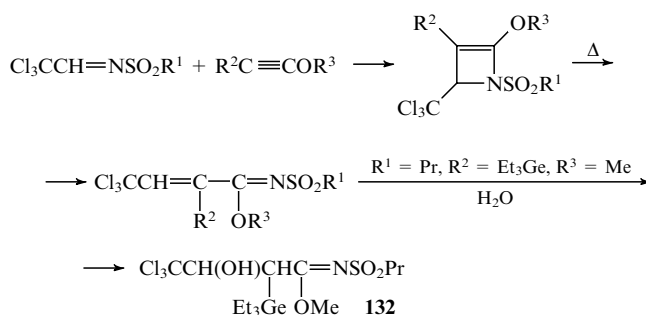
The reactions of imines with several acetylene derivatives have been studied. The chloral imine **3c** reacts with silicon- and germanium-substituted alkoxyacetylenes at room temperature without a catalyst to give a mixture of [4 + 2]-cycloadducts — 6-alkoxy-2-methyl-4-trichloromethyl-5-trialkylsilyl(trialkylgermyl)-4*H*-1,3-oxazines **131** — and *N*- and *O*-element-substituted acyclic compounds isomeric to them.¹⁷²



$\text{R}^1, \text{R}^2 = \text{Me}, \text{Et}; \text{M} = \text{Si}, \text{Ge}$.

It is noteworthy that the reactions of ethoxyacetylene and methoxymethylacetylene with the imine **3c** occur over a period of 20 h at room temperature and give [4 + 2]-cycloadducts of type **131**, 6-alkoxy-2-methyl-4-trichloromethyl-1,3-4*H*-oxazines.⁵²

The reactions of trialkylsilyl(germyl)ethoxyacetylenes with sulfonylimines follow the [2 + 2]-cycloaddition route. The resulting cycloadducts, 1-alkylsulfonyl-2-alkoxy-3-trialkylsilyl(germyl)-4-trichloromethyl-2-azetines, undergo ring opening under thermolysis conditions. The addition of water to the product of recyclisation of the triethylgermyl derivative of azetidine involves the C = C bond and gives compound **132**, the azomethine group remaining intact.⁵²



$\text{R}^1 = \text{Me}, \text{Pr}; \text{R}^2 = \text{Me}_3\text{Si}, \text{Et}_3\text{Si}, \text{Me}_3\text{Ge}, \text{Et}_3\text{Ge}; \text{R}^3 = \text{Me}, \text{Et}$.

Arylsulfonyl-, acetyl- and alkoxy-carbonyl-imines of chloral enter into cycloaddition reactions with azomethines and azadienes. Thus cycloaddition of diphenyl isocyanatophosphite to the imine **3c** yields cycloadducts, the dimerisation of which during the reaction leads to tricyclodecanes **133**.¹⁷⁴ When the imine **3c** reacts with dimethyl alkynylphosphonites, unstable cycloadducts are formed, which are hydrolysed to give linear derivatives **134**.



Chemical reaction scheme showing the synthesis of two phosphorus-containing heterocycles from a common starting material.

The starting material is $(\text{EtO})_2\text{P}(\text{O})\text{C}(\text{Cl})_3$ (trichloromethyl diethylphosphonate).

Reaction 1 (top): Reaction with R_3P yields a 5-membered heterocycle (phosphorinane derivative) containing a phenyl group, a trichloromethyl group, and a diethoxyphosphoryl group.

Reaction 2 (bottom): Reaction with a benzodioxane derivative (containing a PNEt_2 group) yields a 6-membered heterocycle (phosphorinane derivative) containing a phenyl group, a trichloromethyl group, and a diethoxyphosphoryl group, fused to a benzodioxane system.

$$\text{ArCH}=\text{N}(\text{O})\text{R} + \text{Cl}_3\text{CCH}=\text{NCOOEt} \longrightarrow \text{Product } \mathbf{135}$$

R = Ph; Ar = Ph, 4-NO₂C₆H₄, 4-MeOC₆H₄.

$$\text{ArSO}_2\text{N}=\text{CHCCl}_3 + (\text{Ar}'\text{CH}=\text{N})_2 \longrightarrow \text{ArSO}_2\text{N} \begin{array}{c} \text{Ar}' \\ \text{CCl}_3 \\ \text{Cl}_3\text{C} \\ \text{Ar}' \end{array} \text{NSO}_2\text{Ar}$$

2a-c **136**

Ar = Ph, 4-MeC₆H₄, 4-ClC₆H₄; Ar' = Ph, 4-MeOC₆H₄.

$$\begin{array}{c} \text{MeO} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{MeO} \end{array} + \text{Cl}_3\text{CCH}=\text{NC(O)Ph} \quad \mathbf{3a} \longrightarrow \begin{array}{c} \text{MeO} \\ | \\ \text{MeO}-\text{C}-\text{O} \\ | \quad \diagup \\ \text{Cl}_3\text{C} \quad \text{N}=\text{C}-\text{Ph} \end{array} \quad \mathbf{137} \longrightarrow \begin{array}{c} \text{MeO} \\ | \\ \text{MeO}-\text{C}-\text{O} \\ | \quad \diagup \\ \text{Cl}_3\text{C} \quad \text{N}=\text{C}-\text{Ph} \end{array}$$

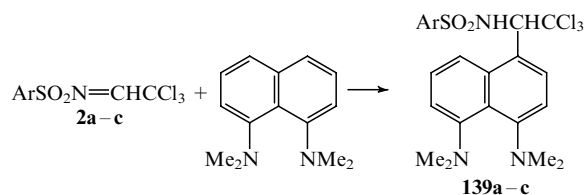
$$\text{FSO}_2\text{N}=\text{CHCCl}_3 + \text{Me}_2\text{C}=\text{CH}_2 \longrightarrow \begin{array}{c} \text{FSO}_2\text{NHCHCCl}_3 \\ | \\ \text{CH}_2\text{C}(\text{Me})=\text{CH}_2 \\ \mathbf{138} \end{array}$$
$$\text{ArSO}_2\text{N}=\text{CHCXC}_2 + \text{C}_6\text{H}_4\text{Y} \longrightarrow \text{ArSO}_2\text{NH}-\text{CH}(\text{CXC}_2)-\text{C}_6\text{H}_4\text{Y}$$

2, 13, 18

$$\text{ArSO}_2\text{N}=\text{CHCXCl}_2 + \text{R-Z} \longrightarrow \text{R-Z-CH(CXCl}_2\text{)NHSO}_2\text{Ar}$$

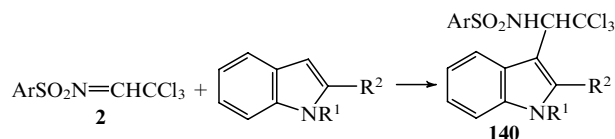
Ar = Ph, 4-ClC₆H₄, 4-MeC₆H₄; X = H, Cl; R = H, Cl, Me;
Z = S, O, NH, NMe.

The sulfonylimines **2a–c** react with 1,8-bis(dimethylamino)naphthalene without heating or catalysts giving rise to 4-[1-(arylsulfonylamino)-2,2,2-trichloroethyl]-1,8-bis(dimethylamino)naphthalenes **139**.¹⁸⁶



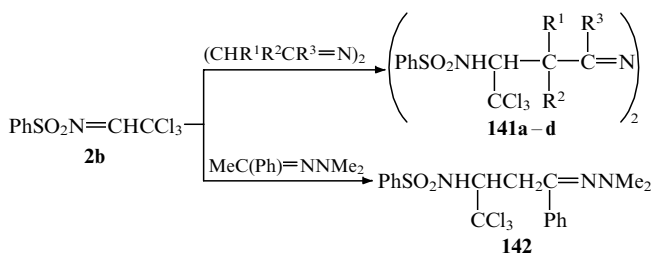
Ar = 4-MeC₆H₄ (**a**), Ph (**b**), 4-ClC₆H₄ (**c**).

The sulfonylimines **2** react equally easily with indole and its substituted derivatives being thus converted in good yields into compounds **140**, resulting from C-amidoalkylation at the 3-position.¹⁸⁷



Ar = Ph, 4-ClC₆H₄; R¹, R² = H, Me.

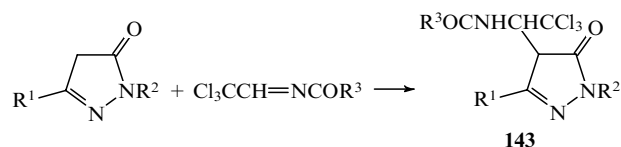
The sulfonylimine **2b** C-amidoalkylates azines and hydrazones of aldehydes and ketones containing α-methylene and α-methine groups; this leads to 3-arylsulfonylamino-4,4,4-trichlorobutyl ketazines **141a,b**, aldazines **141c,d** and hydrazone **142**.¹⁷⁷



R¹ = R² = H; R³ = Me (**a**), Ph (**b**); R¹ = R² = Me, R³ = H (**c**);

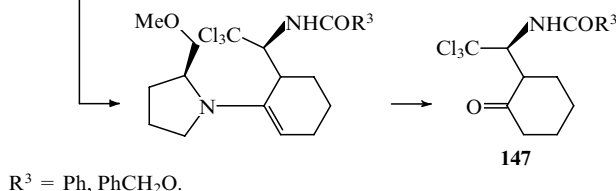
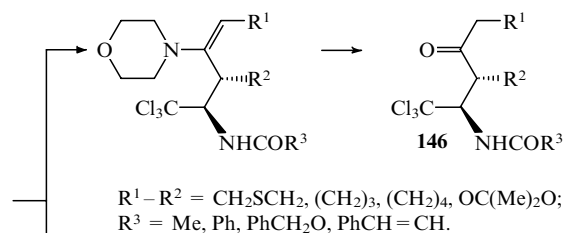
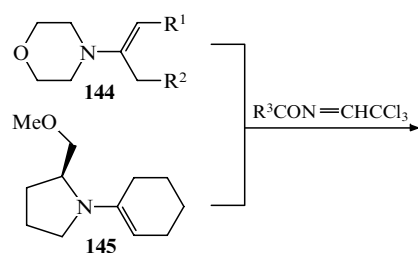
R¹ = R³ = H, R² = Et (**d**).

The use of polyhaloaldehyde imines for C-amidoalkylation of heterocyclic compounds extends the capacity for the preparation of new derivatives. Thus chloral imines of carboxylic and carbamic acids have been used in C-amidoalkylation of pyrazolones. This resulted in the synthesis of 2-aryl(alkyl)-4-[1-acetyl(benzoyl)aminoethyl]-2,2,2-trichloro-3-alkyl(phenyl)-2-pyrazolones **143** in high yields.¹⁸⁸

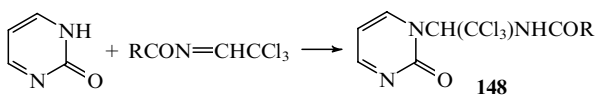


R¹ = Me, Et, Bu^t, Ph; R² = Ph, 2,4,6-Cl₃C₆H₂, Me; R³ = Me, Ph, OEt.

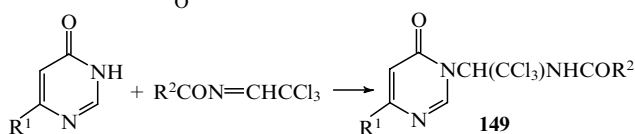
The reactions of N-acyl-N-(2,2,2-trichloroethylidene)amines (which were prepared *in situ* from the corresponding 1,2,2,2-tetrachloroethylamides) with enamines **144** and **145** occur with high diastereo- and enantioselectivity yielding amidoalkylation products, which are hydrolysed to give chiral 2,2,2-trichloroethylamides **146**, **147**.¹⁸⁹



Reactions of various types of monohydroxypyrimidines with N-(benzoyl)trichloroacetalimine **3a** and other acylimines **3**, generated *in situ* from the corresponding tetrachloroethylamides have been studied.^{190,191} It was found that 2-hydroxypyrimidines and 4-hydroxypyrimidines containing no substituents at the 2-position form the products of amidoalkylation of the NH group — 1-(1-acylamino-2,2,2-trichloroethyl)-2- (**148**) and -4-hydroxypyrimidines **149**, respectively.¹⁹⁰



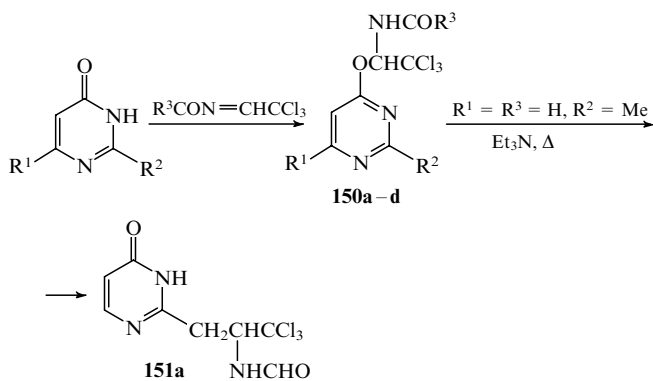
R = Ph, H, Bu^t,



R¹ = H; R² = Ph, H, Bu^t, , 4-ClC₆H₄;

R¹ = Me; R² = Ph, H, Bu^t, .

In the case of 2-alkyl-4-hydroxypyrimidines, the reaction involves the oxygen atom and gives O-(1-acylamino-2,2,2-trichloroethyl)-4-hydroxypyrimidines **150a-d**; in the opinion of the authors cited,¹⁹⁰ this is due to the steric shielding of both nucleophilic centres at the nitrogen atoms.

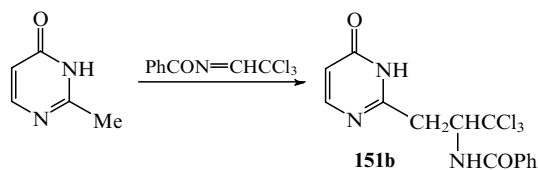


R¹ = H, R² = Me; R³ = H (**a**), Ph (**b**);

R¹ = Me, R² = Prⁱ; R³ = Ph (**c**), 4-ClC₆H₄ (**d**).

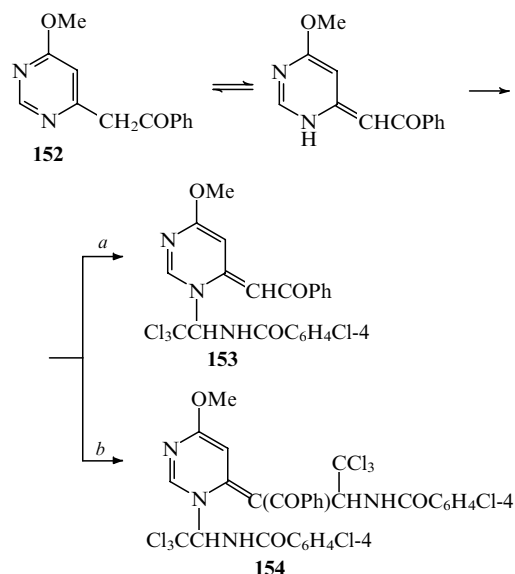
Long refluxing of the imine **3a** with 4-hydroxy-2-methylpyrimidine induces C-amidoalkylation involving the methyl group of the pyrimidine, which affords 2-(2-benzamido-3,3,3-trichloropropyl)-4-hydroxypyrimidine **151b**.¹⁹⁰ The product **151a** with a

similar structure was also isolated when the pyrimidine **150a** was heated in the presence of triethylamine.¹⁹⁰



C-Amidoalkylation of 4-hydroxy-6-methylpyrimidine does not proceed even under rigorous conditions.¹⁹⁰

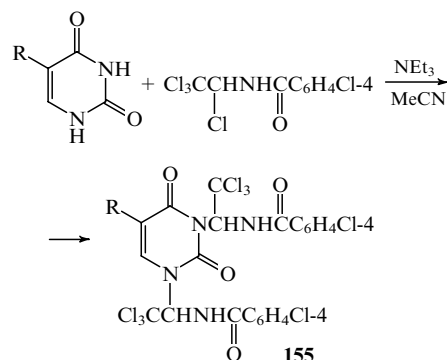
When 4-methoxy-6-phenacylpyrimidine **152** reacts with *N*-(1,2,2,2-tetrachloroethyl)amide of 4-chlorobenzoic acid in the presence of Et₃N, monoamidoalkylation product **153** is formed. When **152** reacts with the imine **3j**, the activated methylene group in the side chain and the ring nitrogen atom may be amidoalkylated simultaneously giving rise to compound **154**.¹⁹¹



(a) Cl₃CCHClNHCO₂C₆H₄Cl-4, Et₃N, Δ; (b) Cl₃CCH=NCOC₆H₄Cl-4 (**3g**).

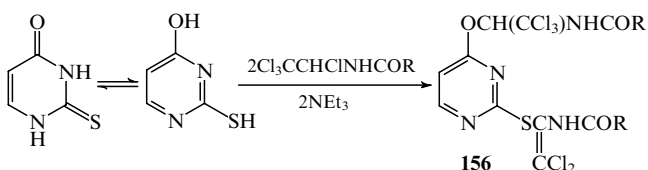
C-Amidoalkylation of the closest analogues of pyrimidine **152** — 4-dimethylamino-, 4-methyl-, 4-benzoylmethyl-6-(benzoylmethyl)-pyrimidines — has been accomplished by introducing these compounds into reactions with *N*-(1,2,2,2-tetrachloroethyl)amide of 4-chlorobenzoic acid in acetonitrile in the presence of triethylamine.¹⁹¹ The alkylation involves the benzoylmethylene group and affords compounds of the type **153** — 4-dimethylamino-, 4-methyl-, 4-benzoylmethyl-6-[3,3,3-trichloro-2-(4-chlorobenzoylamino)-1-benzoylpropyl]pyrimidines.¹⁹¹

Under similar conditions, amidoalkylation of some 5-R-uracils by tetrachloroethylamides of benzoic acids involves both nitrogen atoms and affords 1,3-bis[2,2,2-trichloro-1-(4-chlorobenzoylamino)ethyl]-5-R-pyrimidine-2,4-diones **155**.¹⁹²



R = H, Ph, OMe.

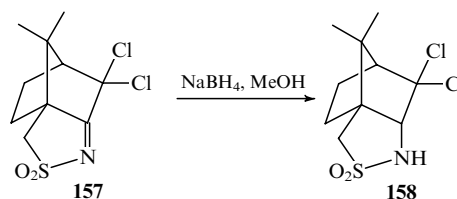
The reaction of 2-thiouracil with tetrachloroethylamides in the presence of triethylamine follows a more complex pathway, which includes not only amidoalkylation at the nitrogen and sulfur atoms but also dehydrochlorination; this gives 2-[(1-amido-2,2-dichlorovinyl)thio]-4-(1-amido-2,2,2-trichloroethoxy)pyrimidines **156**.¹⁹³



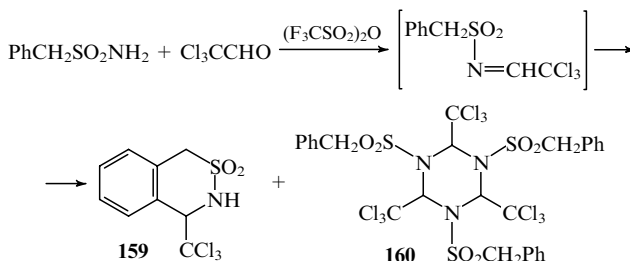
R = Bu^t, Ph, C₆H₄Cl-4, OMe.

7. Other reactions of polyhaloaldehyde imines

Reduction of imines presents interest as a method for the synthesis of amines. Only a single example of diastereoselective reduction of an azomethine group in cyclic dichlorocamphorsulfonylimine **157** to camphorsultam **158** (yield 93%–97%) was reported.¹⁹⁴ In the case of the corresponding bromo-derivative, debromination is the predominant reaction route.



It was found¹⁹⁵ that when benzylsulfonamide reacts with chloral in the presence of trifluoromethanesulfonic anhydride or another similar reagent, the chloral benzylsulfonylimine formed at the first stage undergoes intra- and intermolecular heterocyclization under the reaction conditions to afford 3,4-dihydro-1*H*-1,3-benzothiazine 2,2-dioxide **159** (yield 3%–58%) and 1,3,5-tribenzylsulfonylhexahydrotriazine **160** (yield 17%).



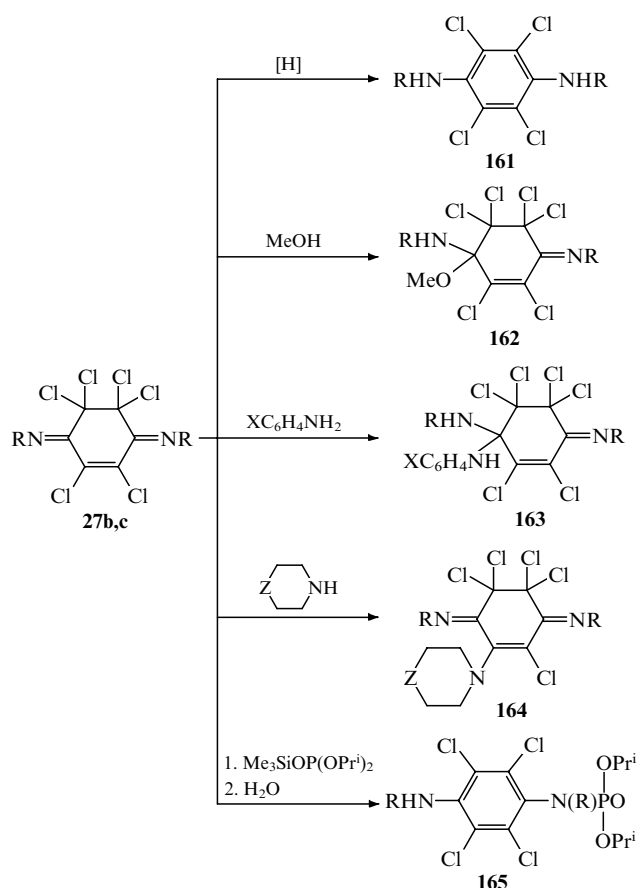
8. Reactivity of arylsulfonyliminopolychlorocyclohexenes

The reactions of bis(arylsulfonylimino)-2,3,5,5,6,6-hexachlorocyclohex-2-enes **27b,c** with reducing agents, organophosphorus and organosilicon compounds, alcohols, primary aromatic amines, secondary cyclic amines^{196, 197} and with hydrazoic acid¹⁹⁸ have been studied.

When the compounds **27b,c** react with Na₂S₂O₄, zinc in acetic acid or with dialkyl phosphites, elimination of two chlorine atoms from the 5- and 6-positions occurs to give the benzoid structure **161**.¹⁹⁶

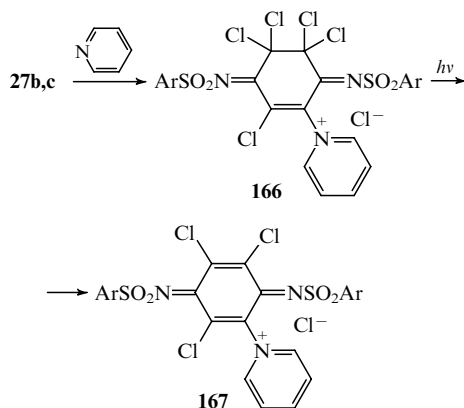
The reactions with methanol give products **162** resulting from addition to one azomethine bond. It was shown that 1,4-bis(arylsulfonylimino)hexachlorocyclohex-2-enes **27b,c** do not react with any other alcohols.¹⁹⁶

The reactions of the bis(sulfonylimines) **27b,c** with aromatic amines containing no electron-withdrawing groups in the aromatic ring also involve the addition to the C=N bond and give rise to compounds **163**.¹⁹⁶



The reactions with morpholine and piperidine occur as nucleophilic substitution of the chlorine atom at the sp^2 -hybridised carbon atom of the bisimine and give products **164**.¹⁹⁶ Two processes — elimination of two chlorine atoms and 1,6-addition to the system of conjugated double bonds — occur simultaneously in the reactions of **27b,c** with trimethylsilyl diisopropyl phosphite. The addition products are subsequently hydrolysed with elimination of the trimethylsilyl group, which leads to compounds **165**.¹⁹⁶

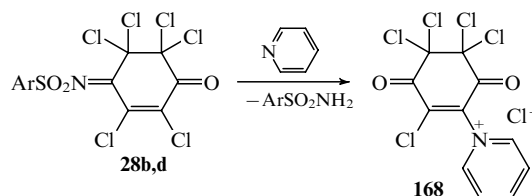
When the bis(sulfonylimines) **27b,c** react with pyridine, this gives the products of substitution of the vinylic halogen atom, *N*-[3,6-di(arylsulfonylimino)-2,4,4,5,5-pentachlorocyclohex-1-en-yl]pyridinium chloride **166**; on exposure to UV radiation or under electron impact, these compounds eliminate two chlorine atoms to give quinone structures, *N*-[3,6-di(arylsulfonylimino)-2,4,5-trichlorocyclohex-1,4-dienyl]pyridinium chlorides **167**.¹⁹⁶



$\text{Ar} = 4\text{-MeC}_6\text{H}_4 \text{ (b)}, 4\text{-ClC}_6\text{H}_4 \text{ (c)}.$

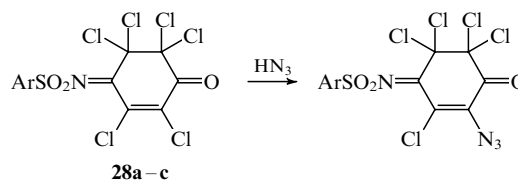
The reaction of 4-arylsulfonyliminohexachlorocyclohex-2-en-1-ones **28b,d** with pyridine results in the isolation of arenesulfonamides and compounds **168**, formed upon the substitution of a pyridinium ion for the chlorine atom in the resulting 1,4-dioxo-2,3,5,5,6,6-hexachlorocyclohex-2-ene.¹⁹⁷

It is of interest that 4-arylsulfonylimino-2,2,3,3-tetrachloro-1-oxo-1,2,4,4-tetrahydronaphthalenes **29** do not react with pyridine.



$\text{Ar} = 4\text{-ClC}_6\text{H}_4 \text{ (b)}, 4\text{-MeC}_6\text{H}_4 \text{ (d)}.$

The reaction of the imines **28a–c** with hydrazoic acid occurs as nucleophilic replacement of the chlorine atom at the sp^2 -hybridised carbon atom located at the 2-position, accompanied by competing elimination of chlorine with restoration of the benzoid structure.¹⁹⁸



$\text{Ar} = \text{Ph} \text{ (a)}, 4\text{-MeC}_6\text{H}_4 \text{ (b)}, 4\text{-ClC}_6\text{H}_4 \text{ (c)}.$

V. Conclusion

Analysis of the published data indicates that *N*-functionally substituted halogenated imines are highly stable and can be prepared by reactions of *N,N*-dihaloamides with 1,2-polyhaloethenes, transformation of an isocyanate bond and by other non-trivial methods, which require further development.

Electronegative substituents at the $\text{C}=\text{N}$ bond account for the high reactivity of *N*-functionally substituted halogenated imines towards nucleophiles. A specific feature of these reactions is that nucleophiles attack the sp^2 -hybridised carbon atom of the $\text{C}=\text{N}$ bond. The enhanced electrophilicity of the $\text{C}=\text{N}$ bond in polyhaloaldimines permits the use of acyl- and sulfonyl-imines for *C*-amidoalkylation of aromatic and heterocyclic compounds. Search for conditions under which acyl- and phosphonyl-imines of polyhalogenated aldehydes and ketones could be involved in similar reactions appears to be topical task.

Chloral acyl- and alkoxycarbonyl-imines can enter into cycloaddition reactions as heterodienes but can also act as dienophiles. Unfortunately, imines of the largest class, polyhaloalkylphosphonylimines, have not been studied in cycloaddition reactions.

Halogen-containing imines are of interest regarding investigation of the enamide–imine tautomerism and *syn–anti* isomerism of azomethines and determination of the energy parameters of tautomerisation and isomerisation.

The synthetic potential of imines is now far from being completely utilised. The data on the reactivity of halogenated imines can serve as the basis for targeted design of required structures with important biogenic groups: acyl-, phosphonyl- and sulfonyl-amide groups and polyhalomethyl groups. It can be expected that more extensive studies along this line would permit the researchers to perform intra- and intermolecular heterocyclisation of imines, reactions involving haloalkyl groups, etc.

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^e — *Chem. Heterocycl. Compd. (Engl. Transl.)*

Combustion of char-forming polymeric systems

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Abstract. Chemical reactions occurring in the combustion and decomposition of char-forming polymeric systems and the effects of the nature of the polymer and additives on the reaction pathways are discussed. The thermal characteristics of the chars formed upon combustion are considered. The bibliography includes 86 references.

I. Introduction

The lowering of ignitability and flammability of polymers and the creation of fire retarding materials is an urgent problem which demands immediate solution. Regulation concerning the prohibition or limited use of flammable polymeric materials in industrial and civil engineering, construction of means of transportation (aircraft, automobiles, railway cars, ships), electrical and electronic engineering and production of special-purpose materials have been passed in many countries.

This circumstance has given a strong impetus to the studies aimed at elaboration and practical application of fire retarding polymeric materials. In the coming years, many commodities prepared on the basis of polymeric materials will be manufactured only in a fireproof form.

The production of fire retarding polymeric materials is following three main directions, *viz.*, synthesis of fire retarding polymeric materials, chemical and physical modification of polymers and the use of fire retardants.

The first trend, which holds especially great promise, consists in the synthesis of polymers of two types, *viz.*, polymers yielding incombustible gases upon decomposition and highly thermostable rigid-chain polymers. The first group of compounds includes fluorine- or nitrogen-containing polymers (*e.g.*, fluoroplastics,

nitroso and triazine elastomers)¹ and organoelement polymers (*e.g.*, polyphosphazenes, polysiloxanes and polycarboranes).^{2–4} The second group comprises polymers containing heterocyclic fragments, such as polysulfones (arylox, bakelite, radel, udel, *etc.*), polyphenylene sulfides, liquid-crystalline polyesters (vectra, econol, *etc.*), polyamides (phenilon, kevlar, polymers containing mesogenic groups), polyimides (kapton, epilex, ultem, torlon, *etc.*) and polyheterocycles, such as polypyrazoles, polyoxazoles, polybenzimidazoles, polybenzoxazoles, polyquinoxalines and polyimidazobenzophenanthrolines (the BBB polymer).⁵ Rigid-chain polymers combine low flammability and high thermostability with other valuable properties, *e.g.*, high chemical and radiation stability, high durability and dielectric characteristics.

Studies^{6–8} of effects of the chemical structure and conditions of preparation of polymers on their flammability and thermal characteristics have demonstrated a good correlation between the yields of non-volatile residues formed upon decomposition of the polymers and their flammability (oxygen index, OI). The yields of carbonised products depend on the chemical structures of polymers.^{6,7} The smaller the number of flexible 'hinge' groups in the polymer molecule the higher the char yield. It is of note that the flammability of poly(ester imides) depends on the method used for their synthesis.⁸ It was shown also that the thermal stability of a polymer is determined by the nature of its end groups and the presence of admixtures.

Unfortunately, the high cost of organoelement and high-performance polymers restricts the fields of application of materials based on them. Today, the production of low-cost polymers which employs less power-consuming synthetic procedures and less expensive monomers seems to have especially great potential.

Chemical and physical modification of polymers is the second trend in the production of fire retarding polymeric materials. In order to decrease the flammability of carbochain polymers, carbochain monomers are copolymerised with halogen- or phosphorus-containing monomers. In addition, chemical modification of synthetic polymeric products can be achieved by treating them with various reagents: this can be effected, *e.g.*, by bromination, chlorination, phosphorylation^{9–12} and polymer-analogous transformations aimed at incorporating halogen- and phosphorus-containing groups into polymers and copolymers.^{13–15} This approach was used to obtain brominated polystyrene¹⁶ and polyphenylene oxides,¹⁷ copolymers of vinyl acetate, ethylene and derivatives of halogen-containing acids¹⁸ and phosphorus-containing epoxy resins (PER).¹⁹

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Physical modification of polymers is based on the treatment of the polymer surface with various types of energy (plasma, thermal and laser beams, UV or IR irradiation, *etc.*). Using this approach, one can obtain fire retarding polymeric materials based on various polymers.²⁰ Unfortunately, modification very often induces significant changes in the properties of the polymers and cannot be used to decrease the flammability of industrial polymers.

The third approach to the preparation of fire retarding polymeric materials, which employs fire retardants, is the most popular and efficient way.

Polybrominated biphenyls and diphenyl oxides are the most widespread compounds endowed with the ability to decrease the flammability of industrial plastic materials. However, there is evidence that combustion and thermal degradation of polymeric materials based on them is accompanied by the formation of highly toxic products.^{21–23} Thus, the need arose for fire retarding materials devoid of low-molecular-weight polybrominated compounds. High-molecular-weight bromine-containing fire retardants meet this demand. It was established^{16, 17, 23} that thermal degradation of brominated polyphenylene oxides and polystyrene was not accompanied by the formation of highly toxic products either in the presence or in the absence of plastic materials. Fire retarding styrene-based plastics have been developed which contain high-molecular-weight fire retardants, their properties are comparable with those of styrene-based materials containing low-molecular-weight fire retardants.²⁴

II. Intumescent systems

The problem of formation of toxic compounds in the combustion of polymeric materials is completely eliminated if intumescent systems (IS) devoid of polybrominated diphenyls or diphenyl oxides are used. An IS represents a mixture of compounds which form foamed cokes on the polymer surface upon heating and thus prevent combustion. The fire-resistance due to foamed coke layers is associated with thermal insulation and barrier properties in mass transfer.^{25, 26}

The superficial foamed coke layer is formed as a result of complex physical and chemical processes, each contributing to the decrease in the polymer flammability. The factors affecting the flammability of IS-containing polymers can be classified as follows:

1. Reversal of the route of the polymer thermal degradation towards the formation of foamed cokes and incombustible volatile products.
2. A change in the heat balance of combustion due to the thermal effects of chemical reactions occurring on intumescence and dilution of fuels with incombustible gaseous products.
3. Thermal insulation of the polymer surface from reverse heat flows.
4. Prevention of fuel diffusion into the combustion zone.
5. Prevention of oxygen diffusion from the environment to the polymer surface.

The first two factors exert their influence on combustion through chemical reactions between individual components of the polymeric composition, while the rest are closely connected with the physical structure of the foamed coke.

III. Types of intumescent systems

1. The use of intumescent systems for decreasing the flammability of carbochain polymers

The following compounds can be used as IS components:^{27, 28} inorganic acids (in free form or as derivatives which generate acids on heating), polyhydroxy derivatives, nitrogen and halogen derivatives.

This classification is arbitrary, since any component may contain several functions. The presence of a nitrogen- or a halogen-containing compound is not always necessary. It is

believed that acids favour carbonisation of polyhydroxy derivatives (carbon source) due to dehydration, whereas nitrogen- or halogen-derivatives (foaming agents) facilitate intumescence of the system due to intense degradation associated with evolution of large quantities of gaseous compounds.

IS that are to be used in polymeric materials should meet the following requirements:²⁹

1. IS must be resistant to temperatures above 200 °C, which are often used in polymer processing.
2. Thermal degradation of polymers must not interfere with the foaming reaction.
3. IS should produce a protective foamed coke layer over the whole polymer surface despite the dilution of the additive with the polymer.
4. IS should not induce any significant changes in the physical and mechanical properties of the polymer or interact with other additives (pigments, stabilisers, *etc.*).
5. The mineral acid formed upon heating of the corresponding derivative used as IS should be high-boiling and should not be a strong oxidant.

Phosphoric acid derivatives (amides, esters, imides) meet these requirements most completely. Of these, high-molecular-weight ammonium polyphosphate (APP), $-\text{P}(\text{ONH}_4)(\text{O})\text{O}-$, where $n = 20-3000$, is the most popular fire retardant.³⁰

The IS containing APP used for decreasing the flammability of carbochain polymers are listed in Table 1. Several other compounds tested as fire retardants for various polymers are listed in Table 2.

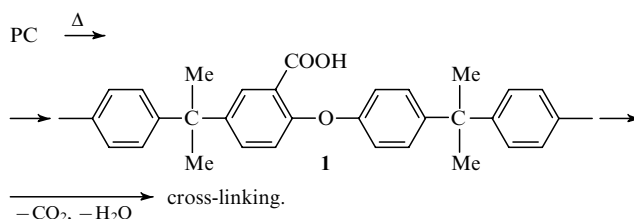
These data suggest that efficient reduction of flammability demands a high degree of polymer filling, which inevitably increases its cost, deteriorates its physical and mechanical properties and impedes its processing.

The mechanisms of action of IS systems are different and depend on the structure of the polymer and the additives. The polymer can take part in the formation of the carbonised layer on the surface of the burning material, but the foamed coke layer can be also formed in the absence of the polymer.

2. The use of intumescent fire retardants for the preparation of polymeric materials based on polycondensation polymers

Polycarbonates are widely employed in electrical engineering, instrument making and automobile construction. These compounds are endowed with valuable and unique properties, such as higher thermal stability and lower flammability compared with polyalkenes and styrene-based plastic materials. Many branches of industry have a great demand for fire retarding polymeric materials based on polycarbonates (PC). The flammability of PC can be lowered if alkali metal salts of organic acids are used as additives. The preparation of materials with OI above 35% demands only small quantities of the additive ($\leq 3\%$).

The mechanism of action of these additives has been studied.^{48, 49} It is known that thermal degradation of polycarbonates occurs through two main routes. The first route consists in isomerisation followed by the formation of aryloxybenzoic acids **1**. Further thermal conversions of the thermal degradation products yield ethers, xanthenes and cross-linked structures:



The second route involves intramolecular transfer reactions, resulting in cyclic oligomers of type **2**. The reaction of product **2** with water and subsequent elimination of CO_2 yield phenols:

Table 1. APP-based intumescent systems.

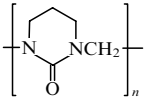
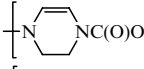
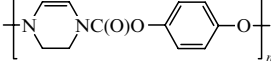
Polymer	Additive	Mass ratio APP : additive	APP content in the polymer (%)	OI	Ref.
Polypropylene	a condensation product of substituted ureas with formaldehyde	2 : 1	25–30	34–35	30–33
	ethylenebis[tris(2-cyanoethyl)]phosphonium bromide	2 : 1	30	30	34
		3 : 1	20	26.5	35
		3 : 1	20	25	35
		3 : 1	20	26.5	36
		3 : 1	20	25.5	36
		3 : 1	20	23.5	36
	a condensation product of aromatic diisocyanates with pentaerythritol and melamine	—	24	37	32
	pentaerythritol phosphate	7 : 3	30	26	37
	pentaerythritol phosphate, melamine	6 : 3 : 1	30	38	37
Shock-resistant polystyrene	ethylenebis[tris(2-cyanoethyl)]phosphonium bromide	1 : 1	30	30	34
Polystyrene	a condensation product of aromatic diisocyanates with pentaerythritol and melamine	—	24	37	38
Polyacrylonitrile	hexabromocyclododecane	1 : 1	20	28–30	39

Table 2. Fire retardants as additives to polyalkenes.

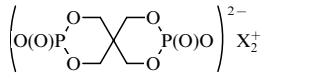
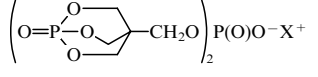
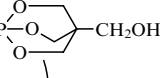
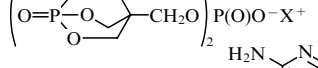
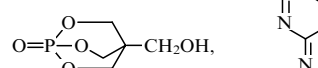
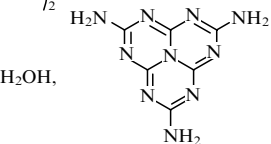
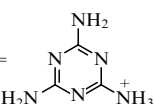
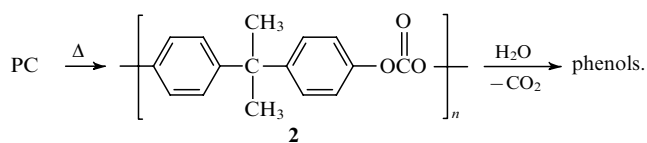
Polymer	IS ^a	IS content in the polymer (%)	OI	Ref.
Polypropylene	a condensation product of P ₂ O ₅ with pentaerythritol and melamine	30	32	40
		30	28.5	41
		30	33	41
	a mixture of piperazine pyrophosphate and melamine phosphate	30	36–38	42
	condensation products of triglycerol isocyanurate with <i>ortho</i> -(poly)phosphoric acid	20	24–25	43, 44
	C(CH ₂ OH) ₄ , 	30	33	37
		30	32.5	37
		30	34.5	37
				

Table 2 (continued).

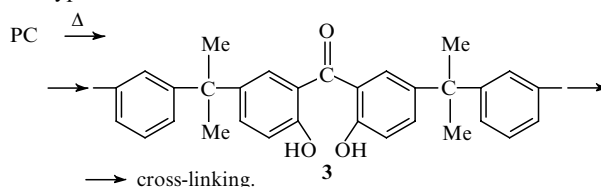
Polymer	IS ^a	IS content in the polymer (%)	OI	Ref.
Polypropylene	$X^+ HPO_4^{2-}, C(CH_2OH)_4$	30	32.5	37
	$Me(O)P \begin{array}{c} \diagup \diagdown \\ O \quad O \\ \diagdown \diagup \\ O \quad O \end{array} P(O)Me, X$	30	24	45
	$C(CH_2OH)_4, \left(O(O)PCMe(OH)P(O)O \right)^{2-} X_2^+$ $\begin{array}{cc} & \\ OH & OH \end{array}$	30	31	45
	$C(CH_2OH)_4, HO(O)PCMe(OH)P(O)O^- X^+$ $\begin{array}{cc} & \\ OH & OH \end{array}$	30	30	45
	$HO(O)PCMe(Cl)P(O)O^- X^+$ $\begin{array}{cc} & \\ OH & Cl \end{array}$	30	21	45
	$(HO)_2PCH_2XCH_2XCHCH_2P(O)(OH)_2$ $\begin{array}{cc} & \\ O & OH \end{array}$	30	28	45
A copolymer of ethylene with propylene	a mixture of piperazine pyrophosphate and melamine phosphate	30	28–30	46
A copolymer of ethylene with vinyl acetate	$X^+ HP_2O_7^-, \left(Me \begin{array}{c} \diagup \diagdown \\ O \quad O \\ \diagdown \diagup \\ O \quad O \end{array} P(O)CH_2 \right)_3$	35	27	47
Polystyrene	$\left(O=P \begin{array}{c} \diagup \diagdown \\ O \quad O \\ \diagdown \diagup \\ O \quad O \end{array} CH_2O \right)_2 P(O)O^- X^+$	30	25–26	41
	$Me(O)P \begin{array}{c} \diagup \diagdown \\ O \quad O \\ \diagdown \diagup \\ O \quad O \end{array} P(O)Me, X$	30	25	45
	$HO(O)PCMe(Cl)P(O)O^- X^+$ $\begin{array}{cc} & \\ OH & Cl \end{array}$	30	23	45
	$(HO)_2PCH_2XCH_2XCHCH_2P(O)(OH)_2$ $\begin{array}{cc} & \\ O & OH \end{array}$	30	22	45
	$Me(O)P \begin{array}{c} \diagup \diagdown \\ O \quad O \\ \diagdown \diagup \\ O \quad O \end{array} P(O)Me, X$	30	23	45
Polyethylene	$C(CH_2OH)_4, HO(O)PCMe(OH)P(O)O^- X^+$ $\begin{array}{cc} & \\ OH & OH \end{array}$	30	30	45
	$HO(O)PCMe(Cl)P(O)O^- X^+$ $\begin{array}{cc} & \\ OH & Cl \end{array}$	30	22	45
	$(HO)_2PCH_2XCH_2XCHCH_2P(O)(OH)_2$ $\begin{array}{cc} & \\ O & OH \end{array}$	30	25	45
	$Me(O)P \begin{array}{c} \diagup \diagdown \\ O \quad O \\ \diagdown \diagup \\ O \quad O \end{array} P(O)Me, X$	30	23	45

^a Designation: $X^+ =$ 



It has been found that the high efficacy of alkali metal salts of organic acids is determined by the fact that they accelerate thermal degradation of PC. This results in the increase in the amount of the char formed and evolution of CO_2 as one of the polymer decomposition products at lower temperatures. In addition, decomposition of PC in the presence of organic acid salts is

accompanied by the Fries rearrangement (migration of acyl groups of phenol esters to the *o*-position of the benzene ring), eventually resulting in the formation of cross-linked structures of the type 3:



Thermal decomposition of polycarbonates occurring along this route leads to the formation of a solid foamed coke layer on the polymer surface, which prevents further spreading of the flame. It was found⁴⁹ that foamed coke is made up of the polymer degradation products, *i.e.*, PC takes an active part in its formation, whereas the additive catalyses this process but is not directly involved in it.

It is known that the main drawback of PC is a drastic decrease in their impact strength at low temperatures.⁵⁰ Polymeric materials based on PC and an acrylonitrile–butadiene–styrene copolymer (ABS) and polyethylene terephthalate (PETP) are free from such defect. Some aromatic sulfonates as well as phosphorus- and bromine-containing compounds were tested as fire retardants for PETP–PC⁵¹ and ABS–PC mixtures.^{49, 52} It was found that aromatic sulfonates become less efficient after addition of ABS to PC.⁴⁹ The decrease in the fire retarding efficacy with the change in the composition of the polymeric matrix is due to the lowering (by 50 °C) of the temperature at which decomposition of PC containing ABS begins. As a result, the fire retardant does not affect the composition of PC pyrolysis products and the antipyr-rogenous effect of aromatic sulfonates on the PC–ABS mixture is not manifested.

Thus, IS prepared from aromatic sulfonates exert rather specific selective action and even minor alterations in the composition of the polymeric mixture may significantly decrease their efficiency.

Phosphorus-containing fire retardants can be recommended for the preparation of polymeric high-resistant materials based on a PC–ABS mixture. Although these compounds are less efficient than the bromine-containing ones, the materials based on them possess better mechanical properties.³⁹ The bromine- and phosphorus-containing fire retardant is especially efficient in PC–PETP and PC–ABS mixtures.^{51, 52}

The combustion of systems prepared from polyurethane and ammonium polyphosphate⁵³ or polyamide and ammonium polyphosphate⁵⁴ yields foamed cokes, predominantly due to the reaction of the polymer with the additive resulting in the formation of cross-linked products. Recently it was shown⁵⁵ that certain melamine salts are efficient as fire retardants for polycapramide, because these compounds also favour the formation of cross-linked products in the reaction of the additive with the polymer. The reactions resulting in the formation of foamed cokes have been considered.

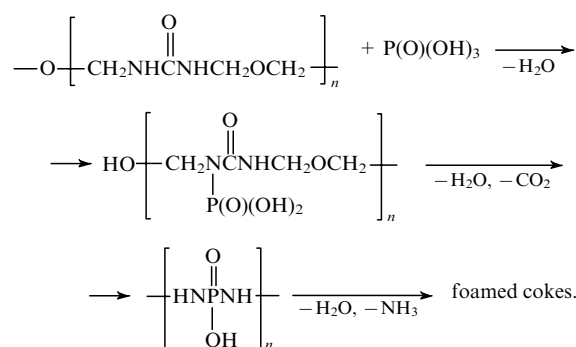
Phosphoric acid is known to be an efficient fire retardant for cellulose.⁵⁶ Phosphoric acid reacts with the polymer, which alters the mechanism of thermal degradation of cellulose towards char formation; therefore, this system can be related to IS.⁵⁷

By virtue of their stability, adhesiveness, dielectric properties, thermal stability and technological efficiency, epoxy resins (ER) and phenol–formaldehyde resins (PFR) are widely employed as binding agents in preparation of reinforced plastic materials in many branches of technics. Fire retardants affecting the mechanism of their thermal degradation are the most efficient for these polymers. Thus the efficiency of some transition metal salts (*e.g.*, cobalt acetate) is due to their catalytic effect on dehydration and dehydrogenation of ER and PFR.^{58, 59} This significantly increases the char yield, while the yield of volatile flammable products formed in thermal degradation of ER decreases in the presence of organophosphorus compounds¹⁹ and certain phosphines.⁶⁰

The effects of the composition of ER on the mechanism of thermal degradation and the composition of the pyrolysis products responsible for the flammability of ER have been discussed.⁶¹ It was shown that enhanced char formation is the determining factor in this process.

Chemical reactions occurring in the presence of phosphoric acid used as IS for carbamide–formaldehyde resin (CFR) have been discussed in detail.⁶² It was shown that in the course of thermal conversions phosphoric acid reacts with the amide groups of CFR to give *N*-phosphorylated products, which lose water,

ammonia and carbon dioxide and eventually turn into foamed cokes



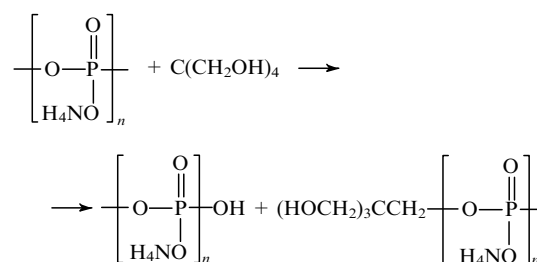
A viscous melt of poly(amidophosphates) favours the formation of a swollen carbonised layer and suppresses thermal oxidation of foamed cokes, which enhances the fire-proof effect.

Phosphorus-containing compounds, like phosphoric acid, react with functional groups of the polymer to yield foamed cokes which protect the polymer surface from the heat flow. It is the formation of foamed cokes that is responsible for the significant lowering of the flammability of the polymers to which a fire retardant has been added.

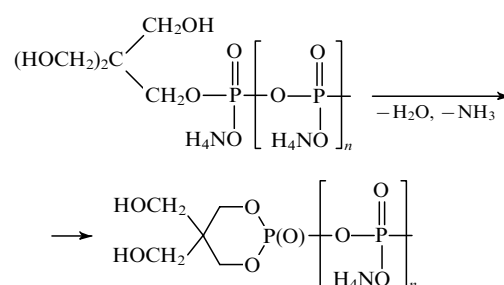
IV. Chemical reactions occurring in the intumescence

Chemical reactions occurring in the intumescence are most extensively studied for IS consisting of ammonium polyphosphate and pentaerythritol. The sequence of chemical and physical processes has been established: decomposition of ammonium polyphosphate at 215 °C, esterification of the alcoholic groups of pentaerythritol with liberation of H₂O, which results in the increase in the bulk of IS, solidification of the swollen carbon–phosphorus residue at 360 °C.³⁰

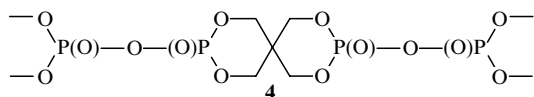
Studies using thermogravimetric analysis (TGA), thermovolumetric analysis and ³¹P NMR spectroscopy have shown^{63–69} that pentaerythritol is phosphorylated with APP at 210 °C with the scission of the main polyphosphate chain of APP and the formation of the –[P(O)OCH₂]– phosphate groups. This reaction does not yield volatile products.



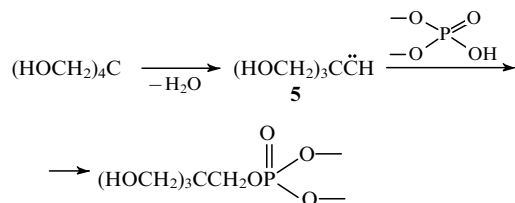
This is followed by the formation of cyclic esters of polyphosphoric acid with elimination of ammonia and water.



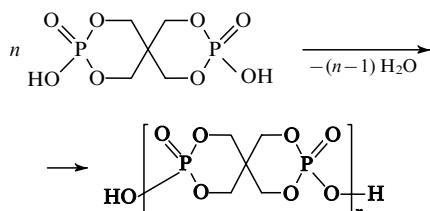
Repetition of these reactions gives the structures of type 4.



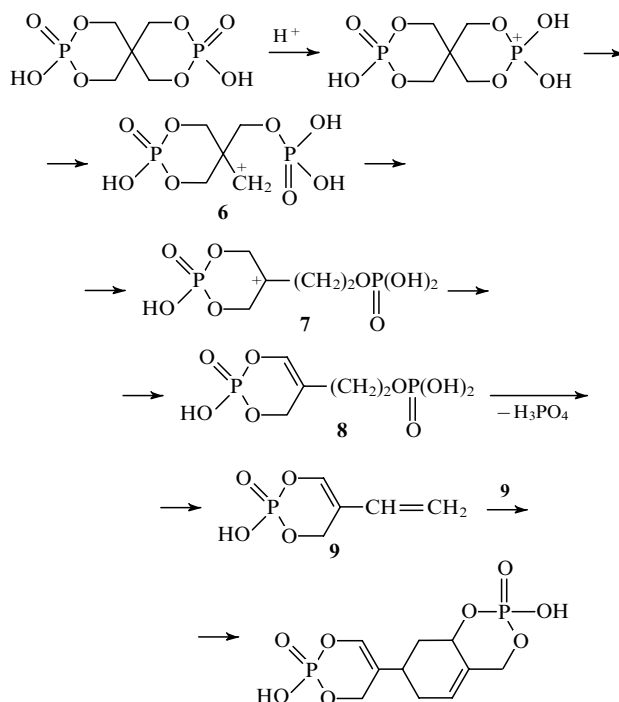
The fact that the APP–pentaerythritol pyrolysis products are paramagnetic has led the authors to suppose that their formation occurs *via* an intermediate carbene **5**.⁶⁹



An alternative hypothesis suggests⁶³ that esterification of APP is preceded by the formation of a carbenium ion. The formation of cyclic structures as intermediates in thermal conversions of APP–pentaerythritol mixtures has made it possible to use bisphosphate of pentaerythritol as a model compound for investigation of a intumescence mechanism.^{63, 64} It was shown that condensation with elimination of water and formation of structures of type **4** is the first step in the degradation of this bisphosphate.

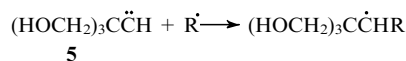


An analysis of ³¹P and ¹³C NMR spectra made it possible to propose the following mechanism for char formation. Its first step is the formation of the carbenium ion **6** owing to protonation and cleavage of the C–O bond. This ion can be rearranged into a stable tertiary carbocation **7**; deprotonation of the latter leads to the formation of the double bond. Subsequent pyrolysis of the ester **8** can occur with the elimination of phosphoric acid resulting in diene derivatives **9** which enter into the Diels–Alder reaction to give polycyclic compounds of the type **10**.



Repetition of these reactions yields conjugated aromatic structures.⁷⁰ The reactions can be accompanied by condensation of phosphoric acids and polymerisation; therefore, the reaction products possess irregular structures. Intumescence occurs within a narrow temperature range (300–350 °C) and results in the formation of a bulky carbonaceous residue containing admixtures of phosphoric acid.

The lack of a sufficient body of evidence does not allow any valid conclusion on the possibility of the interaction of polymers with IS. It was found^{63–68} that polypropylene (PP) has virtually no effect on the mechanisms of intumescence. In turn, IS do not influence the composition of products formed upon polymer decomposition. Experiments with TGA in air have shown^{38, 71} that the contribution of the polymer to char formation is insignificant. Presumably phosphoric acid reacts with alcohols formed in the oxidation of PP with atmospheric oxygen. Enhanced paramagnetic properties of the residue obtained upon pyrolysis of the polymeric composition in comparison with pure IS are attributed to the reaction of free radicals formed upon thermal degradation of the polymer with IS (APP + pentaerythritol).⁶⁹



This assumption was supported by the finding that the mass of the char residue diminishes in the presence of free radicals.

An analysis of the chemical composition of the chars formed upon thermal degradation of PP, polyethylene (PE) and polystyrene (PS) with IS (APP + pentaerythritol) has shown³⁹ that the chars formed at any temperature and with any polymer or without it are made up of identical chemical structures, which represent a combination of fragments containing quaternary carbon atoms with irregular aromatic and phosphorus–oxygen units.

However, there is conclusive evidence⁷² that the chemical structure of a comonomer and its content in the polymer strongly affect the interaction of IS based on APP and pentaerythritol with ethylene copolymers. It was found that butyl acrylate–ethylene and maleic anhydride–ethylene copolymers markedly increase the efficiency of IS due to their interaction in the condensed phase. It was also shown that aluminosilicate zeolites also significantly increase the efficiency of IS.⁷²

Reactions of ammonium polyphosphate with polyols (pentaerythritol, starch, polyvinyl alcohol, glycerol) have been studied in the search for the optimum ratio of reaction components to be used for the filling of polymers in order to decrease their flammability.⁴⁵

Irrespective of the polyol/APP ratio, all the systems examined displayed exothermic peaks of various intensities in the DPA curves. Presumably, this was due to the reaction of the polyol with APP with elimination of ammonia and water in this temperature range. The magnitude of the thermal effect was estimated on the assumption that the maximum thermal effect corresponds to the most complete reaction. It was established⁴⁵ that all the systems under study were characterised by identical mass loss and had identical masses of char residues, but differed in thermal effects.

The optimum APP/polyol ratio for all the systems tested was 7:3 (mass %) as can be judged from the identical mass loss in the reaction. However, no strict correlation between the char yield, mass loss upon esterification and maximum thermal effect was found for systems containing methylphosphonic acid and pentaerythritol.⁴⁵

V. Heat-insulating characteristics of foamed cokes formed upon combustion and thermal degradation of polymeric systems containing intumescent fire retardants

The efficiency of IS is determined primarily by heat-insulating characteristics of foamed cokes formed in the combustion of

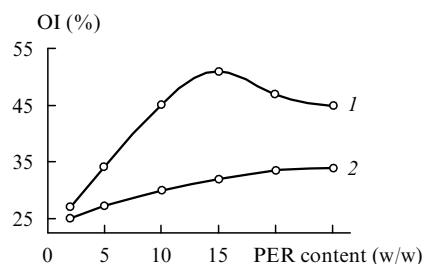


Figure 1. The OI values for specimens burnt under ordinary conditions (1) and for specimens from which 'char caps' were removed during combustion (2).¹⁹

polymers. The role of 'char caps' in the lowering of flammability has been established¹⁹ by comparing OI of specimens burnt by routine methods with those where the foamed coke layer formed in the course of combustion was continuously removed (Fig. 1). The considerable difference in the characteristic curves and much greater values of OI in the former case (Fig. 1, curve 1) suggest that the presence of foamed cokes is the main factor decreasing flammability. Measurements of hydrodynamic resistances have shown⁷³ that foamed cokes cannot prevent the diffusion of degradation products to the combustion zone. It was concluded⁷³ that heat-insulating properties of 'char caps' play the crucial role in flammability reduction. These results are in good agreement with the finding⁷⁴ that the foamed coke layer is permeable by low-molecular-weight liquids. However, the results of microstructural analysis of foamed cokes formed in the combustion of IS-containing PP compositions by scanning electron microscopy led the authors to conclusion⁶² that diffusion of degradation products through the foamed coke layer plays an important role in combustion. The compositions with low OI displayed multiple fissures and breaks in the carbon structure, whereas foamed cokes formed from the compositions with high OI had closed pores.

Evidently, heat-insulating characteristics (HIC) of foamed cokes are responsible for the high efficiency of IS in PP. Model studies of forced combustion,^{36,75} where a polymer sample with a thermocouple inserted at a definite distance from its surface was flame-burnt, have demonstrated that the foamed coke layer formed significantly lowers the polymer temperature. Under these conditions, the rate of the polymer temperature changes, *i.e.*, HIC, of the foamed coke correlated with the OI. No such correlation was found for PP charged with various fillers (10%–30%) in addition to IS.³⁰

The HIC of foamed cokes formed from different compositions and polymeric matrices but containing the same amounts of IS have been investigated.⁷⁶ A great variety of compositions allowed the authors to establish a relationship between the flammability of polymer material and thermal characteristics of foamed cokes in a broad range of OI values. Thus it was found that a satisfactory correlation between OI and HIC was observed only for relatively low (< 25) OI values. In addition, it was shown that the flammability of IS-containing polymeric systems is determined not only by the HIC of 'char caps' but also by the rate of foamed coke layer formation.

Most authors believe that HIC of foamed cokes play the major role in flammability reduction, although no satisfactory correlation between these parameters has been found so far.

Various factors determining the HIC of foamed cokes formed upon combustion have been investigated.^{62,77} A unit used in these studies allows the registration of the light flux and the response in the sample's rear (Fig. 2a). The sample to be tested, which represents a disc (~ 1 mm thick) 10 mm in diameter (Fig. 2b) is mounted on a thin metal stage. The sample surface is irradiated with the light generated by a carbon dioxide laser. Part of the radiant flux is diverted to an ILD-24M irradiation meter by means of a semitransmitting mirror made of a chalcogenide glass. A

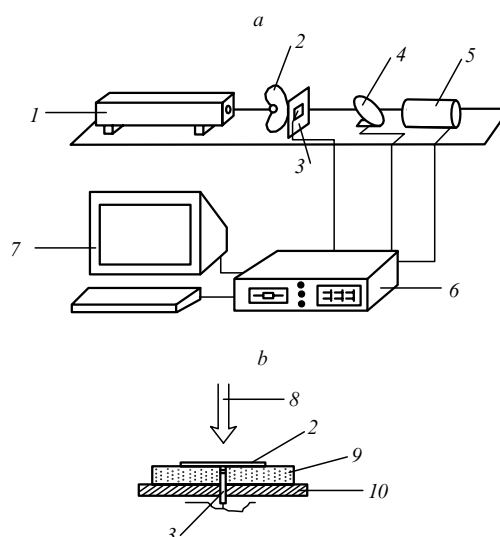


Figure 2. A schematic representation of a unit (a) and a stage (b) for studying heat-insulating characteristics of various materials; (1) carbon dioxide laser; (2) sample; (3) a thermocouple; (4) chalcogenide glass; (5) radiation meter; (6) interface; (7) computer; (8) the radiant flux; (9) asbestos support; (10) base.

chromel-copel thermocouple (0.08 mm thick) is placed on the sample's rear. Having passed through the mirror, the radiant flux reaches the sample and warms it up. The signal of the thermocouple response is passed to a computer. The experiments were carried out with both continuous and pulsating radiant fluxes (in the latter case, the ratio of the pulse length to the pause was equal to two) and ignition of the sample did not occur.

Figure 3 shows the temperature *vs* time curves for the combustion of PS, PP and PE containing IS prepared from APP and pentaerythritol.³⁹ Complete burn-out of polymers containing no fire retardants normally takes 15 s at temperatures ≤ 800 K and does not depend on their chemical nature. Comparison of experimental curves points to significant differences in the properties of foamed cokes at the moment of their formation. The shape of these curves is of complex type; each portion of the curve corresponds to a definite state of the system. A drastic increase in the temperature in the initial moment corresponds to the heating of the composition prior to foamed coke layer formation. Subsequent decline (curves 2 and 3) or a bend (curve 1) correspond to the formation and growth of the foamed coke layer on the polymer surface. The plateau corresponds to the intumescence of the sample in bulk and is associated with heat absorption upon intense degradation. A slow increase in temperature up to the steady-state level in the terminal steps indicates that the intumescence process is completed and the whole mass of the sample has been converted into foamed coke. The shape of the curve for the composition prepared from PE (curve 1) suggests that the

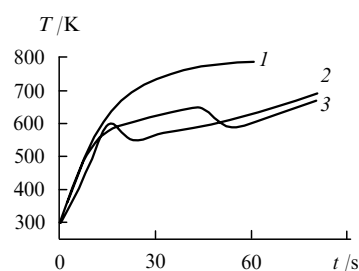


Figure 3. Heat-insulating characteristics of foamed cokes prepared from IS-containing polymeric compositions based on APP and pentaerythritol; (1) PE; (2) PP; (3) PS.

formation of foamed coke occurs at an extremely slow rate and it has low HIC. A small bend on the curve for the compositions prepared from PS (curve 3) points to a relatively high rate of foamed coke formation, which is followed by a decrease in the rate of warm-up for a short period. The shapes of the curves for the compositions prepared from PP and PS (curves 2 and 3) indicate that the formation of, and accumulation of, the foamed coke occur much faster than in the case of the compositions based on PE. These foamed cokes have enhanced HIC, but their shapes and the positions of their extrema point to differences in the kinetics of their intumescence. The sharp maximum on the curve for the composition based on PP (curve 2) suggests that the activation energy of the intumescence reaction is low, while the rate of intumescence and the HIC of foamed cokes formed even at insignificant heat fluxes are high. The maximum on the curve for the composition derived from PS (curve 3) points to the higher rate of intumescence and formation of foamed coke at higher temperature in comparison with the composition prepared from PP. In the final step, the rates at which the temperature changes occur and their limiting values for the compositions prepared from PP and PS coincide (curves 2 and 3), which testifies to identical properties of the 'char caps' formed. The differences in the HIC of 'char caps' at the moment of their formation and the similarity of their HIC in the case of IS-containing PS and PP compositions can be attributed to the differences in their internal structure, which is schematically presented in Fig. 4. In both cases, 'char caps' represent thick walls with large cavities inside. The walls of the 'caps' have porous structures, which differ in pore size and in wall thickness. The foamed coke formed from the composition based on PP has smaller pores and thinner walls; the air fraction (v/v) is greater (Fig. 4a).

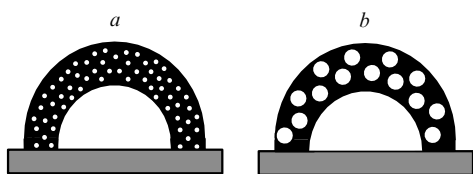


Figure 4. A schematic representation of foamed cokes formed under the action of a heat flux; (a) a composition prepared from PP; (b) a composition prepared from PS.³⁹

Investigations into the effects of phosphorus-containing fire retardants based on methylphosphonic acid on the flammability of PE, PP and PS have demonstrated⁴⁷ that in the case of PE and PP the fire retardants prepared from the adduct of melamine–formaldehyde resin and methylphosphonic acid (MFMA), from the adduct of methylphosphonic acid and melamine (DPM-3) combined with pentaerythritol and from methylphosphonic diamide (MPD) are more efficient than halogen-containing fire retardants currently used.

The temperature *vs* time curves for the combustion of PP and PE containing MFMA as the fire retardant are shown in Fig. 5. Comparison of these curves suggests that MFMA strongly affects the properties of foamed cokes at the moment of their formation. In the case of a PP composition, foamed cokes are formed at a faster rate and have enhanced HIC. Therefore, MFMA can be regarded as a typical IS, although its efficiency and the HIC of the foamed cokes formed are inferior to those of compositions based on APP.

Figure 6 shows the temperature *vs* time curves for the combustion of PP, PS and PE containing a 4:1 DPM-3–pentaerythritol mixture.⁴⁷ Comparison of these curves points to a strong effect of the polymeric matrix on the properties of foamed cokes at the moment of their formation. In the case of PS compositions, the foamed cokes are formed at slow rates and have low HIC. The foamed cokes formed at a fast rate in the

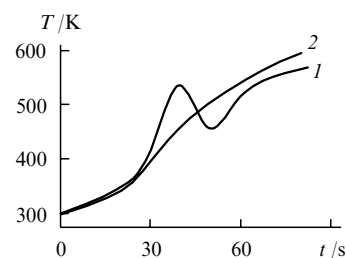


Figure 5. Heat-insulating characteristics of fire retardant-containing compositions prepared from the adduct of melamine–formaldehyde resin with MFMA; (1) PE + MFMA; (2) PP + MFMA.⁴⁷

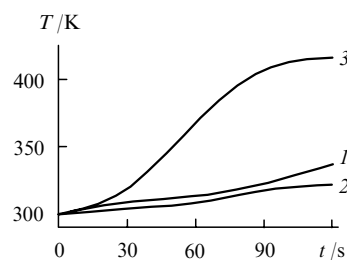


Figure 6. Heat-insulating characteristics of fire retardant-containing polymeric compositions prepared from the adduct of methylphosphonic acid with DPM-3;⁴⁷ (1) PS + DPM-3; (2) PE + DPM-3; (3) PP + DPM-3.

combustion of PP and PE compositions have high HIC. The HIC of foamed cokes show a good correlation with the efficiency of the fire resistant agent. For PP, the efficiency of DPM-3 is close to that of APP, whereas for PE, DPM-3 is more efficient than APP.

The temperature *vs* time curves for the combustion of PP, PS and PE containing MPD are shown in Fig. 7.⁷⁸ As can be seen, the presence of a polymer significantly lowers the rate of foamed cokes formation. It is of note that the chars formed in the decomposition of compounds prepared from PE and PS have very low HIC, whereas the chars formed in the combustion of compositions derived from PP have high HIC.

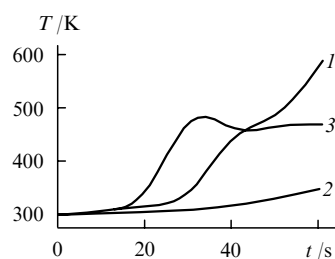


Figure 7. Heat-insulating characteristics of fire retardant-containing compositions prepared from MPD; (1) PS + MPD; (2) PE + MPD; (3) PP + MPD.

The plateau (Fig. 7) corresponding to the intumescence of the bulk of the sample is very low. It may thus be assumed that the amount of the char formed is insufficient for long-term protection of the polymer. Thus, the mechanism of action of MPD as the fire resistant agent is based primarily on the reversal of the destructive processes occurring in PE, which results in smaller quantities of volatile flammable products. Although MPD favours char formation in polymers, it is not the main factor responsible for the flammability reduction, since the char formed cannot protect the polymer in the course of combustion.

MPD has a limited use because fire retarding polymeric compositions containing this fire retardant are difficult to process: phase separation occurs in moulding and casting. One of the clues to the solution of this problem is microencapsulation of the fire retardant prior to its introduction into the system. Besides, the choice of an appropriate shell may not only facilitate compatibility of the fire retardant with the polymeric matrix, but also increase its efficiency.

The effects of various types of shells on HIC and flammability of polymeric materials prepared from PP and PE have been studied.⁷⁷ The following polymeric shells were employed for microencapsulation: high-density PE, polyvinyltriethoxysilane and an aromatic polyamide based on terephthalic acid and *m*-phenylenediamine. It was shown that the chemical nature of the polymeric shell strongly affects the flammability and HIC of polymeric compositions based on PE and PP.

The temperature *vs* time curves for the combustion of PP containing non-encapsulated MPD and MPD encapsulated in PE and polyvinyltriethoxysilane are shown in Fig. 8. As can be seen, the shell strongly affects the physical structure of the char at the moment of its formation. As was noted above, the formation of char in the combustion of PP containing MPD occurs at a very slow rate (Fig. 8, curve 2). The polyethylene film does not influence the combustible and protective properties of the chars formed upon combustion (Fig. 8, curve 3). Char formation accompanying the decomposition of MPD-containing compositions enclosed in polyvinyltriethoxysilane occurs much faster and the chars formed possess enhanced HIC (Fig. 8, curve 1).

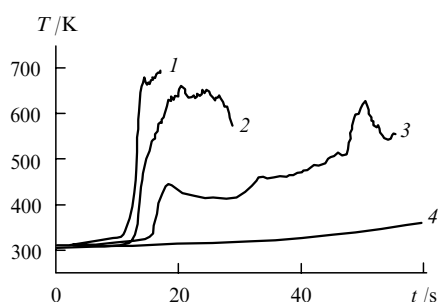


Figure 8. Heat-insulating characteristics of fire retardant-containing compositions prepared from MPD encapsulated in polymeric films:⁷⁷ (1) PP; (2) PP + MPD; (3) PP + MPD encapsulated in PE; (4) PP + MPD encapsulated in polyvinyltriethoxysilane.

Thus, the efficiency of IS (OI of the polymeric compositions) correlates well with the HIC of foamed cokes formed upon combustion. The higher the HIC of the chars formed the greater the efficiency of IS in these compositions.

VI. Conclusion

The major effect of fire retardants used for decreasing the flammability of polymers consists predominantly in increasing the char yields in the combustion and thermooxidative degradation of polymeric materials. The additives favouring char formation upon the interaction of polymeric components on heating are successfully employed for the preparation of fire retarding polymeric materials. The studies^{79–84} published in 1996–1998 have demonstrated that metals and metal-containing materials are best suited for this purpose. This trend of research holds especially great promise, for some metal-containing additives are able to catalyse chemical cross-linking reactions in polymers containing functional groups.^{85,86} Their addition not only affects the yields of chars and the kinetics of their formation but also changes their physical structure.

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Crystal chemistry of compounds containing mercury in low oxidation states

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Abstract. The published data are surveyed and a comparative crystal-chemical analysis is presented for the structures of compounds containing mercury in low oxidation states as cluster Hg_n groups with covalent Hg–Hg bonds. The geometry of compounds with Hg–Hg and Hg–X bonds ($X = \text{O}, \text{S}, \text{Se}, \text{N}$ or Hal) is analysed and the types of coordination of mercury ions, the packing modes and the relationships between structural units are described. The crystallographic and crystal-chemical data for mercury compounds are given. The bibliography includes 124 references.

I. Introduction

It is known that mercury can exist not only in the oxidation state of +2 typical of Group II elements, but also in lower oxidation states which form polyatomic groups of the cluster type. These groups are found in inorganic complex compounds as well as in mercury-containing transition metal clusters. Diatomic groups (the so-called dumbbell-like groups), in which atoms of monovalent[†] mercury¹ are bound through a covalent bond and the Hg–Hg distances vary in the range of 2.5–2.6 Å, are most widespread. A large body of research of Hg(I) compounds confirmed the presence of the $(\text{Hg}_2)^{2+}$ pairs in the linear –X–Hg–Hg–X– fragments ($X = \text{O}, \text{N}, \text{S}, \text{Se}$ or Hal), which contain two almost collinear *sp* bonds, as in the analogous

–X–Hg–X– fragments in Hg(II) compounds. The $(\text{Hg}_2)^{2+}$ pairs were found for the first time in studies of mercurous halides Hg_2X_2 ($X = \text{F}, \text{Cl}, \text{Br}$ or I). These pairs were also observed in approximately twenty minerals.² The Hg_3 ‘triangles’, in which mercury exists in the formal oxidation state of +4/3 and the Hg–Hg distance is ~ 2.7 Å (in metallic mercury, the Hg–Hg distance is ~ 3 Å), are less abundant. A number of compounds contain linear systems of the Hg_n type ($n = 3, 4, \infty$) in which mercury atoms are bound to each other and exist in fractional oxidation states (+2/3, +1/2 or +1/3). As n increases, these compounds approximate metals in properties, and a pronounced correlation between the decrease in the charge on the mercury atom and the increase in the Hg–Hg distance (2.51–2.90 Å) is observed.

The crystal chemistry of mercury differs sharply from the crystal chemistry of its lighter analogues, *viz.*, of zinc and cadmium. Unlike these metals, mercury can form polyatomic Hg_n^{x+} cations. Note that the $(\text{Zn}_2)^{2+}$ ion was found in a Zn/ZnCl_2 melt¹ and the $(\text{Cd}_2)^{2+}$ pair was detected in the $\text{Cd}_2(\text{AlCl}_4)_2$ compound (the distance between the cadmium atoms is 2.576 Å).³

There is no consensus of opinion as to the electronic structures not only of Hg_n^{x+} systems, but also of simple HgX_2 and Hg_2X_2 compounds. This is evidenced by numerous experimental and theoretical studies on the crystal and electronic structures of mercury-containing compounds and on the nature of bonding in these compounds. This heavy element with the closed shell electronic configuration $5d^{10}6s^2$ ‘accumulates’ all the factors, which hinder investigations of the electronic structures of its compounds by quantum-chemical methods. Thus, mercury is characterised by a large atomic number, the absence of unpaired electrons, the filled valence *5d* and *6s* orbitals, the presence of high-lying outer unoccupied *6p* orbitals and a substantial influence of relativistic effects on the electronic state of the mercury atom and ions. Presently, factors, which contribute to the formation of Hg_n^{x+} systems, are not all revealed and the reasons for the changes in their sizes, the geometrical shape and the Hg–Hg distances are not understood.^{4,5}

II. Crystal structures of inorganic compounds containing $(\text{Hg}_2)^{2+}$ groups

More than 30 crystal structures of inorganic compounds containing $(\text{Hg}_2)^{2+}$ groups have been established. These structures belong to different types, *viz.*, to molecular, layered or framework structures. The principal crystal-structural data for these com-

[†] Hereinafter, by monovalent mercury compounds are meant compounds containing $(\text{Hg}_2)^{2+}$ dimers.

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pounds are given in Table 1, in which the compounds are placed in order of increasing complexity of their structures, *viz.*, beginning with simple molecular structures and ending with complicated framework structures.

A system containing the $(\text{Hg}_2)^{2+}$ pair and the oxygen atoms of two water molecules was found in the study⁶ of the atomic arrangement in the $\text{Hg}_2(\text{ClO}_4)_2 \cdot 4\text{H}_2\text{O}$ compound both in aqueous solutions at various concentrations and in the solid state. In this system, the $\text{Hg}-\text{Hg}$ and $\text{Hg}-\text{O}$ distances are 2.50 and 2.14 Å, respectively, and the remaining $\text{Hg}\cdots\text{O}$ distances are larger than 2.70 Å. Apparently, the virtually linear $[\text{H}_2\text{O}-\text{Hg}-\text{Hg}-\text{OH}_2]^{2+}$ groups (the $\text{Hg}-\text{Hg}-\text{O}$ angle is 178.1°) are present both in solution and in the crystal. It was demonstrated that a change in the concentration of the solutions has no effect on the $\text{Hg}-\text{Hg}$ bond length. In addition, the metal-metal bonds in solutions (2.52 Å) and in the solid state (2.50 Å) differ only slightly. In the crystal structure, the $[\text{H}_2\text{O}-\text{Hg}-\text{Hg}-\text{OH}_2]^{2+}$ groups are located parallel to the *b* axis (Fig. 1). Two other water molecules and the oxygen atoms of the $[\text{H}_2\text{O}-\text{Hg}-\text{Hg}-\text{OH}_2]^{2+}$ cations and of the tetrahedral ClO_4^- anions are linked through hydrogen bonds (2.82 Å). In the study cited, mention was made of the existence of yet another hydrate, $\text{Hg}_2(\text{ClO}_4)_2 \cdot 2\text{H}_2\text{O}$, which also contains the $[\text{H}_2\text{O}-\text{Hg}-\text{Hg}-\text{OH}_2]^{2+}$ groups with the $\text{Hg}-\text{Hg}$ and $\text{Hg}-\text{O}$ distances of ≈ 2.48 and ≈ 2.10 Å, respectively.

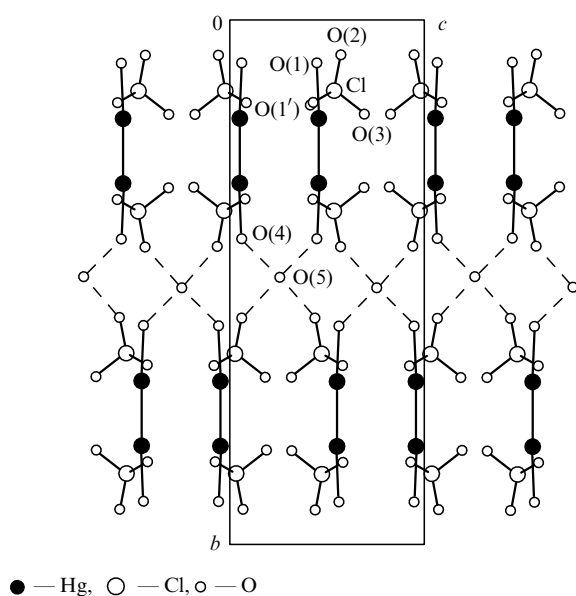


Figure 1. Projection of the crystal structure of $\text{Hg}_2(\text{ClO}_4)_2 \cdot 4\text{H}_2\text{O}$ onto the (100) plane. Hydrogen bonds are indicated by dashed lines.

Analogous linear groups were found in the structures of hydrates $\text{Hg}_2(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$,^{7,8} $\text{Hg}_2\text{SiF}_6 \cdot 2\text{H}_2\text{O}$ (see Ref. 9) and $\text{Hg}_2\text{AlF}_5 \cdot 2\text{H}_2\text{O}$.¹⁰

Two studies were devoted to the structure of $\text{Hg}_2(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$.^{7,8} Originally,⁷ the coordination environment about the mercury atoms in the $(\text{Hg}_2)^{2+}$ pairs was described as a tetrahedron. The rather short distance between the mercury atom and the oxygen atom of the water molecule is indicative of the formation of the aqua $[\text{H}_2\text{O}-\text{Hg}-\text{Hg}-\text{OH}_2]^{2+}$ cations. In the crystal structure, the water molecules and the NO_3^- anions are linked through hydrogen bonds (2.29–2.60 Å). The structure refinement of $\text{Hg}_2(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$ ⁸ confirmed the existence of the aqua $[\text{H}_2\text{O}-\text{Hg}-\text{Hg}-\text{OH}_2]^{2+}$ cation. However, it was demonstrated that the coordination environment about the mercury atom is formed only by the two nearest neighbours, *viz.*, by the mercury atom of the $(\text{Hg}_2)^{2+}$ pair and the oxygen atom of the water molecule. The remaining $\text{Hg}\cdots\text{O}$ distances vary from 2.68 to

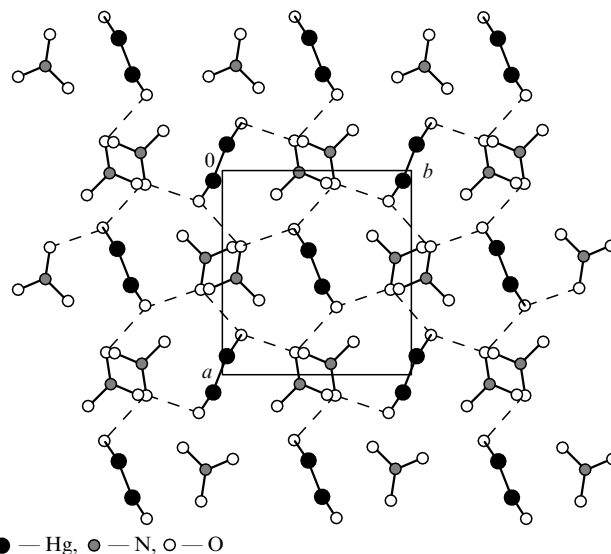


Figure 2. Herringbone molecular packing in the structure of $\text{Hg}_2(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$.

3.03 Å. Two water molecules are linked to the same oxygen atom of the NO_3^- group through the hydrogen bonds between the H_2O molecules and the NO_3^- anion (2.68 and 2.70 Å) (Fig. 2). It should be noted that the $\text{Hg}-\text{Hg}$ and $\text{Hg}-\text{O}$ bond lengths in the $\text{Hg}_2(\text{ClO}_4)_2 \cdot 4\text{H}_2\text{O}$ and $\text{Hg}_2(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$ compounds are virtually identical, but the $[\text{H}_2\text{O}-\text{Hg}-\text{Hg}-\text{OH}_2]^{2+}$ fragments in $\text{Hg}_2(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$ deviate significantly from linearity (the $\text{Hg}-\text{Hg}-\text{O}$ angle is 167.5°), which may be a consequence of the difference in the packing of these fragments in the crystal structures.

The structure of the $\text{Hg}_2\text{SiF}_6 \cdot 2\text{H}_2\text{O}$ compound was described as a ionic structure containing the slightly nonlinear aqua $[\text{H}_2\text{O}-\text{Hg}-\text{Hg}-\text{OH}_2]^{2+}$ cations (the $\text{Hg}-\text{Hg}-\text{O}$ angle is 170.9°).⁹ The mercury atoms each form contacts with three fluorine atoms of the octahedral SiF_6^{2-} anions. The $\text{Hg}-\text{F}$ distances vary from 2.71 to 2.87 Å and the remaining distances are larger than 3 Å. In addition, there are hydrogen bonds between the fluorine atoms and the water molecules ($\text{F}\cdots\text{O}$ 2.58 and 2.65 Å).

The hydrogen bonds between the water molecules and the fluorine atoms ($\text{F}\cdots\text{O}$ 2.56–2.86 Å) are also of great importance in the $\text{Hg}_2\text{AlF}_5 \cdot 2\text{H}_2\text{O}$ compound.¹⁰ These bonds stabilise the framework formed from *trans* chains of the AlF_6 octahedra parallel to the *c* axis. The quasi-linear $[\text{H}_2\text{O}-\text{Hg}-\text{Hg}-\text{OH}_2]^{2+}$ cations are located between the chains at different heights.

Therefore, the above-considered compounds containing the mercury atoms in the oxidation state of +1 and water molecules can be considered as within the ionic structures of the $[\text{Hg}(\text{H}_2\text{O})]_2^{2+}$ cations.

Early investigations of the structures of halides with composition Hg_2X_2 ($\text{X} = \text{Cl}, \text{Br}$ or I) have been devoted to the determination of the unit cell parameters and the atomic coordinates based on X-ray powder data.³ More recently, the structures of Hg_2X_2 ($\text{X} = \text{F}, \text{Cl}$ or Br) were refined based on single-crystal X-ray data.^{11,12} The crystal structure of mercurous chloride Hg_2Cl_2 was determined also by neutron powder diffraction analysis.¹³ It was confirmed that this compound has a linear molecular structure with the $\text{Hg}-\text{Hg}$ and $\text{Hg}-\text{Cl}$ distances of 2.5955 and 2.3622 Å, respectively. Longer intermolecular $\text{Hg}\cdots\text{Cl}$ contacts (3.2059 Å) were also found. The $\text{Cl}\cdots\text{Cl}$ distances between the adjacent linear $\text{Cl}-\text{Hg}-\text{Hg}-\text{Cl}$ molecules along the [001] direction are 3.586 and 3.667 Å.

The molecular character of the structure and virtually linear $-\text{O}-\text{Hg}-\text{Hg}-\text{O}-$ groups were found in the study of the crystal structure of $\text{Hg}_2(\text{BrO}_3)_2$.¹⁴ The $(\text{Hg}_2)^{2+}$ pairs are located

Table 1. Crystallographic and crystal-chemical characteristics of low-valent mercury compounds.

Compound	Space group	Z	Unit cell parameters					$V/\text{\AA}^3$	$d_{\text{calc}}/\text{g cm}^{-3}$	d_{exp}	Bond length / $\text{\AA}$		The Hg—Hg—X angle ^a	Ref.	
			a	b	c	α	β				γ	Hg—Hg			Hg—X ^a
Inorganic monovalent mercury compounds															
Hg ₂ (ClO ₄) ₂ ·4H ₂ O	<i>Imma</i>	4	7.59	20.59	7.55			1162.7	3.839	—	2.50	2.14	178.1	6	
Hg ₂ (NO ₃) ₂ ·2H ₂ O	<i>P2₁/n</i>	2	8.64	7.52	6.30		103.8	397.5	4.683	—	2.54	2.15, 2.40, 2.42	160	7	
Hg ₂ (NO ₃) ₂ ·2H ₂ O	<i>P2₁/n</i>	2	8.633(3)	7.506(4)	6.256(3)		103.8(1)	393.7	4.733	4.785	2.508	2.13	167.5	8	
												2.68–3.03			
Hg ₂ SiF ₆ ·2H ₂ O	<i>P2₁/c</i>	2	5.642(1)	8.601(2)	8.922(2)		123.8(2)	355.9	5.41	5.37	2.495	2.20, 2.713–2.894	170.9	9	
Hg ₂ AlF ₅ ·2H ₂ O	<i>I4cm</i>	4	9.353(5)	9.353(5)	7.241(6)			633.4	5.86	—	2.511	2.144	173.0	10	
												2.827–2.894			
Hg ₂ Br ₂ (kuzminite)	<i>I4/mmm</i>	2	4.663(1)	4.663(1)	11.133(2)			242.1	7.696	—	2.49	2.71, 3.32	180 (Hg—Hg—Br)	11	
Hg ₂ F ₂	<i>I4/mmm</i>	2	3.6700(4)	3.6700(4)	10.901(2)				9.93	—	2.51	2.133	180 (Hg—Hg—F)	12	
Hg ₂ Cl ₂ (calomel)	<i>I4/mmm</i>	2	4.4795(5)	4.4795(5)	10.9054(9)			218.83	7.162	—	2.5955	2.3622, 3.2059	180 (Hg—Hg—Cl)	13	
Hg ₂ (BrO ₃) ₂	<i>C2/c</i>	4	18.806(7)	4.470(1)	8.595(2)		107.19(3)	690.2	6.32	6.20	2.507	2.16	174.0	14	
												2.69, 2.66			
HgReO ₄	<i>P2₁/c</i>	4	5.663(1)	5.070(1)	15.204(2)		110.17(1)	409.7	7.31	—	2.506	2.24–2.62	159.4	15	
Hg ₂ (NO ₂) ₂	<i>P2₁/c</i>	2	4.4145(9)	10.333(2)	6.277(1)		108.83(1)	271.03	6.04	6.20	2.516	2.244	174.2	16	
Hg ₂ (NO ₂) ₂	<i>P2₁/c</i>	2	4.435(1)	10.344(2)	6.301(2)		108.74(2)	273.7	5.99	—	2.520	2.224	173.3	17	
												2.577–2.955			
Hg ₂ (H ₂ PO ₄) ₂	<i>P2₁/n</i>	2	6.0754(5)	14.5034(7)	4.7280(4)		92.172(7)	416.3	4.75	4.70	2.499	2.142, 2.514	167.2	18	
HgVO ₃	$\overline{P1}$	2	3.592(1)	4.752(1)	8.588(1)	88.32(1)	79.60(1)	89.30(1)	144.1	6.901	—	2.543	2.112	174.1	19
												2.708–2.946			
Hg ₂ Mo ₂ O ₇	$\overline{P1}$	1	7.097(2)	7.144(2)	8.038(2)	65.89(1)	66.09(1)	166.45(1)	324.4	7.22	—	2.522	2.079, 2.139	167.3, 178.8	20
												2.735–3.112			
Hg ₂ Mo ₅ O ₁₆	<i>P2₁/c</i>	2	9.139(1)	5.513(1)	14.289(2)		110.65(1)	673.7	5.604	—	2.474	2.208	152.7	21	
												2.553–3.113			
(Hg ₂) ₃ (AsO ₄) ₂	<i>P2₁/c</i>	2	8.73(2)	5.08(1)	15.64(3)		128.4(3)	543.6	9.06	9.05	2.535	2.16–2.23	146–157	23	
												2.42–2.71			
Hg ₂ O ₄	<i>P2/c</i>	2	6.2802(9)	4.4273(5)	8.367(2)		91.76	232.5	7.10	7.05	2.500	2.24, 2.49–2.93	165	24	
Hg ₂ SeO ₄	<i>P2/c</i>	2	6.3507(8)	4.5870(7)	8.499(2)		90.98	247.5	7.27	7.14	2.51	2.21, 2.50–2.90	160	24	
[(Hg ₂) ₂ O(NO ₃)](NO ₃)· ·HNO ₃	<i>Aba2</i>	8	11.222(8)	20.178(2)	9.354(2)			2118	6.306	6.30	2.502–2.513	2.12–2.31	145.9–173.3	27	
												2.46–2.96			
[(Hg ₂) ₅ (OH) ₄ (NO ₃) ₂](NO ₃) ₄	$\overline{P1}$	1	9.990(3)	9.091(4)	7.657(3)	94.05(3)	101.25(3)	109.75(3)	634.9	6.398	6.31	2.495–2.511	2.09–2.22	166.1–178.5	27
												2.61–2.87			
Hg ₂ OH(NO ₃)Hg ₂ (NO ₃) ₂	<i>Cc2a</i>	8	20.171(5)	9.358(3)	11.217(3)			2117	6.31	6.30	2.499–2.505	2.142–2.364	140.5–170.8	29	
												2.488–2.733			
Hg ₁₀ (OH) ₄ (NO ₃) ₆	$\overline{P1}$	1	9.994(5)	9.099(5)	7.659(2)	85.98(4)	78.70(3)	109.83(5)	635.5	6.39	6.20	2.488–2.505	2.052–2.266	165.9–178.8	30
												2.602–2.966			
Hg ₄ (PO ₄)(NO ₃)·H ₂ O	<i>P2₁/n</i>	4	18.38(9)	8.258(3)	5.952(8)		91.2(1)	903.2	7.19	7.10	2.508–2.532	2.11–2.21	147.8–168.1	31	
												2.45–2.85			
AgHg ₂ PO ₄	<i>Pbam</i>	4	9.256(2)	8.614(2)	6.152(2)			—	—	—	2.608	2.224–2.348	101.2, 140.1, 142.9	32	
Hg ₄ OPb ₂ (NO ₃) ₆	<i>Fd3m</i>	8	15.412	15.412	15.412			3660.8	5.823	—	2.458	2.108		33	
K ₅ Cs ₅ [(Hg ₂) ₂ WO(H ₂ O)· ·(AsW ₉ O ₅₃) ₂]	$\overline{P1}$	4	28.99(1)	18.82(1)	16.88(1)	78.49(1)	84.36(8)	78.25(6)	8818	4.86	4.90	2.446–2.545	2.16, 2.34	161.7	34
Hg ₄ SbO ₃ (OH) ₃ (shakhovite)	<i>Im</i>	2	4.871(1)	15.098(3)	5.433(1)		98.86(2)	394.8	8.60	—	2.543	2.135, 2.160, 2.514–2.193	155.0, 166.3	35	

Table 1 (continued).

Compound	Space group	Z	Unit cell parameters					$V/\text{\AA}^3$	$d_{\text{calc}}/\text{g cm}^{-3}$	d_{exp}	Bond length / $\text{\AA}$		The Hg–Hg–X angle ^a	Ref.
			a	b	c	α	β				γ	Hg–Hg		
Hg ₃ OCl (poyarkovite)	<i>C2/c</i>	24	19.009(5)	9.018(4)	16.848(9)		110.81(3)	2696	9.643	—	2.503–2.565	1.96–2.30, 2.60 2.818–3.043 (Cl)	137.8–173.2	36
(Hg ₂) ₃ O ₂ Cl ₂ H (eglestonite)	<i>Ia3d</i>	16	16.036(3)	16.036(3)	16.036(3)			4123.7	8.652	—	2.516	2.165 3.010–3.095 (Cl)	162.7	37
Hg ₂ TeO ₃ (magnolite)	<i>Pbm2</i>	2	5.958(1)	10.576(2)	3.749(1)			236.2	8.108	—	2.532	2.06, 2.69–3.00	167.0	38
Hg ₆ Si ₂ O ₇ (edgarbaileyite)	<i>C2/m</i>	2	11.755(3)	7.678(2)	5.991(2)		111.73(3)	502.3	9.10	—	2.522, 2.524	2.12, 2.21 2.41–2.86	177.2, 164.9	39
(Hg ₂) ₈ (Ni,Mg) ₆ (CO ₃) ₁₂ (OH) ₁₂ — (H ₃ O) ₈ (H ₂ O) _x ($x \sim 3$) (szymanskiite)	<i>P6</i> ₃	1	17.3984(7)	17.3984(7)	6.0078(4)			1574.9	4.86	—	2.494, 2.513	2.099–2.144 2.34–2.44	136.3–175.2	40
Mixed-valence mercury compounds														
Hg ₂ OI	<i>C2/c</i>	8	17.603(8)	6.981(5)	6.701(5)		101.61(2)	807	8.96	—	2.534	2.141	174.6	46
[Hg ₂ (OHg) ₂](NO ₃) ₂	<i>P2</i> ₁ / <i>c</i>	2	5.532(3)	6.659(2)	11.578(5)		98.84(3)	421.4	7.552	7.52	2.510	2.16	177.9	27
Hg ₄ O ₂ (NO ₃) ₂	<i>P2</i> ₁ / <i>a</i>	2	11.580(2)	6.664(1)	5.533(1)		98.82(1)	422	7.54	7.5	2.510	2.136	178.1	48
Hg ₈ O ₄ Br ₃	<i>P2</i> ₁ / <i>n</i>	4	6.8554(9)	6.3033(9)	31.093(3)		96.09(1)	1336	9.49	—	2.517–2.557	2.10–2.24	165.1–172.4	49
Hg ₂ ReO ₅	<i>P</i> $\bar{1}$	4	7.952(2)	8.948(2)	9.015(2)	114.11(1)	101.64(2)	569.7	7.78	—	2.521	2.135, 2.143	170.4, 173.1	15
Hg ₅ Re ₂ O ₁₀ (I)	<i>P2</i> ₁ / <i>b</i>	2	6.401(5)	7.981(5)	11.538(7)		98.87(19)	582.4	8.755	—	2.546	2.14, 2.19	164.0, 173.9	52
Hg ₅ Re ₂ O ₁₀ (II)	<i>P2</i> ₁ / <i>c</i>	4	8.615(1)	12.009(2)	12.039(2)		97.15(1)	1235.8	8.25	—	2.520, 2.508	2.102–2.258	145.7–177.9	53
Hg ₂ VO ₄	<i>P2</i> ₁ / <i>n</i>	8	3.673(1)	16.503(1)	14.255(1)		89.99(1)	864.1	7.934	—	2.536	2.20	153, 173	19
Hg ₉ P ₅ I ₆	<i>P2</i> ₁ / <i>c</i>	4	13.112(5)	12.486(2)	17.031(3)		119.90(2)	2419.0	7.472	—	2.541	2.452 (Hg–P) 3.568–3.675 (Hg–I)	168.7 (Hg–Hg–P)	55
Hg ₅ CrO ₅ S ₂ (deanesmithite)	<i>P</i> $\bar{1}$	2	8.1287(8)	9.4916(7)	6.8940(4)	100.36(1)	110.16(1)	490.13	8.14	—	2.536	2.11, 2.352–2.442 (Hg–S)	171.3 (Hg–Hg–S) 167.6	57
Hg ₅ CrO ₆ (wattersite)	<i>C2/c</i>	4	11.274(2)	11.669(2)	6.603(1)		98.19(2)	859.8	8.891	—	2.526	2.10–2.16	153.3, 169.5	58
HgHg ₆ [Cl(OH)] ₂ O ₃ (hanawaltite)	<i>Pbma</i>	4	11.777(2)	13.891(3)	6.460(1)			1056.9	9.51	—	2.526, 2.56	1.93–2.30	175.4, 177.0	59
Hg ₄ O ₂ Cl ₂ (<i>terlinguaite</i>)	<i>C2/c</i>	4	11.953(4)	5.904(3)	9.466(4)		105.59(6)	643	9.35	9.40	2.703, 2.587(Cl)	2.234, 2.462,	60 (Hg–Hg–Hg)	44
Hg ₃ (AsO ₄)Cl (kuznetsovite)	<i>P2</i> ₁ 3	4	8.379(3)					588.3	8.763	—	2.675	2.17–2.28	60 (Hg–Hg–Hg)	60
Hg ₉ (AsO ₄) ₄	<i>R3c</i>	6	16.603(1)	—	10.830(2)			2585.4	9.038	—	2.662–2.696	2.142–2.343 (Hg–Hg–Hg)	59.5–60.8	
Compounds containing (Hg ₃) ²⁺ groups and Hg _{<i>n</i>} chains														
Hg ₃ (AsF ₆) ₂ , (Hg ₃) ²⁺ group	<i>P2</i> ₁ / <i>c</i>	2	5.981(5)	8.551(6)	11.282(10)		91.16(7)	577.1	5.67	—	2.552	2.38 2.83–2.96	180 (Hg–Hg–Hg) 168.9 (Hg–Hg–F)	63
Hg ₃ (AlCl ₄) ₂ , (Hg ₃) ²⁺ group	<i>P2</i> ₁ / <i>c</i>	4	7.1321(2)	15.0468(3)	14.1771(4)		99.05(3)	1502.5	4.16	3.95	2.551 2.562	2.517, 2.562 (Cl)	174.4 (Hg–Hg–Hg) 172.8, 176.6 (Hg–Hg–Cl)	66
Hg ₃ (NbF ₅) ₂ (SO ₄), (Hg ₃) ²⁺ group	<i>Fdd2</i>	8	18.068(6)	15.734(5)	9.176(4)			2608.6	5.49	5.467	2.562	2.276 (O) 2.809–2.990 (F)	166.6 (Hg–Hg–Hg) 174.8 (Hg–Hg–F)	67
Hg ₃ (TaF ₅) ₂ (SO ₄), (Hg ₃) ²⁺ group	<i>Fdd2</i>	8	18.078(7)	15.705(4)	9.153(2)			2599	6.388	6.387	2.554	2.27 (O) 2.76–3.00 (F)	166.2 (Hg–Hg–Hg)	67
Hg ₄ (Ta ₂ F ₁₁) ₂ , (Hg _{<i>n</i>}) ²⁺ chain	<i>I2/c</i>	4	18.556(8)	7.528(3)	14.714(8)		91.72(4)	2054	—	6.285	2.593, 2.630 3.033 (Hg⋯Hg)	2.74–2.82 2.97–3.23	177.2 (Hg–Hg–Hg) 165.1 (Hg–Hg–F)	67
Hg ₄ (AsF ₆) ₂ , (Hg _{<i>n</i>}) ²⁺ chain	<i>P2</i> ₁ / <i>c</i>	2	5.489(2)	11.633(4)	9.85(6)		92.20(4)	628.5	6.24	—	2.588, 2.620 2.985	2.71–2.95 3.06–3.34 (Hg⋯Hg)	177.3 (Hg–Hg–Hg) 141.3 (Hg–Hg–F)	68

Table 1 (continued).

Compound	Space group	Z	Unit cell parameters					$V/\text{\AA}^3$	$d_{\text{calc}}/\text{g cm}^{-3}$	d_{exp}	Bond length / $\text{\AA}$		The Hg—Hg—X angle ^a	Ref.	
			a	b	c	α	β				γ	Hg—Hg			Hg—X ^a
Hg _{2.86} AsF ₆ , (Hg _{<i>n</i>}) ²⁺ chain	$I4_1/amd$	4	7.538(4)	7.538(4)	12.339(5)				701.1	7.224	—	2.64	2.99	180 (Hg—Hg—Hg)	70
Hg _{2.86} (AsF ₆) _{0.953} , (Hg _{<i>n</i>}) ²⁺ chain	$I4_1/amd$	4	7.549(5)	7.549(5)	12.390(9)				706.1	7.04	7.06	3.24 (Hg⋯Hg)	2.87	180 (Hg—Hg—Hg)	71
												2.98			
Hg _{3−δ} SbF ₆ [δ = 0.10(2)], (Hg _{<i>n</i>}) ²⁺ chain	$I4_1/amd$	4	7.711(2)	7.711(2)	12.641(2)				751.6	7.22	—	2.66	2.86, 2.98	—	72
												3.22 (Hg⋯Hg)			
Hg _{3−δ} TaF ₆ [δ = 0.116(4)], (Hg _{<i>n</i>}) ²⁺ chain	$I4_1/amd$	4	7.711(1)	7.711(1)	12.714(2)				756.0	7.68	—	2.67	2.86, 2.983	—	73
												3.239 (Hg⋯Hg)			
Hg _{3−δ} NbF ₆ [δ = 0.119(2)], (Hg _{<i>n</i>}) ²⁺ chain	$I4_1/amd$	4	7.692(1)	7.692(1)	12.679(2)				750.2	6.95	—	2.67	2.86, 2.97	—	73
												3.222 (Hg⋯Hg)			
Hg _{3−δ} SbF ₆ [δ = 0.134(1)], (Hg _{<i>n</i>}) ²⁺ chain	$I4_1/amd$	4	7.655(1)	7.655(1)	12.558(1)				735.9	7.314	—	2.67	2.81, 2.956	—	74
												3.210 (Hg⋯Hg)			
Hg _{3−δ} TaF ₆ [δ = 0.142(2)], (Hg _{<i>n</i>}) ²⁺ chain	$I4_1/amd$	4	7.634(1)	7.634(1)	12.610(1)				734.9	7.844	—	2.67	2.81, 2.937	—	74
												2.937 (Hg⋯Hg)			
Hg ₃ NbF ₆ , layer (Hg) _{<i>n</i>}	$P\bar{3} 1m$	1	5.02(1)	5.021(1)	7.68(7)			120	167.6	8.0	—	2.90	3.2	—	75
Monovalent mercury compounds with organic ligands															
Hg ₂ (L ¹) ₂ (ClO ₄) ₂	$P2_1/c$	2	5.509(5)	15.110(10)	11.630(10)		98.1(1)		958	2.80	—	2.498	2.16 (N)	176.0	79
Hg ₂ (L ²) ₂ (ClO ₄) ₂	$C2/m$	8	16.49(2)	22.92(4)	5.04(1)		92.4(1)		1904	2.89	2.81	2.487	2.21 (N)	167.4	80
Hg ₂ (L ³) ₂ (ClO ₄) ₂	$P2_1/n$	2	18.639(3)	5.164(1)	11.224(1)		105.95(1)		1038.6	2.75	2.65	2.511	2.03 (N)	174.4	81
Hg ₂ (L ⁴) ₂ (ClO ₄) ₂	$I2/m$	2	10.629(1)	16.841(1)	7.142(1)		99.06(2)		1262.5	2.52	2.51	2.5177	2.15 (N)	180	82
Hg ₂ (L ⁵) ₂ (ClO ₄) ₂ · H ₂ O	$P2_1/n$	4	15.913	25.794	5.979		95.42		2443.2	2.738	—	2.501	2.16, 2.21 (N)	162.8, 171.5	83
Hg ₂ (L ⁶)(ClO ₄) ₂	$P\bar{1}$	2	10.206(2)	12.006(8)	14.411(6)	69.60(5)	83.04(13)	66.53(4)	1518.02	2.294	2.31	2.506	2.20 (N); 2.63, 2.69 (O)	170.3, 172.9	84
												2.227 (N)			
Hg ₂ (L ⁷) ₄ (ClO ₄) ₂	$P2_1/c$	2	11.729(1)	10.896(1)	18.392(2)		96.20(1)		2336.7	1.78	1.77	2.5084	2.476 (N)	153.9, 118.4	85
														87.5 (N—Hg—N)	
Hg ₂ (L ⁸) ₄ (ClO ₄) ₂	$P\bar{1}$	2	8.68(1)	12.76(2)	14.00(2)	115.2(1)	85.8(1)	97.5(1)	1390	2.34	2.35	2.523	2.19 (O)	105.9–159.9	87
													2.34–2.56		
Hg ₂ (Ph ₂ Se) ₄ (ClO ₄) ₂ (yellow form)	$P2_1/n$	2	13.910(8)	14.575(9)	12.109(6)		92.60		2452	2.08	2.27	2.5579	2.701, 2.802 (Se) 2.705 (O)	116.4, 141.1 (Hg—Hg—Se)	88
														103.3 (Hg—Hg—O)	
														100.56 (Se—Hg—Se)	
Hg ₂ (Ph ₂ Se) ₄ (ClO ₄) ₂ (red form)	$P2_1/n$	2	11.609	14.462	14.391		98.20		2392	2.13	2.27	2.553	2.653, 2.919 (Se) 2.626 (O)	104.4, 152.0 (Hg—Hg—Se)	89
														109.6 (Hg—Hg—O)	
														102.7 (Se—Hg—Se)	
Hg ₂ (Ph ₃ PO) ₆ (ClO ₄) ₂	$P\bar{1}$	1	12.55(1)	14.47(2)	16.05(2)	120.0(1)	82.3(1)	95.2(1)	2499	1.51	1.50	2.522	2.29–2.43 (O)	116.0–140.0	90
														79.4–86.4 (O—Hg—O)	
Hg ₂ Phen(NO ₃) ₂	$P\bar{1}$	2	6.83(2)	10.55(3)	10.58(3)	98.6(1)	93.0(1)	97.6(1)	744	3.15	3.04	2.516	2.30–2.48 (N) 2.227–2.590 (O)	131.7, 136.7, 171.3	91
Hg ₂ (L ⁹) ₂ (NO ₃) ₂	$C2/c$	4	10.628(9)	10.219(8)	18.236(15)		100.35(6)		1948.34	2.67	2.61	2.551	2.168 (N)	164.4	92
Hg ₂ (L ¹⁰) ₂ (NO ₃) ₂	$C2/c$	4	26.969(4)	5.273(1)	16.956(4)		100.89(1)		2368.0	2.56	—	2.517	2.192 (N)	160.5	93
Hg ₂ (L ¹¹) ₂ (NO ₃) ₂	$P2/c$	2	8.6819(5)	5.3696(6)	19.7645(8)		95.138(12)		917.74	2.70	2.75	2.518	2.233 (N), 2.658 (O)	164.3, 113.9	94

Table 1 (continued).

Compound	Space group	Z	Unit cell parameters						$V/\text{\AA}^3$	$d_{\text{calc}}/\text{g cm}^{-3}$	d_{exp}	Bond length / $\text{\AA}$		The Hg–Hg–X angle ^a	Ref.
			<i>a</i>	<i>b</i>	<i>c</i>	α	β	γ				Hg–Hg	Hg–X ^a		
Hg ₂ (L ¹²) ₂ (NO ₃) ₂	$P\bar{1}$	2	5.4878(1)	8.4085(1)	9.6062(1)	92.599(3)	94.763(3)	89.614(3)	441.283	2.865	—	2.524	2.209 (N)	169.5	95
Hg ₂ (L ¹³) ₂ (NO ₃) ₂	$P2_1/c$	4	6.970(5)	15.205(8)	11.185(8)		96.0(6)		1178.9	3.67	3.55	2.541	2.496, 2.584 (S) 2.516 (O)	173.5, 138.7	96
[Hg ₂ (L ¹⁴) ₂](NO ₃) ₂	$P2_1/n$	2	11.755(9)	10.798(8)	8.760(8)		110.74(4)		1039.86	1.972	—	2.549	2.469, 2.489 (S) 2.636, 2.652 (O)	162.0, 163.3 101.3, 113.0	97
Hg ₂ (L ¹⁵) ₂ (H ₂ O) ₂	$C2/c$	4	9.989(9)	11.788(9)	13.527(13)		94.350(9)		1588.22	3.151	—	2.494	2.203 (N), 2.621 (O)	165.7	98
Hg ₂ (L ¹⁶) ₂	$C2/c$	4	23.624(4)	6.057(9)	14.857(3)		126.23(7)		1714.86	2.89	2.80	2.500	2.179 (N)	170.7	99
Hg ₂ (L ¹⁷) ₂	$P\bar{1}$	1	9.311(9)	7.347(3)	6.985(3)	114.80(15)	92.69(4)	86.41(7)	432.80	2.86	2.80	2.515	2.187 (N), 2.68 (O)	169.6, 107.3	99
Hg ₂ (L ¹⁷) ₂ (H ₂ O) ₂	$P2_1/n$	2	11.944(3)	7.588(2)	10.345(4)		105.44(6)		903.74	2.87	2.80	2.522	2.201 (N) 2.711, 2.715 (O)	172.8 89.7, 107.1	99
Hg ₂ (L ¹⁸) ₂	$C2/c$	8	26.330(20)	6.254(2)	12.90(10)		116.94(3)		1893.4	3.96	4.03	2.519	2.08, 2.16 (O)	171. 175	100
Hg ₂ (L ¹⁹) ₂	$P\bar{1}$	1	5.038(1)	5.970(1)	15.774(6)	80.77(2)	86.42(2)	84.38(2)	465.5	3.151	3.12	2.514	2.13 (O)	173.9	101
Hg ₂ (CF ₃ CO ₂) ₂	$C2/c$	4	14.866(5)	9.337(5)	8.230(5)		124.4(2)		943.8	4.412	4.391	2.505	2.14 (O)	166.6	102
Hg ₂ [C(CN) ₃] ₂	$P\bar{1}$	2	5.2794(1)	9.9297(1)	11.3376(2)	71.004(4)	76.459(2)	74.601(4)	534.647	3.611	—	2.506	2.287, 2.508 (N)	123.9, 121.3 123.0–140.0	103
Hg ₂ (C ₇ NH ₄) ₂	$P2_1/n$	2	9.9193(1)	5.6912(2)	13.3806(1)		92.544(2)		754.63	3.007	—	2.503	2.207–2.560 (N)	162.2, 116.5	104
Hg ₂ (L ²⁰) ₂ (AlCl ₄) ₂ ·C ₇ H ₈	$P2_1/c$	4	21.160(10)	10.951(7)	18.80(10)		104.9(1)		4209.9	1.823	—	2.515	2.416, 2.672 (C)	—	105
Mercury-containing transition metal clusters															
Hg ₂ Co ₂ [N(C ₂ H ₄ PPh ₂) ₃]·THF	$P\bar{1}$	2	25.691(9)	13.387(5)	13.471(4)	119.56(8)	97.51(8)	87.25(7)	3994.48	1.578	—	2.651	2.429, 2.444		106
{Hg ₂ Pt ₆ [(Ph ₂ P) ₂ (CH ₂) ₆] ₃ — —(C ₈ H ₉ NC) ₆ }·2(C ₆ H ₆)	$C2/c$	4	56.86(8)	15.120(8)	31.01(3)		141.29(6)		16673	1.545	—	2.872 (Pt—Pt) 2.656–2.672	2.878–2.993		107
[(Ph ₃ P) ₂ N] ₂ [Hg ₂ Os ₁₈ (CO) ₂₀ C ₂]	$P\bar{1}$	1	18.711(4)	16.379(3)	11.724(2)	111.242(2)	84.284(1)	105.994(2)	3220.08	3.147	—	2.744 (Os—Os) 2.743–3.038	2.636–2.907		108
[(Ph ₃ P) ₂ N] ₄ [Hg ₂ Os ₁₈ (CO) ₄₂ C ₂]· ·CH ₂ Cl ₂	$P\bar{1}$	1	19.121(2)	16.638(4)	17.676(4)	89.23(2)	117.24(2)	94.03(2)	5053.91	2.326	—	2.820 (Os—Os) 2.748–3.092	2.474–2.898		109
{Hg ₃ [(Ph ₂ P) ₂ CH ₂] ₃ }(SO ₄) ₂ ·1.5H ₂ O	$P2_1/n$	4	15.069(2)	24.025(2)	22.405(2)		93.88(1)		8092.8	1.620	—	2.764–2.802	—		110
[(Ph ₃ P) ₂ N] ₂ [Hg ₃ Ru ₁₈ C ₂ (CO) ₄₂]· ·CH ₂ Cl ₂	$P\bar{1}$	1	19.042(4)	15.729(3)	15.197(3)	115.59(2)	68.51(2)	115.46(2)	2983.18	2.66	—	2.919–2.934 2.733–3.010 (Ru—Ru)	2.640–2.734		111
(C ₃₆ H ₃₀ NP ₂) ₂ [Hg ₃ Os ₉ (CO) ₂₁ C ₂]· ·CH ₂ Cl ₂	$P\bar{1}$	1	19.022(4)	15.737(3)	15.205(3)	115.66(2)	68.32(2)	115.45(3)	3609.39	2.910	—	2.919, 2.931	2.678–2.762		112
Hg ₂ Ag[(Ph ₂ P) ₂ CH ₂] ₃ (CF ₃ SO ₃) ₃	$P2_1/n$	4	15.256(3)	28.028(8)	21.863(3)		92.14(1)		9342	1.500	—	2.660	2.805, 2.853		114
[Nb(η-C ₅ H ₅) ₂ {HgS ₂ CN(C ₂ H ₅) ₂ }] ₃	$P2_1/n$	4	12.302(10)	18.385(11)	16.077(5)		108.18(5)		3454.66	2.441	—	2.901, 2.883	2.777–2.808		115
[(η ⁵ -C ₅ H ₅)Mn(CO) ₂ Hg] ₄	$I\bar{4}$	2	15.959(2)	15.959(2)	7.683(1)		—		1956.8	2.64	—	2.888	2.640		116
[(η ⁵ -C ₅ H ₅)Re(CO) ₂ Hg] ₄	$C2/c$	8	20.036(14)	16.143(8)	22.111(13)		78.66(5)		—	3.85	—	2.92	2.74		117
[(C ₁₂ H ₃₆) ₃ Rh] ₄ Hg ₆	$Ccmm$	4	12.909(2)	25.274(4)	25.176(4)		—		8213.9	2.05	—	3.131–3.149	2.690–2.724		118
[(C ₈ H ₁₈ P) ₂ Pt] ₄ Hg ₆	$C2/c$	4	12.738(3)	48.692(6)	16.602(3)		95.16(2)		10255.47	2.037	—	3.081–3.274	2.671–2.876		119
[Hg ₉ Co ₆ (CO) ₁₈]·2(C ₃ H ₆ O)	$P2_1/c$	4	14.341(6)	21.024(6)	18.543(9)		94.50(4)		5574	3.11	—	3.066–3.216	2.521–2.609		120

Note. Samples of natural and synthetic (italicised) minerals were studied; the unit cell parameters *a*, *b* and *c* are given in Å, the angles α , β , γ and Hg–Hg–X are given in deg.

^a For inorganic monovalent mercury compounds, mixed-valence mercury compounds and compounds containing (Hg₃)²⁺ groups and Hg_n chains X = O or Hal; for monovalent mercury compounds with organic ligands, X = N, O, Se or S; for mercury-containing transition metal clusters, X = Hg, Pt, Os or Ru.

nearly parallel to the a axis. The distances between the nearest pairs are 4.5 Å. The Hg—O distance in the —O—Hg—Hg—O— group is 2.16 Å. In addition, there are Hg $\cdots$ O distances (2.66 and 2.69 Å). Taking into account the latter contacts, the coordination environment about the mercury atoms can be described as a distorted tetrahedron. The Hg₂(BrO₃)₂ molecules are linked in linear chains along the c axis through weak O $\cdots$ O contacts (2.66 Å). The rows of the mercury pairs alternate with double rows of the BrO₃[−] anions along the a axis (Fig. 3). The effect of the mercury atoms on the BrO₃[−] groups consists in the increase in the distance between the bromine atom and the oxygen atom bound to the mercury pair. This distance is 1.76 Å, whereas two other Br—O bond lengths are 1.64 and 1.65 Å.

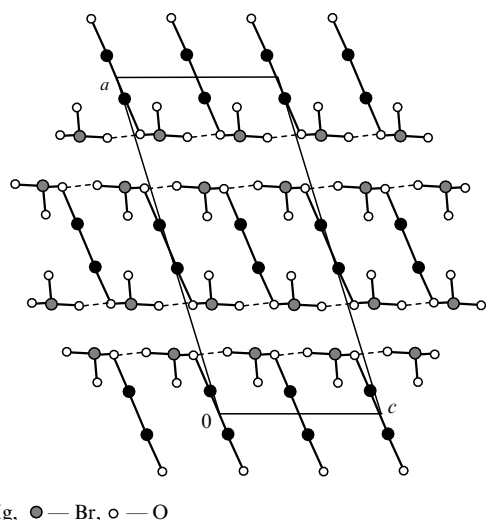


Figure 3. Projection of the crystal structure of Hg₂(BrO₃)₂ onto the (010) plane. The O $\cdots$ O contacts are indicated by dashed lines.

The crystal structure of HgReO₄ consists of discrete (O₃Re—O—Hg—Hg—O—ReO₃) groups, which are substantially nonlinear (the Hg—Hg—O angle is 159.4°), apparently, due to the type of the molecular packing in the monoclinic unit cell.¹⁵ The mercury atoms each form contacts with the oxygen atoms of other structural units (the distances are larger than 2.49 Å) along with the short Hg—O bonds.

The virtually linear groups were also found in the first structurally studied monovalent mercury nitride, Hg₂(NO₂)₂, consisting of the planar centrosymmetrical molecular NO₂—Hg—Hg—NO₂ groups.¹⁶ The nonbonded Hg $\cdots$ O interactions (2.84 and 2.93 Å) are analogous to those found by Grdenic.⁷ Taking into consideration these contacts, the coordination number of the mercury atom increases to 4. In the crystal structure of Hg₂(NO₂)₂, the molecules are packed in a herringbone fashion.^{7,8} The structure of this compound was also studied by Ohba and coworkers.¹⁷ In this study, the Hg $\cdots$ O bond (2.577 Å) was found along with the Hg—O (2.24 Å) bond, *i.e.*, both oxygen atoms of the NO₂[−] group are bound to the mercury atoms of the (Hg—Hg)²⁺ cations to form a planar centrosymmetrical molecule. In addition, Hg $\cdots$ O contacts (2.826 Å) between the adjacent molecules were revealed. The authors believed that the yellow colour of the crystals is associated with the bridging function of the (Hg₂)²⁺ pairs.

A rather short Hg—Hg distance (2.499 Å) was observed in the structure of Hg₂(H₂PO₄)₂.¹⁸ Each mercury atom has an oxygen atom as the nearest neighbour at a distance of 2.14 Å. The —O—Hg—Hg—O— fragment is nonlinear (the Hg—Hg—O angle is 167.2°). The distances between the mercury atom and the remaining oxygen atoms are larger than 2.5 Å. The structure of the complex consists of the discrete Hg₂(H₂PO₄)₂ molecules linked in a three-dimensional framework *via* hydrogen bonds (O $\cdots$ O

2.52–2.79 Å). The herringbone molecular packing in the crystal of the complex is analogous to those observed in anhydrous Hg₂(NO₂)₂ (see Refs 16 and 17) and its dihydrate Hg₂(NO₂)₂·2H₂O.⁸

What the crystal structures of the two known mercurous vanadates, *viz.*, HgVO₃ and the mixed-valence Hg₂VO₄, have in common is a distorted five-vertex coordination polyhedron about the vanadium formed by the oxygen atoms.¹⁹ In both structures, the polyhedra of the vanadium atoms are linked *via* shared edges to form infinite [(VO₃)_n][−] chains. In the structure of HgVO₃, these chains are linked through the (Hg₂)²⁺ pairs in two-dimensional corrugated infinite (Hg₂)_n²⁺[(VO₃)_n][−] layers, which are linked *via* weak interlayer Hg $\cdots$ O contacts (2.71–2.95 Å), unlike the mixed-valence Hg₂VO₄ compound, in which the [(VO₃)_n][−] chains do not form strong bonds with the mercury atoms.

Only three mercury molybdates were structurally characterised. The compound HgMoO₄ contains the divalent mercury atom. The Hg₂Mo₂O₇ and Hg₂Mo₅O₁₆ polymolybdates contain the (Hg₂)²⁺ ions. The layered structures of Hg₂Mo₂O₇ (see Ref. 20) and Hg₂Mo₅O₁₆ (see Ref. 21) are based on the MoO₄ tetrahedra linked in Mo₂O₇ groups and Mo₅O₁₆ fragments, respectively. The coordination environment about the molybdenum atoms is a distorted octahedron. In both compounds, the Mo octahedra are linked in two-dimensional infinite layers *via* shared vertices and edges. The layers are separated by the (Hg₂)²⁺ pairs (Fig. 4). In the structure of Hg₂Mo₂O₇, the Hg—Hg and Hg—O distances have standard values, whereas the Hg—Hg bond in Hg₂Mo₅O₁₆ is rather short (2.474 Å) and the —O—Hg—Hg—O— fragments deviate significantly from linearity (the Hg—Hg—O angle is 152.7°). Noteworthy is the similarity of the structures of Hg₂Mo₅O₁₆ and Cs₂Mo₅O₁₆.²²

In the crystal structure of the synthetic analogue of the mineral chursinite (Hg₂)₃(AsO₄)₂ (see Ref. 23), the (Hg₂)²⁺ cations and the AsO₄^{3−} anions are packed in such a manner that three of the four oxygen atoms of the AsO₄^{3−} groups are bound to three different mercury pairs (the Hg—O distances are 2.16, 2.22 and 2.23 Å) to form puckered layers. The fourth oxygen atom is bound to three mercury atoms of the adjacent layer (the Hg $\cdots$ O distances are 2.48, 2.46 and 2.71 Å) and has a distorted tetrahedral coordination, the As—O distance with this oxygen atom (1.78 Å) being larger than the remaining three As—O distances (the average value is 1.68 Å). These characteristic groups are linked to each other along the a axis through Hg $\cdots$ O contacts (2.68 and 2.42 Å) and along the c axis through Hg $\cdots$ O contacts (2.47 Å). Taking into account all interactions, the structure of (Hg₂)₃(AsO₄)₂ can be considered as a three-dimensional framework (Fig. 5). It should be noted that the —O—Hg—Hg—O— fragments are substantially nonlinear (the Hg—Hg—O angles are 146–157°).

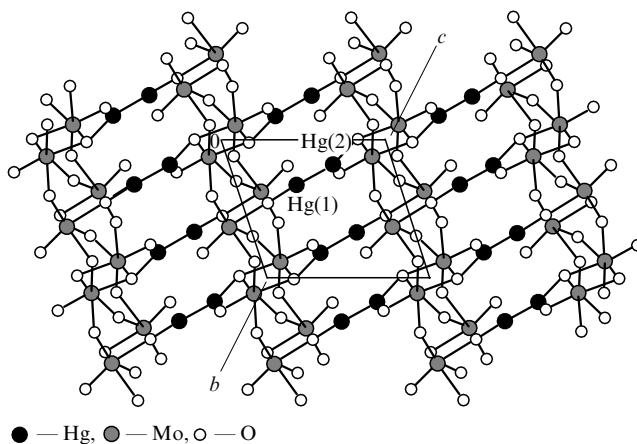


Figure 4. Crystal structure of Hg₂Mo₂O₇.

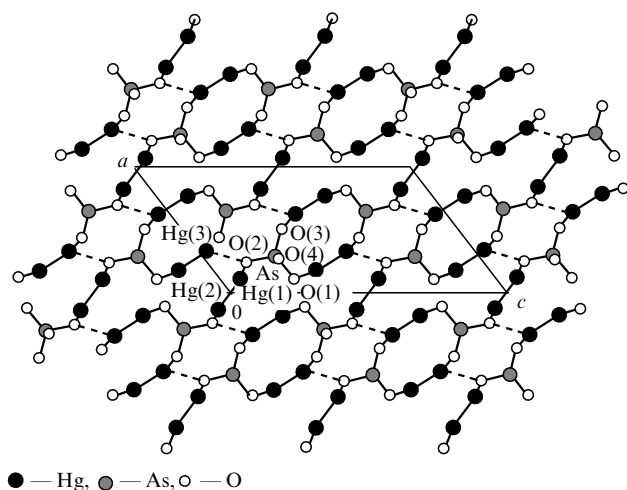


Figure 5. Projection of the crystal structure of $(\text{Hg}_2)_3(\text{AsO}_4)_2$ onto the (010) plane. The $\text{Hg}\cdots\text{O}$ contacts are indicated by dashed lines.

The mercury pairs, which are linked in infinite $-\text{O}-\text{Hg}-\text{Hg}-\text{O}-\text{Hg}-\text{Hg}-\text{O}-$ chains *via* the XO_4^{2-} groups ($\text{X} = \text{S}$ or Se), were observed in the isostructural Hg_2SO_4 and Hg_2SeO_4 compounds.²⁴ The chains intersect the unit cells along the diagonals nearly parallel to the ac planes. In Hg_2XO_4 , there are $\text{Hg}\cdots\text{O}$ contacts (2.49 and 2.50 Å in Hg_2SO_4 and Hg_2SeO_4 , respectively), which link chains. The $-\text{O}-\text{Hg}-\text{Hg}-\text{O}-$ fragments deviate from linearity (the $\text{Hg}-\text{Hg}-\text{O}$ angles are 165° and 160° in Hg_2SO_4 and Hg_2SeO_4 , respectively). No noticeable changes in the size and no distortions of the XO_4^{2-} tetrahedra are observed in the structures.

More than 30 compounds were found and described in the ternary $\text{Hg}_2\text{O}-\text{N}_2\text{O}_5-\text{H}_2\text{O}$ system.²⁵ In the studies devoted to the hydrolysis products of nitrate $\text{Hg}_2(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$,²⁶ the authors confirmed the existence of only three low-valent mercury oxonitrates, *viz.*, $[(\text{Hg}_2)_2\text{O}(\text{NO}_3)]\text{NO}_3 \cdot \text{HNO}_3$ and $[(\text{Hg}_2)_5(\text{OH})(\text{NO}_3)_2](\text{NO}_3)_2$ containing monovalent mercury and the mixed-valence $[(\text{Hg}_2)(\text{OHg})_2](\text{NO}_3)_2$ compound.

In spite of the difficulties associated with the preparation of single crystals of these compounds, their structures were studied by X-ray diffraction analysis.²⁷ In the structure of $[(\text{Hg}_2)_2\text{O}(\text{NO}_3)]\text{NO}_3 \cdot \text{HNO}_3$, three $(\text{Hg}_2)^{2+}$ pairs are linked together through the oxygen atoms (the $\text{Hg}-\text{O}$ distances are 2.12, 2.19 and 2.31 Å) to form a planar (the height is 0.31 Å) trigonal pyramid with the $\text{O}-\text{Hg}-\text{O}$ angles varying from 112.9 to 123.5° . The analogous function of the oxygen atom was pointed out in the structures of mercury(II) oxochloride Hg_3OCl_4 (see Ref. 28), the mineral eglestonite $(\text{Hg}_2)_3\text{Cl}_3\text{O}_2\text{H}$ (see Ref. 3) and in a number of other mercury compounds. The structure of $[(\text{Hg}_2)_2\text{O}(\text{NO}_3)]\text{NO}_3 \cdot \text{HNO}_3$ as a whole consists of infinite mercury-oxygen chains linked in a three-dimensional framework through the NO_3^- ions, which coordinate the mercury atoms (the $\text{Hg}\cdots\text{O}$ contacts are in the range of 2.45–2.96 Å). The hydrogen atom was not located in the structure refinement of this compound. Based on the known data on the structures of the oxonium mercury salts, the authors²⁷ suggested that HNO_3 exists as a molecule of solvation linked to the nitrate ion through a hydrogen bond ($\text{O}-\text{H}\cdots\text{O}$, 2.81 Å). The structure of this compound was more accurately established by an independent research group.²⁹ The position of the hydrogen atom of the hydroxy group was revealed. This group is coordinated to three $(\text{Hg}_2)^{2+}$ pairs ($\text{O}-\text{H}$, 1.26 Å) (Fig. 6). As a result, the structure is additionally stabilised through weak hydrogen bonds between the oxygen atoms of the hydroxy groups and the adjacent nitrate ions ($\text{Hg}\cdots\text{O}$, 2.803–2.863 Å). Based on this fact, the authors²⁹ proposed that the formula of the compound should be written as $\text{Hg}_2\text{OH}(\text{NO}_3) \cdot \text{Hg}_2(\text{NO}_3)_2$.

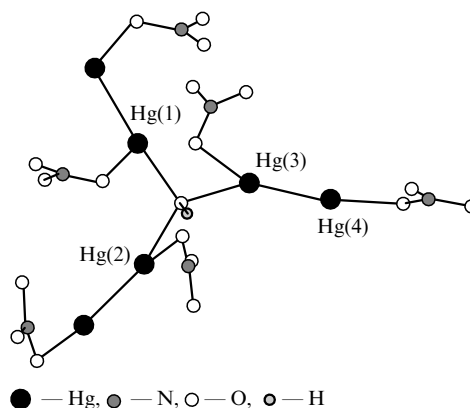


Figure 6. Fragment of the structure of $\text{Hg}_2\text{OH}(\text{NO}_3) \cdot \text{Hg}_2(\text{NO}_3)_2$.

The structure of the $[(\text{Hg}_2)_5(\text{OH})(\text{NO}_3)_2](\text{NO}_3)_4$ compound contains the finite cationic $[(\text{Hg}_2)_5(\text{OH})(\text{NO}_3)_2]^{4+}$ chains linked *via* weak van der Waals interactions between the adjacent mercury and oxygen atoms ($\text{Hg}\cdots\text{O}$, 2.642 and 2.745 Å).^{27,30} The chains form ribbons extended along the $[100]$ direction. The $-\text{O}-\text{Hg}-\text{Hg}-\text{O}-$ fragments are virtually linear. The coordination environment about the mercury atoms involves the additional NO_3^- anions ($\text{Hg}\cdots\text{O}$, 2.763–2.887 Å), which are responsible for the formation of a loose framework.

The structure of mercurous nitrophosphate $\text{Hg}_4\text{PO}_4\text{NO}_3 \cdot \text{H}_2\text{O}$ is built of the PO_4^{3-} and NO_3^- anions and the water molecules bound to the $(\text{Hg}_2)^{2+}$ pairs, which form zigzag chains (the $\text{Hg}-\text{Hg}$ distances are 2.508 and 2.532 Å; the $\text{Hg}-\text{O}$ distances range from 2.11 to 2.21 Å; the $\text{Hg}-\text{Hg}-\text{O}$ angles vary from 147 to 168°). These chains are linked in a three-dimensional framework through additional bonds.³¹ No significant changes in the size and configuration of the anions in the crystal were observed.

The isostructural monophosphates and monoarsenates of silver and monovalent mercury were prepared as early as 1909. However, the crystal structure of AgHg_2PO_4 was established only in 1978.³² The structure of the latter compound consists of the tetrahedral PO_4^{3-} anions and the $\text{Ag}-\text{Ag}$ (2.824 Å) and $\text{Hg}-\text{Hg}$ pairs (2.608 Å). Interestingly, this structure does not contain the linear $-\text{O}-\text{M}-\text{M}-\text{O}-$ fragments ($\text{M} = \text{Ag}$ or Hg) typical of the above-considered compounds and each mercury atom is coordinated by three oxygen atoms of different PO_4 tetrahedra with elongated $\text{Hg}-\text{O}$ bonds (2.224–2.346 Å). Therefore, the coordination environment about the mercury atoms in the $\text{Hg}-\text{Hg}$ dimer is a tetrahedron ($\text{Hg} + 3\text{O}$). Each silver atom is coordinated by two oxygen atoms ($\text{Ag}-\text{O}$, 2.289 Å). The $\text{Hg}-\text{Hg}$ and $\text{Ag}-\text{Ag}$ dimers are in the mutually perpendicular arrangement and are rather closely spaced (the $\text{Hg}-\text{Ag}$ distances are 2.840 and 2.941 Å). These data suggest the existence of the tetrahedral Ag_2Hg_2 clusters.

The three-dimensional $(\text{Hg}_4\text{O}^{2+})_n$ framework of hexagons formed by the $-\text{O}-\text{Hg}-\text{Hg}-\text{O}-$ fragments ($\text{Hg}-\text{Hg}$, 2.458 Å; $\text{Hg}-\text{O}$, 2.108 Å) was found in the crystal of the $\text{Hg}_4\text{OPb}_2(\text{NO}_3)_6$ compound.³³ The Pb^{2+} ions occupy the cavities of the framework and six statistically disordered NO_3^- groups act as bidentate ligands with respect to Pb^{2+} ($\text{Pb}-\text{O}$, 2.77–2.89 Å). The $\text{Hg}_4\text{OBa}_2(\text{NO}_3)_6$ compound isomorphous to $\text{Hg}_4\text{OPb}_2(\text{NO}_3)_6$ was also obtained.

Heteropolytungstate $\text{K}_5\text{Cs}_5[(\text{Hg}_2)_2\text{WO}(\text{H}_2\text{O})(\text{AsW}_9\text{O}_{53})_2]$ was synthesised and structurally characterised for the first time in the study.³⁴ In this complicated structure, both $[\text{As}_2\text{W}_{19}\text{Hg}_4\text{O}_{67}(\text{H}_2\text{O})]_{10}^-$ polyanions of one asymmetrical unit contain two $(\text{Hg}_2)^{2+}$ pairs, in which each mercury atom is bound to two oxygen atoms (the $\text{Hg}-\text{O}$ distances vary from 2.16 to 2.34 Å). All eight mercury atoms of the asymmetrical unit form a distorted cube, whose vertices alternately correspond to the

covalent Hg—Hg bonds (2.446–2.545 Å) and the Hg...Hg distances (3.303–3.796 Å).

The structures of a series of mercury minerals containing the $(\text{Hg}_2)^{2+}$ pairs were analysed in detail.² These structures are also characterised by three-dimensional frameworks. Thus, in shakhovite $\text{Hg}_4\text{SbO}_3(\text{OH})_3$, the $\text{O}\cdots\text{O}$ contacts (2.618–2.932 Å) between the oxygen atoms of the adjacent SbO_6 octahedra link these octahedra in layers parallel to the (001) plane, which, in turn, are linked in a three-dimensional framework through the $(\text{Hg}_2)^{2+}$ pairs (Fig. 7).³⁵

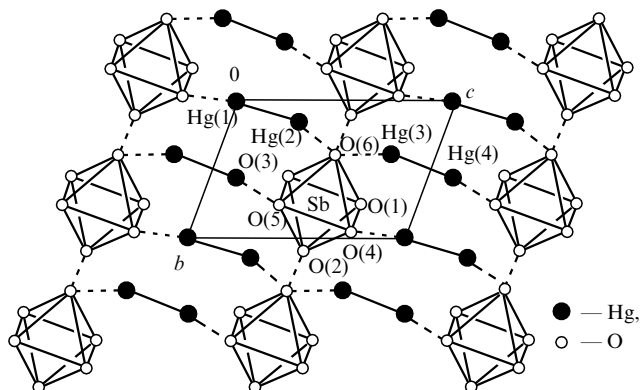


Figure 7. Projection of the crystal structure of shakhovite $\text{Hg}_4\text{SbO}_3(\text{OH})_3$ onto the (100) plane. The $\text{O}\cdots\text{O}$ and $\text{Hg}\cdots\text{O}$ contacts are indicated by dashed lines.

In the crystal structure of the rare mineral poyarkovite Hg_3OCl , six $(\text{Hg}_2)^{2+}$ pairs were found;³⁶ the distances between the mercury atoms vary from 2.503 to 2.565 Å. The $(\text{Hg}_2)^{2+}$ cations are located along three mutually perpendicular directions. Each oxygen atom forms four tetrahedrally directed Hg—O bonds (1.94–2.51 Å) through which the mercury pairs are linked in a framework (Fig. 8).

The above-mentioned structure of the mineral eglestonite $(\text{Hg}_2)_3\text{Cl}_3\text{O}_2\text{H}$ (see Ref. 37) consists of four interpenetrating cubic three-dimensional frameworks $(\text{Hg}_2)_3\text{O}_2$ (see Ref. 1), in which the oxygen atoms are involved in three Hg—O bonds and link the $(\text{Hg}_2)^{2+}$ pairs located along each bond of the framework.

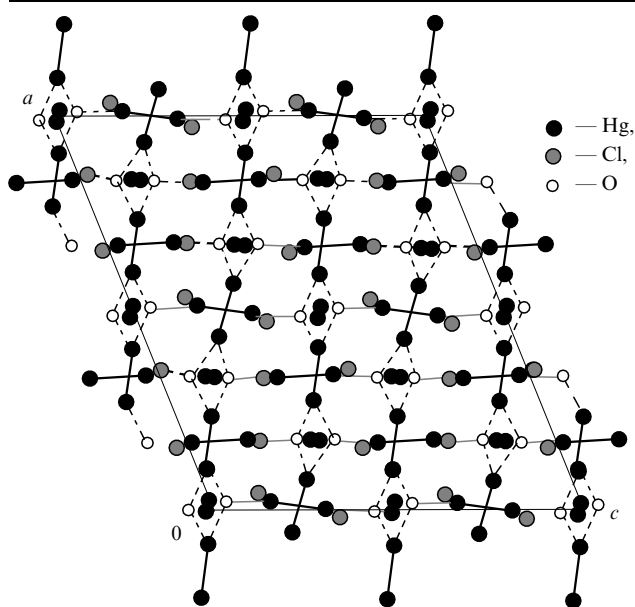


Figure 8. Systems of the mutually perpendicular $(\text{Hg}_2)^{2+}$ pairs in the structure of poyarkovite Hg_3OCl .

The frameworks are linked to each other through short $\text{O}\cdots\text{H}\cdots\text{O}$ hydrogen bonds ($\text{O}\cdots\text{O}$, 2.59 Å) and chlorine atoms.

In the structure of magnolite Hg_2TeO_3 , the $-\text{O}-\text{Hg}-\text{Hg}-\text{O}-$ fragments are linked *via* the tellurium atoms ($\text{Te}-\text{O}$, 1.93 Å) in zigzag chains extended along the [010] direction. The chains are linked through $\text{Hg}\cdots\text{O}$ contacts (2.692–2.998 Å). There are also short $\text{O}\cdots\text{O}$ distances (2.817 and 2.750 Å).³⁸

The study of edgarbaileite $\text{Hg}_6\text{Si}_2\text{O}_7$ demonstrated³⁹ that the Hg—Hg pairs in this structure are parallel to each other and the $-\text{O}-\text{Hg}-\text{Hg}-\text{O}-$ fragments are virtually linear. Each mercury atom is additionally coordinated by two oxygen atoms (the Hg—O distances are 2.41–2.86 Å). The Si_2O_7 groups are located between the mercury pairs and are linked in a framework through the Hg—O bonds (2.21 and 2.63 Å).

The distinguishing feature of the structure of szymanskiite $\text{Hg}_{16}(\text{Ni},\text{Mg})_6(\text{CO}_3)_{12}(\text{OH})_{12}(\text{H}_3\text{O})_8\cdot 3\text{H}_2\text{O}$ is that the MO_6 octahedra ($\text{M} = \text{Ni}$ or Mg) are linked to the linear $-\text{O}-\text{Hg}-\text{Hg}-\text{O}-$ fragments in a rigid framework with large channels (the diameter is 13.6 Å) (Fig. 9).⁴⁰ The channels are occupied by the disordered CO_3 groups and the water molecules, which are rather weakly bound to each other. This gives grounds to consider this mineral as a nonsilicate zeolite. Note that in the structure of szymanskiite, like in the structure of AgHg_2PO_4 (see Ref. 32), the mercury atoms belonging to one type of the $(\text{Hg}_2)^{2+}$ pairs have an umbrella-shaped coordination with the involvement of three oxygen atoms of the CO_3 groups located at longer distances (Hg—O, 2.34 and 2.44 Å). This coordination is rarely observed in monovalent mercury compounds.

Analysis of the structures of inorganic compounds containing $(\text{Hg}_2)^{2+}$ groups with different ligands demonstrates that the Hg—Hg distances vary from 2.45 to 2.59 Å. No distinct correlations between the Hg—Hg and Hg—X distances in the $\text{X}-\text{Hg}-\text{Hg}-\text{X}$ groups and the nature of inorganic ligands X were observed. In the series of the compounds with the NO_3^- , BrO_3^- , TeO_3^{2-} and VO_3^- ligands, the Hg—Hg distances increase from 2.50 to 2.54 Å, which can be related to a decrease in the electronegativity of the ligands in this series of anions. In the series of the compounds with the ReO_4^- , PO_4^{3-} and AsO_4^{3-} ligands, the Hg—Hg distances vary from 2.506 to 2.535 Å. The shortest distance was observed in the HgReO_4 compound because the total negative charge of the ReO_4^- anion is smaller than the effective negative charge of the oxygen atom due to the higher oxidation state of the rhenium atom compared to the phosphorus and arsenic atoms. The increase in the Hg—Hg distance from 2.50 Å in mercury nitrate to 2.52 Å in mercury nitrite can also be attributed to the lower degree of oxidation of the nitrogen atom in the NO_2^- anion compared to that in the NO_3^- anion. The longest Hg—Hg distance in the three-dimensional Hg—O framework (2.56 Å) is observed if the coordinating oxygen atoms bind only

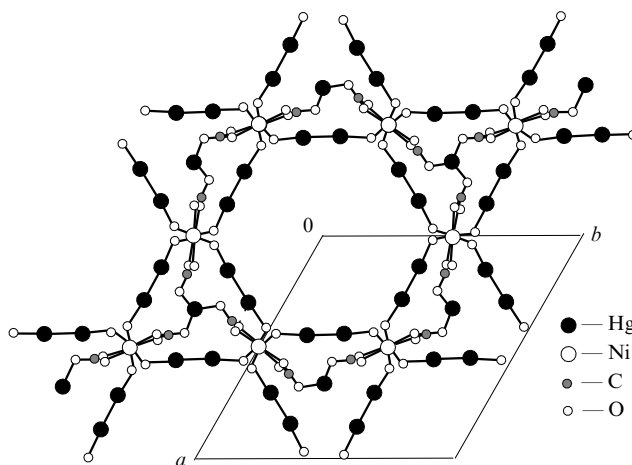


Figure 9. Fragment of the crystal structure of szymanskiite.

(Hg_2) $^{2+}$ groups, *i.e.*, a competing cation is absent. An increase in the Hg–Hg distance can also occur, apparently, due to an increase in the covalence of the Hg–X bond.⁵

A noticeable effect of a strong metal–metal bond on the configuration of compact tetrahedral SO_4^{2-} , SiO_4^{4-} , PO_4^{3-} and AsO_4^{3-} anions was observed only in some instances, for example, in the (Hg_2) $_3(\text{AsO}_4)_2$ compound.²³ An increase in the length of one Br–O bond compared to the remaining bond lengths was also found in $\text{Hg}_2(\text{BrO}_3)_2$.¹⁴

Hence, the coordination of the mercury atoms in oxygen-containing compounds is generally linear with one short Hg–O distance (~ 2.10 Å) and one-to-two additional atoms located at substantially larger distances. In the mineral szymanskiite and in phosphate AgHg_2PO_4 , some mercury atoms in the Hg–Hg dimers are nonlinearly coordinated by the oxygen atoms [an umbrella of three oxygen atoms with the larger Hg–O distances (2.22–2.44 Å)].

III. Mixed-valence inorganic mercury compounds

The data on a number of rather rare mixed-valence compounds containing Hg^{2+} cations and Hg_n groups ($n = 2$ or 3), in which the oxidation state of the mercury atoms is lower than +2, are available. The principal crystal-structural characteristics of these compounds are given in Table 1.

The existence of a compound containing mercury in two oxidation states, *viz.*, in +2 and +1, was first reported in a study,⁴¹ in which the results of X-ray diffraction study of the synthetic analogue of the rare mineral terlinguaite $\text{Hg}_4\text{O}_2\text{Cl}_2$ were discussed. Several studies were devoted to the crystal structures of the natural samples and their synthetic analogues.^{41–44} The studies confirmed the fact that the mercury atoms in terlinguaite exist in different oxidation states, *viz.*, in +2 and +4/3 (in the unique triangular Hg_3 clusters).

Two new mercury oxohalides, *viz.*, the bromine and iodine analogues of terlinguaite, were synthesised in the study.⁴⁵ Dark-red platelet-like crystals of Hg_2OI were grown by the hydrothermal method at 450 K from a stoichiometric mixture of HgO and Hg_2I_2 . X-Ray diffraction study of the resulting compound, whose stoichiometry is identical to that of terlinguaite, demonstrated that this compound, though also mixed-valence, has quite a different structure. The structure of Hg_2OI (see Ref. 46) consists of infinite zigzag chain $\text{Hg}^{2+} - \text{O} - \text{Hg}^{2+}$ along the *b* axis. These chains are linked through the (Hg_2) $^{2+}$ pairs to form 14-membered rings, which, in turn, are linked in a three-dimensional framework through weak additional $\text{Hg}^{2+} \cdots \text{O}$ bonds (2.47 Å) (Fig. 10). The iodine atoms occupy the cavities in the layers and form weak contacts with the Hg^{2+} cations. The coordination $\text{Hg}^{2+} - \text{O}$ bonds in the structure of Hg_2OI are somewhat longer (2.13 and 2.16 Å) and the $\text{O} - \text{Hg}^{2+} - \text{O}$ angles are smaller (165°) than the corresponding values in divalent mercury compounds.⁴⁷ Apparently, this is attributable to the contacts of the Hg^{2+} cation with the oxygen atom (2.47 Å) and with the iodine atoms (3.05 and 3.14 Å). Taking into account these weak bonds, the coordination polyhedron about Hg^{2+} can be described as a distorted square pyramid. The mercury atoms of the (Hg_2) $^{2+}$ pairs are linearly coordinated by the oxygen atoms and the shortest (Hg_2) $^{2+} \cdots \text{I}$ distance is 3.47 Å.

In the middle 80s, two research groups^{27,48} independently prepared and studied lemon-yellow crystals of the hydrolysis product of $\text{Hg}_2(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$, *viz.*, the mixed-valence $\text{Hg}_4\text{O}_2(\text{NO}_3)_2$ compound, whose stoichiometry is identical to that of Hg_2OI . These compounds are partially similar in structure. In the crystal structure of $\text{Hg}_4\text{O}_2(\text{NO}_3)_2$, as in the structure of Hg_2OI , the $\text{O} - \text{Hg}^{2+} - \text{O}$ chains and the (Hg_2) $^{2+}$ pairs also form analogous 14-membered rings. However, unlike the structure of Hg_2OI , the rings in $\text{Hg}_4\text{O}_2(\text{NO}_3)_2$ are linked in corrugated layers parallel to the (201) plane (Fig. 11) rather than in a three-dimensional framework. The Hg–Hg (2.510 Å) and Hg–O (2.136 Å) bonds within the layers are covalent and the layers are

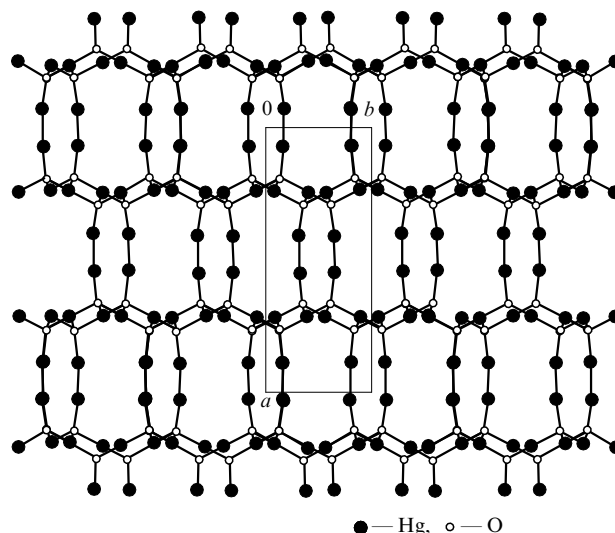


Figure 10. Framework of the 14-membered $[-(\text{Hg}_2)_2^{2+} - \text{O}_6 - \text{Hg}_4^{4+} -]$ rings in the structure of Hg_2OI .

linked through the weak (Hg_2) $^{2+} \cdots \text{O}$ contacts (2.84 Å) and the NO_3^- ions, which act as bridging ligands for the mercury atoms. This layered structure accounts for the noticeable cleavage of the crystals of $\text{Hg}_4\text{O}_2(\text{NO}_3)_2$ parallel to the (201) plane. The coordination numbers of the Hg^{2+} cation and the mercury ions in the (Hg_2) $^{2+}$ pair are equal to 2. It is worthy of note that the bonds between the mercury atoms of the (Hg_2) $^{2+}$ pair and the oxygen atoms are substantially longer than the $\text{Hg}^{2+} - \text{O}$ distances.

In attempting to synthesise the bromine analogue of terlinguaite, *viz.*, Hg_2OBr (see Ref. 45) (hydrothermal synthesis at 460 K from a stoichiometric mixture of HgO and Hg_2Br_2), crystals with composition $\text{Hg}_8\text{O}_4\text{Br}_3$, were obtained and studied by X-ray diffraction analysis.⁴⁹ The structure of $\text{Hg}_8\text{O}_4\text{Br}_3$ differs from the structures of terlinguaite $\text{Hg}_4\text{O}_2\text{Cl}_2$,⁴⁴ Hg_2OI ⁴⁶ and $\text{Hg}_4\text{O}_2(\text{NO}_3)_2$.^{27,48} There are five independent routes by which monovalent mercury atoms form three (Hg_2) $^{2+}$ pairs (2.517–2.557 Å) and three independent Hg^{2+} ions per asymmetric unit. The metal atoms in the (Hg_2) $^{2+}$ pairs have the oxygen

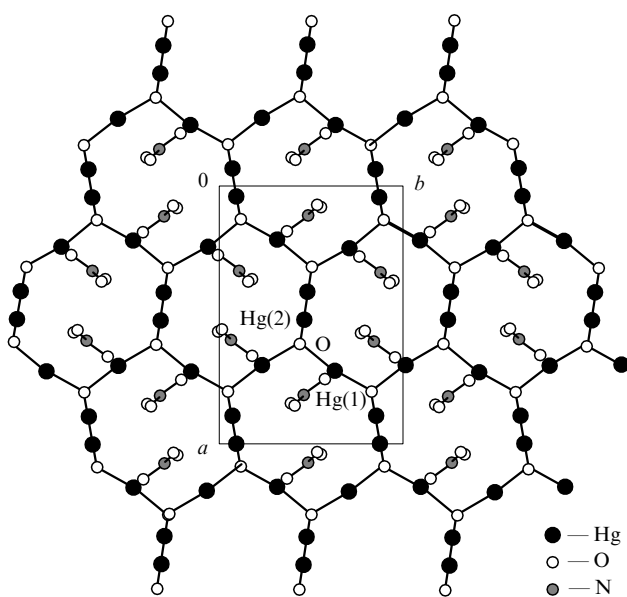


Figure 11. Layer of the 14-membered $[-(\text{Hg}_2)_2^{2+} - \text{O}_6 - \text{Hg}_4^{4+} -]$ rings in the structure of $\text{Hg}_4\text{O}_2(\text{NO}_3)_2$.

atoms as the nearest neighbours at distances of 2.14–2.24 Å through which the 12-membered $[-O-(Hg_2)^{2+}-O-]_4$ rings are formed. These rings are linked in infinite chains *via* the $(Hg_2)^{2+}$ dimers (Fig. 12). The Hg^{2+} ions coordinated by the oxygen atoms form helical chains (the $Hg^{2+}-O$ distances vary from 2.01 to 2.18 Å) similar to those found in two modifications of HgO .^{50, 51} The oxygen atoms bind the 'divalent' and 'monovalent' portions of the structure to form a three-dimensional framework with the bromine atoms located in the cavities (the shortest $Hg\cdots Br$ contact is 3.02 Å).

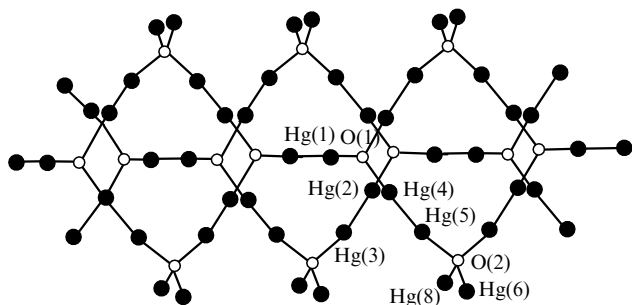


Figure 12. 12-Membered $[-O-(Hg_2)^{2+}-O-]$ rings linked through the $(Hg_2)^{2+}$ pairs in the structure of $Hg_8O_4Br_3$.

In the ternary $Hg-Re-O$ system, four compounds containing formally monovalent mercury,¹⁵ *viz.*, $HgReO_4$, and mixed-valence $Hg_5Re_2O_{10}$ (two modifications) and Hg_2ReO_5 , were structurally characterised. Unlike the molecular structure of $HgReO_4$, all three mixed-valence compounds have polymeric structures. The polycations of the fused $[(Hg_2)^{2+}-O-(Hg^{2+})-O]_n$ rings of different types form puckered two-dimensional infinite networks separated by the tetrahedral ReO_4^- anions.

The structure of Hg_2ReO_5 (see Ref. 15) contains 14-membered rings consisting of the oxygen atoms, Hg^{2+} cations and $(Hg_2)^{2+}$ pairs, which are analogous to those found in the structure of $Hg_4O_2(NO_3)_2$ (see Refs 27 and 48). These rings are linked in infinite two-dimensional (but with another type of corrugation) polycationic $[(Hg_2)^{2+} \cdot 2HgO]_n$ networks.

A comparison of two modifications of $Hg_5Re_2O_{10}$ suggested that these compounds have related structures.^{52, 53} Both compounds contain two-dimensional infinite corrugated networks with composition $[Hg^{2+} \cdot 2(Hg_2)^{2+}O]_n$, which are separated by the tetrahedral ReO_4^- cations. The networks in the first modification of $Hg_5Re_2O_{10}$ consist of fused 16-membered rings.⁵² The networks in the second modification contain the 10- and 22-membered rings⁵³ (Fig. 13). Analogous networks were also found in the structure of Hg_3CrO_6 .⁵⁴

Presently, the structures of about ten mercury oxovanadates are known, among which are two compounds containing mercury in the formal oxidation state of +1, *viz.*, $HgVO_3$ and the mixed-valence Hg_2VO_4 compound.¹⁹ The architecture of the crystal structure of Hg_2VO_4 is very unusual, namely, the $(Hg_2)^{2+}$ pairs and the Hg^{2+} ions together with certain of the oxygen atoms form infinite helical chains, which are located on the surface of the adjacent infinite channels in such a manner that the structure projected along the short *a* period appears as the structure consisting of fused 14-membered rings similar to those described above in the structures of Hg_2OI ,⁴⁶ $Hg_4O_2(NO_3)_2$,^{27, 48} and Hg_2ReO_5 .¹⁵ The mercury ions in the $(Hg_2)^{2+}$ pairs and the Hg^{2+} cations have a normal linear coordination. The trigonal-bipyramidal VO_5 groups are linked *via* shared edges to form infinite $[(VO_3)^-]_n$ chains parallel to each other and located in the centres of mercury–oxygen channels. These chains have no strong bonds with mercury atoms ($Hg\cdots O > 2.57$ Å). The formula of this compound can be described as follows: $[(Hg_2)^{2+} \cdot 2(Hg^{2+}O)]_n \cdot [(VO_3)^-]_{2n}$.

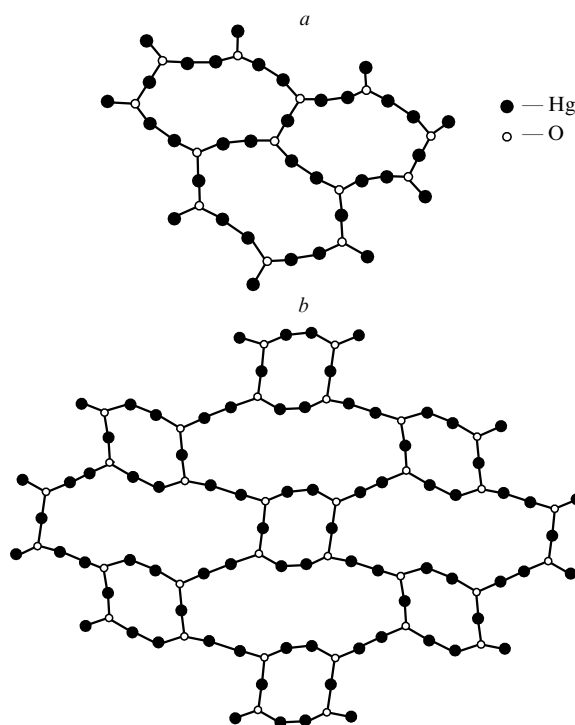


Figure 13. Types of the $Hg-O$ rings in the crystal structures of two modifications of $Hg_5Re_2O_{10}$. Modification: (a) I; and (b) II.

The new $Hg_9P_5I_6$ compound,⁵⁵ which possesses semiconducting properties, contains the mercury and phosphorus atoms in different oxidation states (+2, +1 and -3, -2, respectively), the low-valent phosphorus atoms existing as $(P_2)^{2-}$ dimers with the $P-P$ distance of 2.10 Å. The Hg^{2+} ions form tetrahedra about the phosphorus atoms and octahedra, whose centres are occupied by the $(P_2)^{2-}$ dimers. The P_2Hg_6 octahedra are linked *via* shared vertices to form layers parallel to the (100) plane. These layers are linked through the ditetrahedral P_2Hg_7 groups and the $(Hg_2)^{2+}$ pairs. In this structure, the $P-Hg-P$ and $P-Hg-Hg$ groups have an almost linear configuration. The coordination environment about the mercury atoms is completed by the iodine atoms (the $Hg-I$ distances vary from 3.097 to 3.691 Å). Taking into account the different valence states of the mercury and phosphorus atoms, it was suggested⁵⁵ that the formula of the compound be written as $(Hg-Hg)^{2+}Hg_2^{2+}(P-P)_4^{4-}P_2^{3-}I_{12}$.

Presently, only a few natural mixed-valence mercury compounds are known. These compounds, like the rare minerals containing only $(Hg_2)^{2+}$ pairs, are very unstable. The X-ray structural studies of these compounds are very laborious. Recently, the crystal structures of three natural mercury chromates, *viz.*, edoylerite $(Hg^{2+})_3S_2CrO_4$ (Ref. 56), deanesmithite $(Hg^+)_2(Hg^{2+})_3OS_2CrO_4$ (Ref. 57) and wattersite $(Hg^+)_4Hg^{2+}O_2CrO_4$ (Ref. 58), have been studied. The last two mixed-valence compounds represent new structural types containing the polymeric $-O-Hg-O-$ and $-O-(Hg_2)^{2+}-O-$ fragments typical of mercury compounds. In the structure of sulfur-containing deanesmithite, the infinite $\cdots(Hg_2)^{2+}-O-Hg^{2+}-O-(Hg_2)^{2+}-[(Hg^{2+}-S)_6]-(Hg_2)^{2+}\cdots$ chains involving the 12-membered $[(Hg_2)^{2+}-S]_6$ rings can be distinguished. The $O-(Hg_2)^{2+}-S$ groups are virtually linear.

In wattersite $(Hg^+)_4Hg^{2+}O_2CrO_4$, the CrO_4 tetrahedra and the distorted Hg^{2+} octahedra form ribbons with composition $[Hg^{2+}CrO_6]^{6-}$, which are linked in slightly distorted layers parallel to the (100) plane through the $(Hg_2)^{2+}$ pairs.

In the structure of natural mercury oxochloride, *viz.*, in the mineral hanawaltite $(Hg^+)_6Hg^{2+}O_3Cl_2$, the $-O-Hg^{2+}-O-$ and $-O-(Hg_2)^{2+}-O-$ fragments form a three-dimensional framework whose cavities are occupied by the chlorine atoms.⁵⁹

The distinguishing feature of this structure is that all $(\text{Hg}_2)^{2+}$ pairs lie approximately in the (001) plane and form corrugated layers. The researchers attributed the planar (001) habit of the mineral to the presence of strong Hg—Hg bonds in this plane and ascribed the good cleavage in the direction perpendicular to the c axis to weak bonds, which occur between the layers along this direction through the Hg^{2+} ions.

Another natural mercury oxochloride, *viz.*, the above-mentioned terlinguaite $\text{Hg}_4\text{O}_2\text{Cl}_2$,⁴⁴ contains alternating layers of $\{\text{Hg}^{2+}\text{Cl}_2\}$ and $\{(\text{Hg}_3)^{4+}\text{O}_2\}$. The latter layers contain the triangular $(\text{Hg}_3)^{4+}$ clusters (Hg—Hg, 2.707 Å), which are in a single plane (Fig. 14). The resulting structure may be represented as a three-dimensional mercury-oxygen framework with Cl atoms in the cavities. The layers containing strong Hg—Hg bonds are responsible for the anisotropy of the physical properties of hanawaltite and terlinguaite.

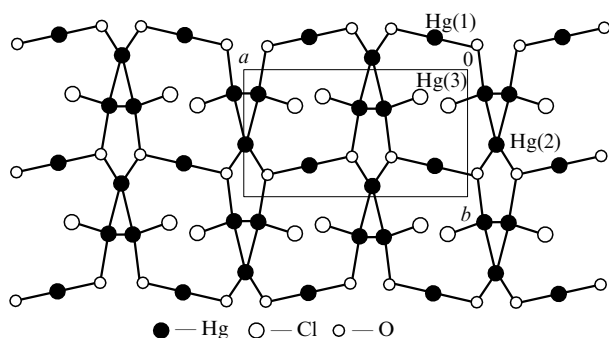


Figure 14. Crystal structure of terlinguaite $\text{Hg}(\text{Hg}_3)\text{O}_2\text{Cl}_2$.

Only three inorganic mercury compounds, whose structures contain the triangles $(\text{Hg}_3)^{4+}$ in which the mercury atoms exist in the formal oxidation state of $+4/3$, are known. Hence, although two compounds considered below are not mixed-valence, it is reasonable to describe their structures in this section. Recently, the crystal structure of the rare hypergene mineral kuznetsovite $\text{Hg}_3\text{AsO}_4\text{Cl}$, whose structure has been previously established based on X-ray powder data,⁶¹ was refined.⁶⁰ This is the second naturally occurring compound containing the cyclic $(\text{Hg}_3)^{4+}$ group (Hg—Hg, 2.675 Å). In the cubic structure, the Hg_3 triangles and the AsO_4^{3-} tetrahedra alternate along all crystallographic axes (Fig. 15). Taking into account only short Hg—O bonds (2.17 and 2.28 Å), a framework can be distinguished. The cavities of this framework are occupied by the chlorine atoms in a diamond-like fashion.

The third compound, *viz.*, pale-yellow crystals of $\text{Hg}_9\text{As}_4\text{O}_{16}$, was prepared upon thermal decomposition (550 °C) of $(\text{Hg}_2)_3(\text{AsO}_4)_2$.⁶² The crystal structure of this compound consists of the $(\text{Hg}_3)^{4+}$ triangles (Hg—Hg, 2.662–2.696 Å) and the AsO_4^{3-}

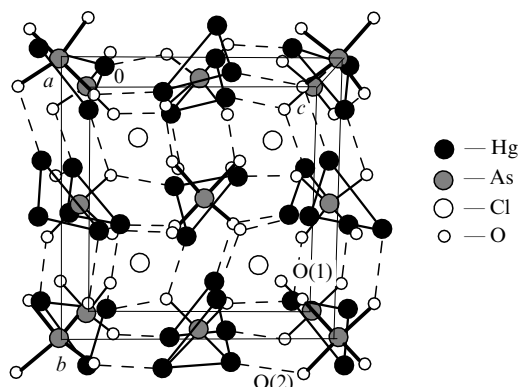


Figure 15. Crystal structure of kuznetsovite $\text{Hg}_3\text{AsO}_4\text{Cl}$.

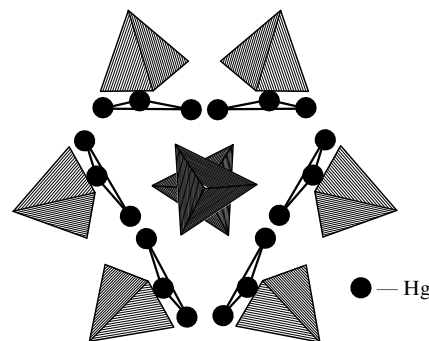


Figure 16. Arrangement of the Hg_3 triangles and the AsO_4 tetrahedra in the crystal structure of $(\text{Hg}_3)_3(\text{AsO}_4)_4$.

tetrahedra and corresponds to the formula $[(\text{Hg}_3)^{4+}]_3[(\text{AsO}_4)^{3-}]_4$. The coordination environment about the mercury atoms is a distorted tetrahedron with the Hg—O distances of 2.14–2.34 Å. The remaining distances vary from 2.58 to 2.93 Å (Fig. 16).

The tendency of mercury-oxygen groups to polymerisation, which is characteristic of divalent mercury compounds, is retained in compounds containing mercury atoms in different oxidation states.⁴⁷ The pairs of the monovalent mercury atoms form the linear $\text{O}-(\text{Hg}_2)^{2+}-\text{O}$ groups, which (along with the linear $\text{O}-\text{Hg}^{2+}-\text{O}$ units) are involved in the formation of polycations of different types, *viz.*, rings, infinite chains, corrugated and planar networks, layers or frameworks. The triangular $(\text{Hg}_3)^{4+}$ group plays a similar role. Fragments containing the groups of monovalent mercury are characterised by larger deviations from linearity (the Hg—Hg—O angles are 145–178 °) and by elongated Hg—O bonds (2.10–2.34 Å) compared to the groups containing Hg^{2+} (the O—Hg—O angle is 180 °; the average Hg—O distance is 2.06 Å). Apparently, this is due to the effect of the strong metallic Hg—Hg bond, whose length changes only slightly and is virtually independent of the coordination environment about the mercury atoms.

Analysis of the bond lengths in the mixed-valence and cluster mercury derivatives demonstrates that the divalent mercury atoms are not only linearly coordinated by two atoms with the shortest distances, but also are generally surrounded by several atoms located at distances of > 2.5 Å. When describing the structures, these atoms are often included in the coordination environment about the mercury atoms. Since the environment about the mercury atoms is often formed by atoms of different types, the spread in the distances in the polyhedra is large and the polyhedra are strongly distorted. This is also true for the environment about the monovalent mercury atoms in the $(\text{Hg}_2)^{2+}$ pairs and $(\text{Hg}_3)^{4+}$ triangles. The description of the coordination polyhedra about the individual mercury atoms becomes even more arbitrary in the presence of strong metallic bonds because these polyhedra are very distorted.

From the crystal-chemical standpoint, it is worthwhile to consider this series of structures as structures containing the overall complex Hg_n^{x+} cations with the coordinates of the geometric centres of the complexes and to describe the coordination environment about the Hg_n^{x+} cation as a whole. For example, the environment about the $(\text{Hg}_2)^{2+}$ pair in the structure of chursinite $(\text{Hg}_2)_3(\text{AsO}_4)_2$ is a trigonal antiprism formed by the oxygen atoms of the AsO_4 tetrahedra²³ (Fig. 17a). In the study of the structure of kuznetsovite $\text{Hg}_3\text{AsO}_4\text{Cl}$,⁶¹ the environment about the triangular mercury cluster was described as a convex 16-vertex polyhedron, *viz.*, Friauf's polyhedron (Fig. 17b) formed by twelve oxygen atoms and four chlorine atoms. The application of this approach to other structures demonstrated that the environment about the $[\text{Hg}_3]^{4+}$ cation (6O+6Cl) in terlinguaite $\text{Hg}(\text{Hg}_3)\text{O}_2\text{Cl}_2$ is a hexagonal analogue of cuboctahedron (Fig. 17c)⁴⁴ and the environment about the analogous cation in $(\text{Hg}_3)_3(\text{AsO}_4)_4$ is a cuboctahedron formed by 12 oxygen atoms

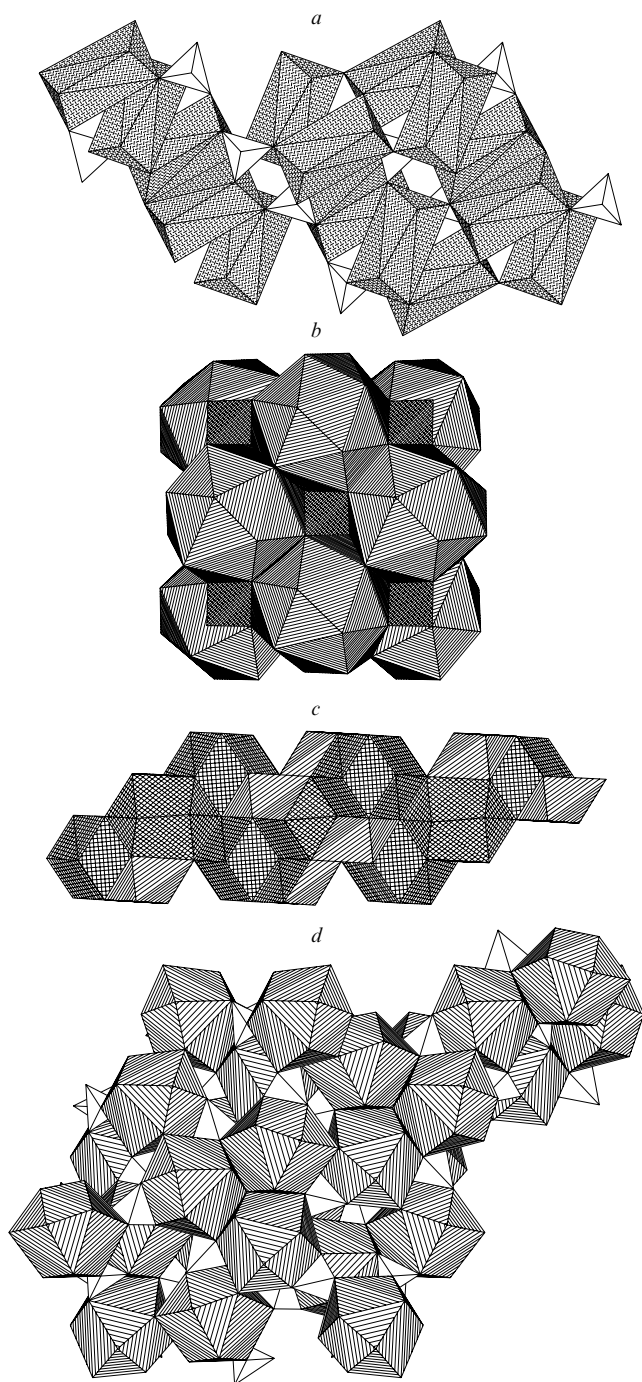


Figure 17. Coordination Hg_n polyhedra in the structures of $(\text{Hg}_3)_2 \cdot (\text{AsO}_4)_2$ (a), $\text{Hg}_3\text{AsO}_4\text{Cl}$ (b), $\text{Hg}(\text{Hg}_3)\text{O}_2\text{Cl}_2$ (c) and $(\text{Hg}_2)_3(\text{AsO}_4)_4$ (d).

(Fig. 17 d).⁶² The symmetry and the convexity of the coordination polyhedron as well as a small spread in the distances from the centre of the mercury group to the vertices of the polyhedra and a small spread in the lengths of the edges of the polyhedron can serve as criteria for choosing the polyhedral environment about the Hg_n^{x+} cation. Note that this method would never do for describing the coordination environment about cluster mercury groups if the distances between the atoms of the adjacent mercury groups are close to the cation–anion bond lengths [for example, in the structure of pyarkovite Hg_3OCl ,³⁶ in which the shortened distances (3.11–3.13 Å) were observed between the mercury atoms of some adjacent $(\text{Hg}_2)^{2+}$ pairs].

IV. Compounds containing polyatomic Hg_n^{x+} cations ($n > 2$)

Salts, which contain linear Hg_n^{x+} systems of metal atoms directly bound to each other (where $n > 2$, i.e., the formal oxidation state of mercury is lower than +1) as ions, are formed in strongly acidic nonaqueous solvents and exist as stable crystalline compounds with particular anions.¹ For example,⁶³ the reactions of mercury with AsF_5 and SbF_5 in liquid SO_2 yielded the $(\text{Hg}_3)^{2+}$ and $(\text{Hg}_4)^{2+}$ ions, which were isolated as crystalline salts with the AsF_6^- and $\text{Sb}_2\text{F}_{11}^-$ anions. Attempts to prepare analogous salts with other anions according to this procedure failed, apparently, due to the fact that no other pentafluorides, which can oxidise mercury in an SO_2 medium at room temperature, were found. More recently, a universal procedure was developed for the preparation of compounds with the $(\text{Hg}_3)^{2+}$ and $(\text{Hg}_4)^{2+}$ cations, which involves the reaction of mercury with hexafluorides $\text{Hg}(\text{MF}_6)_2$. Dull-yellow crystals of $\text{Hg}_3(\text{AsF}_6)_2$ and dark-red crystals of $\text{Hg}_4(\text{AsF}_6)_2$ as well as analogous compounds with niobium, tantalum and antimony were prepared according to this procedure.⁶⁴ The reaction of mercury and HgCl_2 in a melt of AlCl_3 afforded the $\text{Hg}_3(\text{AlCl}_4)_2$ compound.⁶⁵ It should be noted that all these salts undergo rapid disproportionation in the presence of water to form elemental mercury and $(\text{Hg}_2)^{2+}$ salts. The principal crystal-structural data for compounds of this type are given in Table 1.

X-Ray diffraction studies of the $\text{Hg}_3(\text{AsF}_6)_2$ (see Ref. 63) and $\text{Hg}_3(\text{AlCl}_4)_2$ (see Ref. 66) compounds revealed the linear groups of the mercury atoms of the $(\text{Hg}_3)^{2+}$ type. The $\text{Hg} - \text{Hg}$ bond lengths in these groups have equal or close values. Thus, the structure of $\text{Hg}_3(\text{AlCl}_4)_2$ consists of discrete molecules with the linear central $-\text{Cl} - \text{Hg} - \text{Hg} - \text{Hg} - \text{Cl}-$ skeleton (the $\text{Hg} - \text{Hg}$ bond lengths are 2.551 Å and 2.562 Å), which involves the chlorine atoms of the tetrahedral AlCl_4 groups, whereas in the structure $\text{Hg}_3(\text{AsF}_6)_2$ containing the $(\text{Hg}_3)^{2+}$ cations and the octahedral AsF_6^- anions, the $(\text{Hg}_3)^{2+}$ cation is linear and centrosymmetrical with the $\text{Hg} - \text{Hg}$ bond length of 2.552 Å (Fig. 18). The $\text{Hg} \cdots \text{F}$ contacts between the terminal mercury and fluorine atoms of the adjacent AsF_6^- anions (2.38 Å) are collinear with the $\text{Hg} - \text{Hg}$ bonds. These contacts are, most likely, covalent in character because their lengths are intermediate between the reference values of 2.10 and 2.46 Å, respectively.⁶³

The $\text{Hg}_3(\text{NbF}_5)_2\text{SO}_4$ and $\text{Hg}_3(\text{TaF}_5)_2\text{SO}_4$ compounds are isostructural and also contain the nearly linear centrosymmetrical $(\text{Hg}_3)^{2+}$ cations linked to the $[\text{F}_5\text{MOSO}_2\text{OMF}_5]^{2-}$ anions

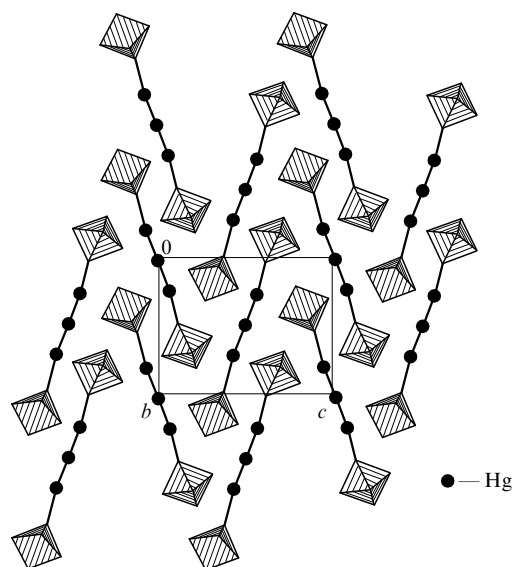


Figure 18. Linear $(\text{Hg}_3)^{2+}$ cations in the crystal structure of $\text{Hg}_3(\text{AsF}_6)_2$.

(M = Nb or Ta) through the terminal oxygen atoms to form chains along the [110] and $[1\bar{1}0]$ directions.⁶⁷ The coordination environment about the mercury atoms in the $(\text{Hg}_3)^{2+}$ cations is analogous to those observed in $\text{Hg}_3(\text{AsF}_6)_2$ (see Ref. 63) and $\text{Hg}_3(\text{AlCl}_4)_2$ (see Ref. 66).

The structure of the $(\text{Hg}_4)^{2+}$ ion was established in the studies of the crystal structures of $\text{Hg}_4(\text{Ta}_2\text{F}_{11})_2$ (see Ref. 67) and $\text{Hg}_4(\text{AsF}_6)_2$ (see Ref. 68). The terminal Hg–Hg bonds (2.630 Å⁶⁷ and 2.620 Å⁶⁸) in these compounds are somewhat longer than the central bonds (2.593 and 2.588 Å, respectively) and the bonds in the $(\text{Hg}_3)^{2+}$ cation.^{63,66} The structures of these compounds consist of the nearly linear $(\text{Hg}_4)^{2+}$ cations (the Hg–Hg–Hg angles are 177.3 and 177.4°, respectively) and the $\text{Ta}_2\text{F}_{11}^-$ and AsF_6^- anions, respectively. The distinguishing feature of these structures is that the distances between the adjacent $(\text{Hg}_4)^{2+}$ cations (3.033 Å⁶⁷ and 2.985 Å⁶⁸) are close to the shortest Hg–Hg distance in metallic mercury (2.99 Å).⁶⁹ Hence, taking into account these contacts, the $(\text{Hg}_4)^{2+}$ cations can be considered as being linked in infinite zigzag chains (along the *c* axis) with weak interactions between the terminal mercury atoms (Fig. 19). Thus, the interaction between the $(\text{Hg}_4)^{2+}$ cation and the AsF_6^- anion in the $\text{Hg}_4(\text{AsF}_6)_2$ compound in the direction nearly collinear with the terminal Hg–Hg bonds may be considered as being replaced by the $\text{Hg}\cdots\text{Hg}$ intercationic interaction at an angle of 124° to the terminal Hg–Hg bond [107.9° in $\text{Hg}_4(\text{Ta}_2\text{F}_{11})_2$] and by several weak Hg $\cdots$ F contacts with the anions. The latter contacts are substantially longer (> 2.7 Å) than the short interactions (2.38 Å) in $\text{Hg}_3(\text{AsF}_6)_2$, which are collinear with the Hg–Hg bonds, and are similar in length to the analogous contacts in other compounds with noncollinear Hg $\cdots$ F interactions (for example, the shortest Hg $\cdots$ F contacts in $\text{Hg}_{2.86}\text{AsF}_6$ are 2.87 and 2.98 Å).^{70,71}

The reactions of mercury with AsF_5 , SbF_5 or $\text{Hg}(\text{MF}_6)_2$ (M = Nb or Ta) on the surface of liquid mercury afforded gold-coloured crystals, which were similar in appearance to metallic crystals and existed for 10–15 min. Then these crystals were converted into soluble $(\text{Hg}_3)^{2+}$ salts. It was possible to store and isolate these crystals by choosing a weaker oxidising agent. These crystals appeared to be the most interesting substance among the compounds of the general formula $\text{Hg}_{3-\delta}\text{MF}_6$ (M = As, Sb, Nb or Ta) because they possess anisotropic metallic conductivity. The $\text{Hg}_{3-\delta}\text{AsF}_6$ and $\text{Hg}_{3-\delta}\text{SbF}_6$ compounds exhibit superconducting properties at low temperatures ($T_c = 4$ and 14 K, respectively).⁶⁴

The crystal structure of the unique anisotropic superconductor of the empirical formula Hg_3AsF_6 can be described as a sublattice containing the octahedral AsF_6^- anions arranged in the tetragonal unit cell in a cubic close packing fashion.⁷⁰ There are linear nonintersecting channels in two nearly perpendicular directions (parallel to the *a* and *b* axes) within this sublattice. The infinite disordered chains of the mercury atoms in the formal oxidation state of +1/3 (Hg–Hg, 2.64 Å) are located along these channels (Fig. 20). The unit cell parameters $a = b = 7.54$ Å are not proportional to the threefold Hg–Hg distance (7.92 Å).

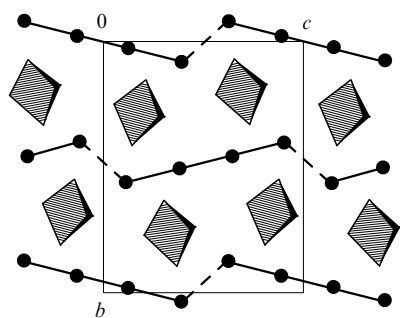


Figure 19. Linear $(\text{Hg}_4)^{2+}$ cations in the crystal structure of $\text{Hg}_4(\text{AsF}_6)_2$. The bonds between the cations are indicated by dashed lines.

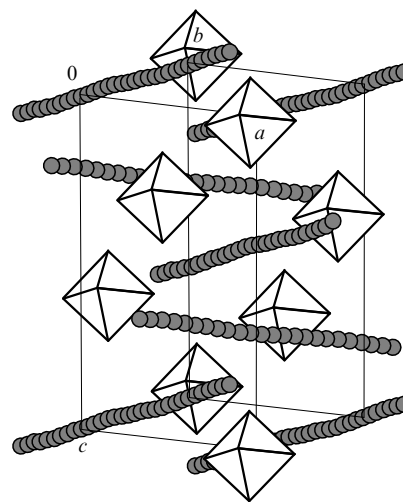


Figure 20. Infinite disordered Hg_n chains in the structure of $\text{Hg}_{3-\delta}\text{AsF}_6$.

Hence, the empirical formula of the compound under consideration can be formally obtained from the ratio $7.54 : 2.64 = 2.86$ and may be written as $\text{Hg}_{2.86}\text{AsF}_6$. Neutron diffraction study of Hg_3AsF_6 confirmed the formula $\text{Hg}_{2.86}\text{AsF}_6$ and the above-described crystal structure of the compound.⁷¹

However, according to the structural data, the disordered Hg_n chains are not precisely one-dimensional and the sites of the mercury atoms are only partially occupied. In addition, the maximum deviation of the mercury atoms from the axes of the chains in the [001] direction was 0.07 Å at room temperature and the shortest Hg–Hg contacts between the chains are 3.24 Å. If the chains were exactly linear, these distances would be $c/4 = 3.098$ Å. It was concluded⁷¹ that the incommensurate structure is stabilised by anionic vacancies so that the unit cell contains four $\text{Hg}_{2.86}(\text{AsF}_6)_{0.953}$ formula units.

Hence, the structure of $\text{Hg}_{2.86}\text{AsF}_6$ contains the unique metal-bonded infinite polymeric cations, which form a portion of the ionic crystal lattice. The shortest contacts between the mercury and fluorine atoms (2.99 Å) are somewhat larger than the sum of the van der Waals radii (2.85 Å), *i.e.*, the crystal structure contains the AsF_6^- anions and the Hg_n chains, in which the average charge on the mercury atoms is equal to $1/2.86 = +0.35$. In this crystal, the ionic character of the bonds between the positively charged Hg_n chains and the AsF_6^- anions predominates. In addition, it should be noted that the Hg–Hg distance (2.64 Å) is substantially shorter than that in metallic mercury (2.99 Å). However, the coordination number of Hg in metallic mercury is 12, whereas in the compound under consideration, this value is equal to 2. The character of the structure under consideration is consistent with the anisotropy of conductivity in the crystal along the *a* and *b* axes.

The syntheses of a series of compounds with nonstoichiometric compositions of the general formula $\text{Hg}_{3-\delta}\text{MF}_6$ (M = Sb,⁷² Nb or Ta⁷³) at room temperature and of the general formula $\text{Hg}_{3-\delta}\text{MF}_6$ (M = Sb or Ta⁷⁴) at 173 and 150 K, respectively, were reported. It was confirmed that these compounds are isostructural to the Hg_3AsF_6 compounds studied previously.^{70,71}

Based on the comparison of the structures of three types of the above-considered compounds and taking into account the short contacts (2.985 Å) between the terminal atoms of the adjacent cations $(\text{Hg}_4)^{2+}$, it can be concluded that the structure of $\text{Hg}_4(\text{AsF}_6)_2$ is intermediate between the structure of $\text{Hg}_3(\text{AsF}_6)_2$, in which short contacts between the cations are absent, and the structure of $\text{Hg}_{3-\delta}\text{AsF}_6$, which contains infinite Hg_n chains and in which there are no discrete cations. Taking into account the high electrical conductivity of compounds containing infinite Hg_n chains, the authors⁶⁸ believed that the conductivity can occur along the zigzag chains in $\text{Hg}_4(\text{AsF}_6)_2$.

The preparation and investigation of gold-coloured crystals containing infinite Hg_n chains with compositions $\text{Hg}_{3-\delta}\text{NbF}_6$ and $\text{Hg}_{3-\delta}\text{TaF}_6$ led to the unexpected discovery of a new type of mercury compounds, which contain Hg_n layers, but differ from chain compounds.⁷⁵ If the gold-coloured crystals were not removed from the reaction mixture containing unconsumed mercury and $(\text{Hg}_3)^{2+}$ and $(\text{Hg}_4)^{2+}$ ions in the solution, these crystals were transformed over a period of time (from several hours to several months) into thin pliable silvery plates reminiscent of aluminium foil. The reaction performed in the cold (-35°C) afforded silvery crystals without intermediate formation of gold-coloured crystals. Unlike the gold-coloured crystals, the silvery crystals have the exactly stoichiometric composition Hg_3MF_6 ($\text{M} = \text{Nb}$ or Ta), which is determined by its close-packed structure. The crystals with this composition exhibit superconducting properties ($T_c = 7\text{ K}$).⁶⁴

X-Ray diffraction studies of the Hg_3NbF_6 and Hg_3TaF_6 compounds revealed close-packed layers of the MF_6^- octahedra separated by hexagonal layers of the mercury atoms (Fig. 21).⁷⁵ Each mercury atom is surrounded by six nearest neighbours at distances of $2.90\text{ \AA}$ within the Hg layer and by six fluorine atoms from the adjacent MF_6 layers at distances of $3.2\text{ \AA}$ (three atoms from each adjacent layer). The mercury and fluorine atoms form the cubic close packing and the M atoms occupy 1/3 of the octahedral cavities between the fluorine atoms. The Hg–Hg distances in the mercury layers are longer than those in the chains, in which the mercury atoms are bound only to two neighbours, but are shorter than in elemental mercury, in which metal atoms have 10 or 12 neighbours. It should be noted that the silvery crystals were rapidly converted into the gold-coloured crystals in the presence of liquid SO_2 at 120°C . Hence, it can be stated that there is a reversible structural transition between the chain and layered structures. However, the role of SO_2 in this transition is not entirely known (this transition does not occur at room temperature and below room temperature in the absence of SO_2).

The synthesis, structure and electrical properties of salts containing polyatomic $(\text{Hg}_3)^{2+}$ and $(\text{Hg}_4)^{2+}$ cations and compounds with chain $(\text{Hg}_{3-\delta}\text{MF}_6)$, where $\text{M} = \text{As}$, Sb , Nb or Ta) and layered $(\text{Hg}_3\text{NbF}_6)$ and Hg_3TaF_6) structures were considered in greatest detail in the study.⁶⁴

In none of the known compounds containing $(\text{Hg}_2)^{2+}$ and $(\text{Hg}_3)^{2+}$ ions, these ions tend to bind to each other. The $(\text{Hg}_4)^{2+}$ ions in the compounds form zigzag chains through weak bonds. The limiting case is observed in the structures of $\text{Hg}_{3-\delta}\text{MF}_6$ ($\delta = 0.1$), ($\text{M} = \text{As}$, Sb , Nb or Ta) consisting of infinite chains, in which the oxidation state of mercury is close to $+1/3$ and the chains are virtually linear and uniform. The tendency of the ions to form chains, apparently, results from the low oxidation state and chains are formed if the charge on the mercury atom is lower than $\sim +1/2$. It should be noted that infinite linear chains of mercury atoms were found in $\beta\text{-Hg}$.⁶⁹ The layers of mercury atoms were observed in the graphite intercalation compound with composi-

tion KHgC_4 .⁷⁶ Although the Hg–Hg distances in KHgC_4 are close to those in Hg_3NbF_6 (2.85 and $2.90\text{ \AA}$, respectively), the layers in these structures differ in that each mercury atom in Hg_3NbF_6 has 6 neighbours and the formal charge of $+1/3$, whereas each mercury atom in the intercalation compound has only three neighbours and the formal charge of 0.

Therefore, analysis of the structures of mercury compounds with fluorine and MF_6^- anions shows the strict relationship between the value of the averaged formal charge on the mercury atom, the shortest Hg–F distances, the structure of the Hg_n^{x+} cation and the Hg–Hg distance in this cation. As the charge on the mercury atom decreases from $+1$ to $+1/3$, the shortest Hg–F distances increase from 2.133 in Hg_2F_2 to $3.2\text{ \AA}$ in Hg_3NbF_6 and the sizes of the Hg_n^{x+} cation increase going from the finite and virtually linear Hg_n^{2+} groups ($n = 2-4$) to the infinite Hg_n chains and then to a two-dimensional close-packed layer of the mercury atoms. The Hg–Hg distances in this series of the cations increase from 2.51 to $2.90\text{ \AA}$.

V. Monovalent mercury compounds with organic ligands

Presently, 30 complex compounds with organic ligands containing $(\text{Hg}_2)^{2+}$ groups have been synthesised and structurally characterised. The principal crystallographic and crystal-chemical characteristics of these compounds are given in Table 1. Most organic ligands, which are constituents of the complexes under consideration, are shown in Fig. 22.

Many amines, including pyridine, cause disproportionation of the dimeric $(\text{Hg}_2)^{2+}$ cation

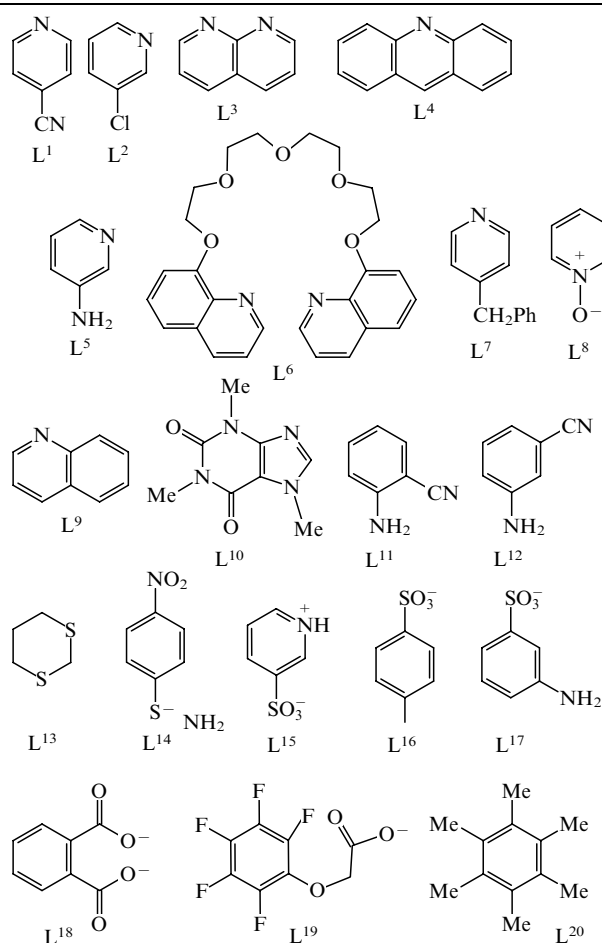
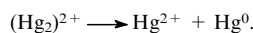


Figure 22. Types of organic ligands in monovalent mercury complexes.

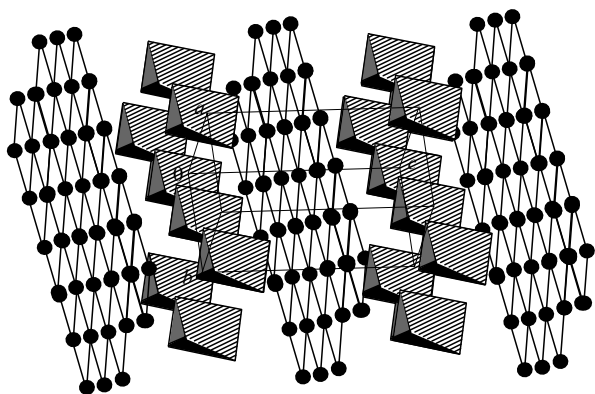


Figure 21. Hexagonal Hg_n layers in the structure of Hg_3NbF_6 .

The possibility of formation of stable monovalent mercury complexes with low-basicity nitrogen bases was confirmed for the first time by the detection of the $(\text{Hg}_2)^{2+}$ complex with aniline in solution.⁷⁷ Apparently, the introduction of an acceptor substituent at position 4 of the pyridine ring leads to a decrease in the donor ability of the nitrogen atom. Some substituted low-basicity pyridines and anilines also form stable $[\text{Hg}_2\text{L}_2]\text{X}_2$ complexes,⁷⁸ the basicity of the ligand depending on both the electronic and steric properties of the substituents. Structural study of the isolated $[\text{Hg}_2(\text{L}^1)_2](\text{ClO}_4)_2$ compound⁷⁹ demonstrated that the $(\text{Hg}_2)^{2+}$ ion can be covalently coordinated to the N-donor ligands through both mercury atoms.

The virtually linear N—Hg—Hg—N fragments (the Hg—Hg—N angles vary from 162.8 to 180°) were found in dimercury perchlorates with low-basicity N-containing organic ligands of the general formula $[\text{Hg}_2\text{L}_n](\text{ClO}_4)_2$ ($n = 2$);^{79–83} the Hg—Hg and Hg—N bond lengths are in the ranges of 2.487–2.518 and 2.03–2.22 Å, respectively. The structures of the complexes contain the dimeric $[\text{Hg}_2\text{L}_2]^{2+}$ cations and the ClO_4^- anions. Noteworthy is the existence of nonbonded contacts between the mercury atoms of the $(\text{Hg}_2)^{2+}$ ions and the oxygen atoms of the ClO_4^- anions. The lengths of these contacts (2.93–3.13 Å) are somewhat larger than the sum of the van der Waals radii of the mercury and oxygen atoms (2.90 Å). The shorter Hg...O contacts were observed in the $[\text{Hg}_2(\text{L}^2)_2](\text{ClO}_4)_2$ (2.71 Å),⁸⁰ $[\text{Hg}_2(\text{L}^3)_2](\text{ClO}_4)_2$ (2.79 Å)⁸¹ and $[\text{Hg}_2(\text{L}^5)_2](\text{ClO}_4)_2$ (2.77 Å)⁸³ compounds. In the complex with acridine $[\text{Hg}_2(\text{L}^4)_2](\text{ClO}_4)_2$, the lengths of these contacts are 2.96 Å,⁸² and hence one can say that only weak electrostatic interactions occur between the cations and the anions. The short Hg—N distance in the complexes with the ratio $(\text{Hg}_2)^{2+}:\text{L} = 1:2$ was found in $[\text{Hg}_2(\text{L}^3)_2](\text{ClO}_4)_2$.⁸¹ The Hg—Hg distance (2.518 Å) in this compound is somewhat larger than those in the $[\text{Hg}_2(\text{L}^1)_2](\text{ClO}_4)_2$ (2.498 Å)⁷⁹ and $[\text{Hg}_2(\text{L}^2)_2](\text{ClO}_4)_2$ (2.487 Å)⁸⁰ complexes. The arrangement of the $[(\text{Hg}_2)^{2+}(\text{L}^1)_2]$ cations in the structure of the complex, which is analogous to the arrangement of the molecules in $\text{Hg}_2(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$, is the so-called herringbone packing (see Fig. 2).^{7,8} In the remaining complexes, the linear N—Hg—Hg—N fragments are primarily located parallel to one of the crystallographic axes.^{80–83}

In the $[\text{Hg}_2(\text{L}^6)_2](\text{ClO}_4)_2$ complex⁸⁴ with the stoichiometry $(\text{Hg}_2)^{2+}:\text{L}^6 = 1:2$, the ligand is coordinated to the mercury atoms of the $(\text{Hg}_2)^{2+}$ pair through the nitrogen and oxygen atoms, the coordination environment about the mercury atoms being different. The environment about the Hg(1) atom is formed by the adjacent mercury atom (Hg—Hg, 2.506 Å), the nitrogen atom (2.20 Å) and two oxygen atoms (2.63 and 2.69 Å). The coordination about the Hg(2) atom involves the mercury, nitrogen (2.20 Å) and oxygen (2.66 Å) atoms. The remaining Hg...O(L⁶) distances are in the range of 2.89–4.15 Å. The ClO_4^- anions are not coordinated to the metal atoms.

The coordination number of 3 is typical of the mercury atoms in the structures of the $\text{Hg}_2\text{L}_4(\text{ClO}_4)_2$ compounds. Thus, the dimercury perchlorate complex with 4-benzylpyridine (L^7) consists of the centrosymmetrical $[\text{Hg}_2(\text{L}^7)_4]^{2+}$ cations and the ClO_4^- anions, which are linked *via* weak Hg...O contacts (2.899 and 3.026 Å).⁸⁵ Without considering these contacts, the coordination about the mercury atoms is intermediate between planar-trigonal and the so-called T-shaped⁸⁶ (one of the Hg—Hg—N angles is close to 180°; Hg—Hg is 2.508 Å, Hg—N are 2.227 and 2.476 Å) (Fig. 23). It should be noted that the L^7 ligand possesses the highest basicity in the series of the above-mentioned N-donor ligands, which is manifested in the distortion of the T-shaped environment towards the planar-trigonal coordination. A comparison of the structural data on the dimercury complexes with sterically unhindered ligands, such as 4-cyanopyridine (L^1),⁷⁹ 3-chloropyridine (L^2)⁸⁰ and 4-benzylpyridine (L^7),⁸⁵ revealed an interesting correlation between the stereochemistry and the basicity of the ligands (pK_a is 1.86, 2.81 and 5.59, respectively).⁸⁵ There are weak contacts between the mercury atoms and the

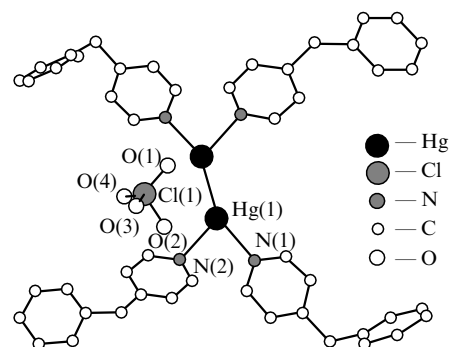


Figure 23. Molecular structure of $[\text{Hg}_2(\text{L}^7)_4](\text{ClO}_4)_2$.

oxygen atoms of the ClO_4^- anions in all three complexes regardless of the initial coordination of ligands in the axial positions with respect to the $(\text{Hg}_2)^{2+}$ pair. As the basicity of the above-mentioned ligands increases, the secondary coordination becomes more essential. In particular, the secondary Hg...L contacts [2.86 Å (O), 2.77 Å (O) and 2.476 Å (N)] become shorter and the Hg—Hg—L angles increase (100°, 109° and 118.4°), due to which the second ligand approaches the strong acceptor axial centre of the $(\text{Hg}_2\text{L}_2)^{2+}$ dimer. Correspondingly, the coordination is weakened, which is manifested in the increase in the Hg—N bond length (2.16, 2.21 and 2.23 Å). The deviation of the N—Hg—Hg—N fragment from linearity also increases (the N—Hg—Hg angles are 176.0°, 167.4° and 153.9°). Hence, it is evident that the deviation of the N—Hg—Hg—N fragments from linearity in stable dimercury complexes with N-donor ligands of the $[\text{Hg}_2\text{L}_n]\text{X}_2$ type ($n > 2$) is caused by the additional coordination of the metal atoms by more remote ligands.

The coordination polyhedra about the mercury atoms in the $[\text{Hg}_2(\text{L}^8)_4](\text{ClO}_4)_2$ compound are distorted tetrahedra formed by the mercury atom (Hg—Hg, 2.522 Å) and three oxygen atoms of the ligands (Hg—O, 2.197–2.558 Å).⁸⁷ An analogous coordination with the elongated Hg—O bonds, which is untypical of mercury atoms, was also found in Hg_2AgPO_4 (see Ref. 32) and in the mineral szymanskiite.⁴⁰ The remaining Hg...O contacts are longer than 2.78 Å. The $[\text{Hg}_2(\text{L}^8)_4]^{2+}$ dimers lie in the (010) plane. The distances between the adjacent dimers are 3.90 and 4.17 Å (Fig. 24). In addition, there is a rather long contact (2.96 Å) between the mercury atom and the oxygen atom of the ClO_4^- anion. Therefore, the structure of the $[\text{Hg}_2(\text{L}^7)_4](\text{ClO}_4)_2$ complex contains only discrete cations with the three-coordinate mercury

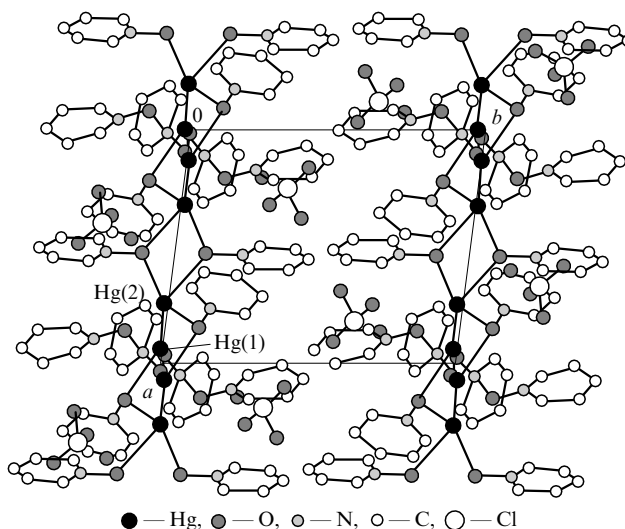


Figure 24. Projection of the structure of $[\text{Hg}_2(\text{L}^8)_4](\text{ClO}_4)_2$ onto the (001) plane.

atoms, whereas three of four ligands in the $[\text{Hg}_2(\text{L}^8)_4](\text{ClO}_4)_2$ complex act as bridges between the adjacent $(\text{Hg}_2)^{2+}$ cations.⁸⁵

The compound $\text{Hg}_2(\text{Ph}_2\text{Se})_4(\text{ClO}_4)_2$ exists in two forms, viz., in the 'yellow'⁸⁸ and 'red'⁸⁹ forms. The 'yellow' complex contains the centrosymmetrical $[(\text{Ph}_2\text{Se})_2\text{Hg}_2(\text{Ph}_2\text{Se})_2]^{2+}$ cations with positively charged trivalent selenium atoms.⁸⁸ One of the oxygen atoms of each ClO_4^- anion is bound to the $(\text{Hg}_2)^{2+}$ group. Each mercury atom has the trigonal environment formed by the mercury atom ($\text{Hg}-\text{Hg}$, 2.558 Å), the selenium atom ($\text{Hg}-\text{Se}$, 2.70 Å) and the oxygen atom of the ClO_4^- anion ($\text{Hg}-\text{O}$, 2.705 Å). In addition, there is a contact between the mercury atom and the selenium atom (2.80 Å), which completes the coordination about the mercury atom to a distorted tetrahedron. The observed $\text{Hg}-\text{Hg}$ distance belongs to the longest distances found in the $(\text{Hg}_2)^{2+}$ groups. The value of one of the $\text{Hg}-\text{Hg}-\text{Se}$ angles (141°) indicates that the linear coordination about the mercury atom is distorted upon addition of the second diphenyl selenide group. Correspondingly, the $\text{Hg}-\text{Se}$ distance is 2.70 Å at the $\text{Hg}-\text{Hg}-\text{Se}$ angle of 141° , while this distance increases to 2.80 Å at the angle of 116° . In the centrosymmetrical molecule of the 'red' form, the central Hg_2Se_4 fragment is planar.⁸⁹ The fourth coordination site at the mercury atom is occupied by an oxygen atom of the ClO_4^- anion ($\text{Hg}-\text{Hg}$, 2.554 Å; $\text{Hg}-\text{Se}$, 2.653 and 2.918 Å; $\text{Hg}-\text{O}$, 2.626 Å; the $\text{Hg}-\text{Hg}-\text{Se}$ angle is 151.9°). Therefore, the 'yellow' and 'red' forms of the $\text{Hg}_2(\text{Ph}_2\text{Se})_4.(\text{ClO}_4)_2$ compound are characterised by the different structures of the Hg_2Se_4 fragments and the different molecular packings in the crystals.

In the $\text{Hg}_2[(\text{Ph}_3\text{PO})_6](\text{ClO}_4)_2$ complex with the stoichiometry $(\text{Hg}_2)^{2+}:\text{L} = 1:6$, the coordination environment around each mercury atom is a tetrahedron formed by three ligands and the adjacent mercury atom of the $(\text{Hg}_2)^{2+}$ pair. As a result, the discrete complex cation is formed ($\text{Hg}-\text{Hg}$, 2.522 Å; $\text{Hg}-\text{O}$, 2.29–2.43 Å).⁹⁰ The ClO_4^- anions are not involved in the coordination sphere about the mercury atoms. In this complex, the mercury atoms have the so-called umbrella-type coordination formed by the oxygen atoms of the ligands with elongated $\text{Hg}-\text{O}$ bonds. This coordination is analogous to that found in $\text{Hg}_2\text{Ag}.\text{PO}_4$,³² szymanskiite⁴⁰ and the $[\text{Hg}_2(\text{L}^8)_4](\text{ClO}_4)_2$ complex.⁸⁷

It should be noted that compounds of the $\text{Hg}_2\text{L}_2\text{X}_2$ type contain discrete dimeric cations, in which each mercury atom is linearly coordinated. The $\text{Hg}-\text{L}$ bonds are in the range of 2.03–2.35 Å and the X anions are located at large distances from the mercury atoms (2.8–3.0 Å). In the compounds with composition $\text{Hg}_2\text{L}_4\text{X}_2$, the coordination about the mercury atoms is intermediate between linear and tetrahedral. Besides, data on polymeric complexes with bridging N-containing L ligands, which are analogous to those found in $[\text{Hg}_2(\text{L}^8)_4](\text{ClO}_4)_2$ with O-containing ligands, are lacking.⁸⁷ Only in the $\text{Hg}_2[(\text{Ph}_3\text{PO})_6].(\text{ClO}_4)_2$ compound, is the coordination environment about the mercury atoms a tetrahedron.⁹⁰

The existence of the stable mercury complex with 1,10-phenanthroline (Phen) confirms the possibility of complexation of dimercury ions with low-basicity amines. The $\text{Hg}_2\text{Phen}(\text{NO}_3)_2$ complex with the ratio $(\text{Hg}_2)^{2+}:\text{L} = 1:1$ has a layered structure. The discrete $[\text{Hg}_2(\text{Phen})]^{2+}$ cations are separated by layers of the NO_3^- anions.⁹¹ The mercury atoms have different coordinations. Thus, the $\text{Hg}(1)$ atom has four nearest neighbours; the tetrahedron is formed by the $\text{Hg}(2)$ atom ($\text{Hg}-\text{Hg}$, 2.516 Å), the nitrogen atoms of the phenanthroline molecule (2.30 and 2.48 Å) and the oxygen atom of NO_3^- anion (2.59 Å). Another oxygen atom of the NO_3^- anion is located at a distance of 2.91 Å. The nearest environment about the $\text{Hg}(2)$ atom is formed by the $\text{Hg}(1)$ atom and the oxygen atom of the NO_3^- anion. The remaining oxygen atoms are at distances of 2.75–2.95 Å. Therefore, the 1,10-phenanthroline molecule is bound to only one mercury atom of the $(\text{Hg}_2)^{2+}$ pair. Attempts to isolate the compound with composition $\text{Hg}_2(\text{Phen})_2(\text{NO}_3)_2$ failed.

In compounds with the stoichiometry $\text{Hg}_2^{2+}:\text{L} = 1:2$ [$\text{Hg}_2(\text{L}^9)_2](\text{NO}_3)_2$ and [$\text{Hg}_2(\text{L}^{10})_2](\text{NO}_3)_2$, the nearly linear

$-\text{N}-\text{Hg}-\text{Hg}-\text{N}-$ groups were found with the $\text{Hg}-\text{Hg}$ distances of 2.551⁹² and 2.517 Å⁹³ and the $\text{Hg}-\text{N}$ distances of 2.168 Å⁹² and 2.193 Å.⁹³ The shortest distances to the oxygen atoms of the NO_3^- anions are 2.696–3.000 Å. The authors⁹³ believed that the contacts, characterised by these lengths, play a decisive role in the molecular packing of the complex.

The structures of [$\text{Hg}_2(\text{L}^{11})_2](\text{NO}_3)_2$ (see Ref. 94) and [$\text{Hg}_2(\text{L}^{12})_2](\text{NO}_3)_2$ (see Ref. 95) contain the nearly linear $-\text{N}-\text{Hg}-\text{Hg}-\text{N}-$ groups ($\text{Hg}-\text{Hg}$, 2.518 Å⁹⁴ and 2.524 Å⁹⁵; and $\text{Hg}-\text{N}$, 2.233 Å⁹⁴ and 2.209 Å⁹⁵). Taking into account the $\text{Hg}\cdots\text{O}$ distance (2.659 Å), the coordination about the mercury atoms is close to T-shaped.⁹⁴ In addition, each mercury atom has contacts with the oxygen atom of the NO_3^- anion ($\text{Hg}\cdots\text{O}$, 2.769 Å) and the nitrogen atom of the nitrile group (2.906 Å). The NO_3^- anions are involved in hydrogen bonding with the NH_2 groups of the adjacent molecules ($\text{N}\cdots\text{O}$, 2.88 and 3.02 Å) through the noncoordinated and coordinated oxygen atoms to form chains along the [100] direction. These chains are linked in layers parallel to the (010) plane through the $\text{Hg}-\text{N}_{\text{CN}}$ interactions (2.906 Å).

The mercury atoms in the dimeric cation of the $\text{Hg}_2(\text{L}^{13})_2(\text{NO}_3)_2$ complex have different coordinations. Thus, the $\text{Hg}(1)$ atom is coordinated to the $\text{Hg}(2)$ atom at a distance of 2.541 Å and, in addition, forms a covalent bond with the sulfur atom of the ligand (2.49 Å). The $\text{S}-\text{Hg}-\text{Hg}-\text{S}$ fragment is virtually linear (the $\text{Hg}-\text{Hg}-\text{S}$ angle is 173.5°).⁹⁶ The coordination environment about the $\text{Hg}(2)$ atom is more complicated. The nearest environment involves the oxygen atoms of two NO_3^- groups (2.516 and 2.651 Å) along with the sulfur atom of the ligand (2.584 Å). In addition, there are $\text{Hg}\cdots\text{O}$ contacts between the $\text{Hg}(1)$ atom and the NO_3^- groups (2.773 and 2.820 Å). The L^{13} ligands serve as bridges between the mercury pairs. In the structure, the $-\text{L}^{13}-(\text{Hg}_2)^{2+}-\text{L}^{13}-$ chains are extended parallel to the [101] direction.

The $\text{Hg}_2(\text{L}^{14})_2(\text{NO}_3)_2$ compound contains the $[-(\text{Hg}_2)^{2+}-\text{S}-(\text{Hg}_2)^{2+}-]$ chains with the three-coordinate sulfur atoms and the NO_3^- anions ($\text{Hg}-\text{Hg}$, 2.548 Å; $\text{Hg}-\text{S}$, 2.488 and 2.477 Å; the $\text{Hg}-\text{Hg}-\text{S}$ angles are 161.9 and 163.8°).⁹⁷ $\text{Hg}\cdots\text{O}$ contacts (2.64–3.14 Å) are observed. The O(3) atom of the NO_3^- anion acts as a bridge [$\text{Hg}(1)-\text{O}(3)$, 2.652 Å; and $\text{Hg}(2)-\text{O}(3)$, 2.636 Å], completes the coordination about the mercury atom to T-shaped and links the chains in corrugated ribbons along the b axis (Fig. 25).

In the crystal of the complex $\text{Hg}_2(\text{L}^{15})_2(\text{H}_2\text{O})_2$, the molecules exist as zwitter-ions with the formal positive charge on the nitrogen atom and the negative charge on the sulfate ion.⁹⁸ The $\text{N}-\text{Hg}-\text{Hg}-\text{N}$ fragment has a nearly linear configuration. The

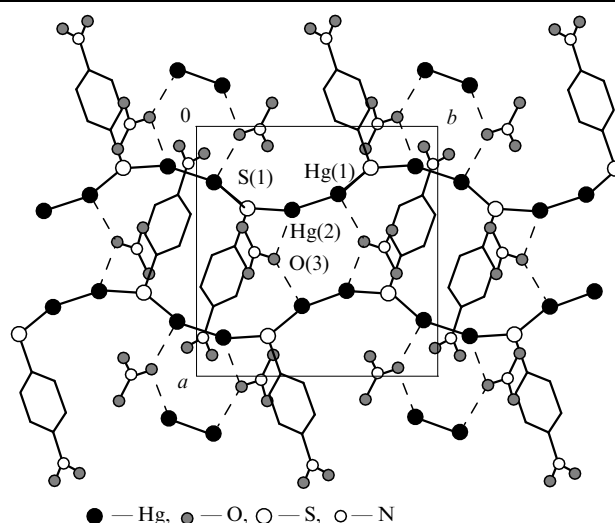


Figure 25. Corrugated ribbons extended along the b axis in the crystal structure of $\text{Hg}_2(\text{L}^{14})_2(\text{NO}_3)_2$.

Hg—Hg bond is rather short (2.494 Å). The mercury atoms form additional contacts with the oxygen atoms of the water molecules (2.621 Å) and of the SO_3^- groups of the L^{15} ligand (2.680 Å).

The structures of $\text{Hg}_2(\text{L}^{16})_2$, $\text{Hg}_2(\text{L}^{17})_2$ and $\text{Hg}_2(\text{L}^{17})_2(\text{H}_2\text{O})_2$ contain the centrosymmetrical complexes, in which the mercury atoms are coordinated by the nitrogen atoms to form the nearly linear $[-\text{N}-\text{Hg}-\text{Hg}-\text{N}-]$ fragments.⁹⁹ The Hg—Hg bond lengths are 2.500, 2.515 and 2.522 Å in $\text{Hg}_2(\text{L}^{16})_2$, $\text{Hg}_2(\text{L}^{17})_2$ and $\text{Hg}_2(\text{L}^{17})_2(\text{H}_2\text{O})_2$, respectively. The Hg—N bond lengths are virtually identical (the average value is 2.19 Å). In the $\text{Hg}_2(\text{L}^{16})_2$ and $\text{Hg}_2(\text{L}^{17})_2(\text{H}_2\text{O})_2$ compounds, the $(\text{Hg}_2)^{2+}$ pairs are rotated with respect to each other by 78 and 68°, respectively. In $\text{Hg}_2(\text{L}^{17})_2$, these pairs are parallel to each other. There are weak Hg...O interactions, whose lengths are close to the sum of the van der Waals radii. Thus, there are contacts with three oxygen atoms of two ligand molecules (2.67, 2.92 and 2.99 Å) in the $\text{Hg}_2(\text{L}^{16})_2$ compound, contacts with the oxygen atoms of the SO_3^- group (2.68 Å) in $\text{Hg}_2(\text{L}^{17})_2$ and contacts with the oxygen atoms of the ligand (2.711 Å) and of the water molecule (2.715 Å) in $\text{Hg}_2(\text{L}^{17})_2(\text{H}_2\text{O})_2$. The $\text{Hg}_2(\text{L}^{16})_2$ and $\text{Hg}_2(\text{L}^{17})_2(\text{H}_2\text{O})_2$ complexes are linked in layers and the $\text{Hg}_2(\text{L}^{17})_2$ complexes are linked in chains through the ligand molecules (Fig. 26). In the $\text{Hg}_2(\text{L}^{17})_2$ and $\text{Hg}_2(\text{L}^{16})_2$ compounds, the oxygen atoms of the SO_3^- groups are involved in intermolecular hydrogen bonding with the NH_2 groups ($\text{N}\cdots\text{O}$, 2.85–3.06 Å). In $\text{Hg}_2(\text{L}^{17})_2(\text{H}_2\text{O})_2$, the oxygen atoms are involved in hydrogen bonding with the water molecules ($\text{O}\cdots\text{O}$, 2.777 and 2.784 Å).

The nearest environment about each mercury atom of *o*-phthalate $\text{Hg}_2(\text{L}^{18})_2$ involves the oxygen atom. In this case, the virtually linear O—Hg—Hg—O fragments are formed (Hg—Hg, 2.519 Å; and Hg—O, 2.16 and 2.08 Å). The $(\text{Hg}_2)^{2+}$ pairs link the *o*-phthalate groups to form infinite zigzag chains.¹⁰⁰ In the unit cell, eight crystallographically equivalent chains are linked in pairs and are located parallel to the *b* axis, *i.e.*, along the longest crystallographic axis.

The typical pseudosymmetrical dimer with the Hg—Hg bond (2.514 Å) was also found in the $[\text{Hg}_2(\text{L}^{19})_2]_n$ compound.¹⁰¹ The L^{19} ligand is involved in one strong bond (Hg—O, 2.13 Å) and one weak intermolecular Hg...O bond (2.63 Å) through which the $(\text{Hg}_2)^{2+}$ dimers are linked in chains along the [100] direction. Taking into account this bond, the coordination about the mercury atom is close to T-shaped.

The crystal structure of $\text{Hg}_2(\text{CF}_3\text{CO}_2)_2$ consists of discrete Hg_2L_2 molecules. The $[-\text{O}-\text{Hg}-\text{Hg}-\text{O}-]$ fragments are virtually linear (Hg—Hg, 2.505 Å; and Hg—O, 2.14 Å).¹⁰² The additional Hg...O distances (2.81 and 2.88 Å) have no substantial effect on the characteristic coordination about the mercury atom. The $\text{Hg}_2(\text{CF}_3\text{CO}_2)_2$ molecules are linked in corrugated ribbons along the [001] direction through intermolecular Hg...O bonds (2.64 Å) (Fig. 27). Taking into account this contact, the coordination about the mercury atom is T-shaped. In the crystal structure, the ribbons are linked in layers *via* F...F contacts (2.78–3.12 Å).

In the $\text{Hg}_2[\text{C}(\text{CN})_3]_2$ complex,¹⁰³ the $(\text{Hg}_2)^{2+}$ ions form three elongated bonds with the nitrogen atoms of the CN^- groups (Hg—N, 2.287–2.508 Å) along with the Hg—Hg bond (2.506 Å). This coordination is analogous to the coordination about the mercury atoms of the $(\text{Hg}_2)^{2+}$ pairs mentioned in several studies.^{32, 40, 87, 90} The centres of the $(\text{Hg}_2)^{2+}$ pairs coincide with the inversion centres. The ligands are bridging and tridentate. All the nitrogen atoms of each ligand are involved in coordination about different mercury atoms to form a three-dimensional framework (Fig. 28).

In the centrosymmetrical cation of the $\text{Hg}_2(\text{C}_7\text{HN}_4)_2$ complex, the mercury atoms have the distorted trigonal environment formed by the adjacent mercury atom and the nitrogen atoms of two carbanions of the ligand (Hg—Hg, 2.503 Å; Hg—N, 2.207 and 2.560 Å; the Hg—Hg—N angles are 162.2 and 116.5°).¹⁰⁴ The cations are linked in chains along the *a* axis through the ligands. The mercury atoms form weak Hg...N contacts (2.753 and 2.935 Å) through which the chains are linked in layers (Fig. 29).

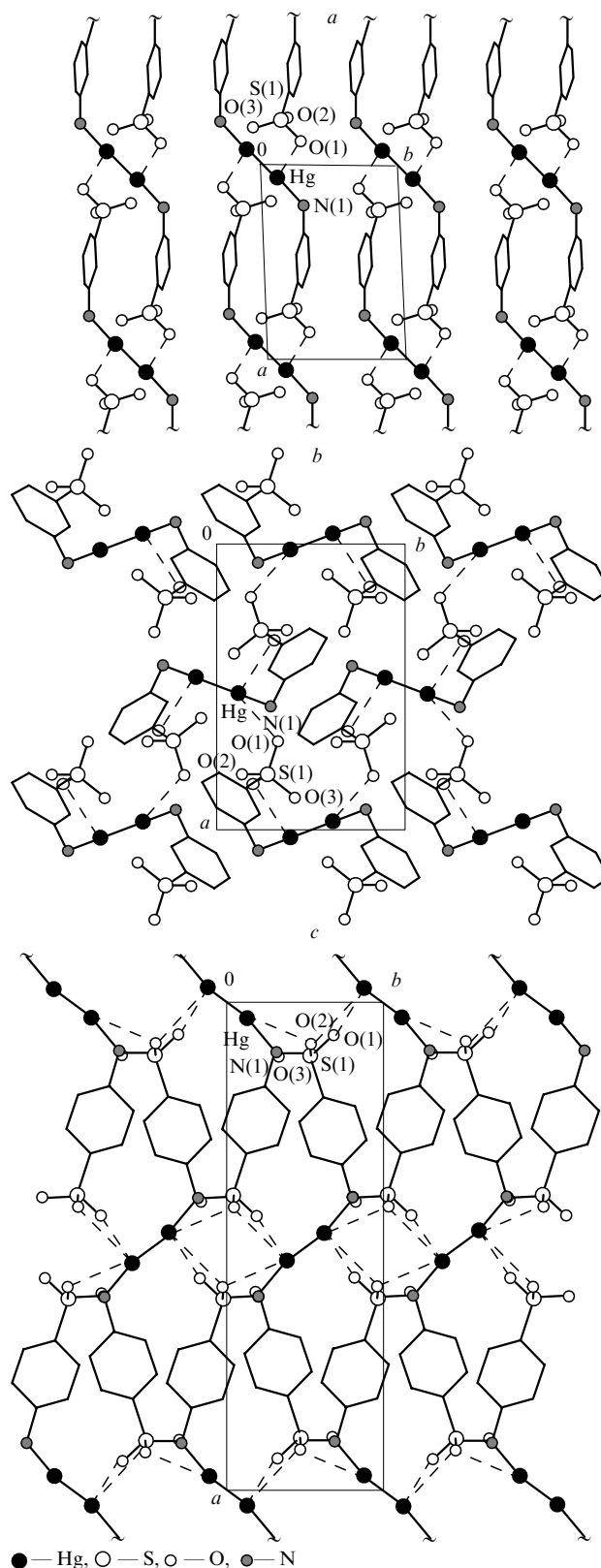


Figure 26. Molecular packings in the structures of the complexes: (a) $\text{Hg}_2(\text{L}^{16})_2$; (b) $\text{Hg}_2(\text{L}^{17})_2(\text{H}_2\text{O})_2$; and (c) $\text{Hg}_2(\text{L}^{17})_2$.

The rather unusual complex with hexamethylbenzene with composition $[\text{Hg}_2(\text{L}^{20})_6](\text{AlCl}_4)_2 \cdot \text{C}_7\text{H}_8$ was described.¹⁰⁵ The hexamethylbenzene L^{20} ligands are asymmetrically coordinated to the $(\text{Hg}_2)^{2+}$ dimer in the η^2 fashion. The distances from the mercury atoms to the planes of the ligands are 2.356 and 2.367 Å. In the crystal structure, the complexes with the Hg—Hg bonds

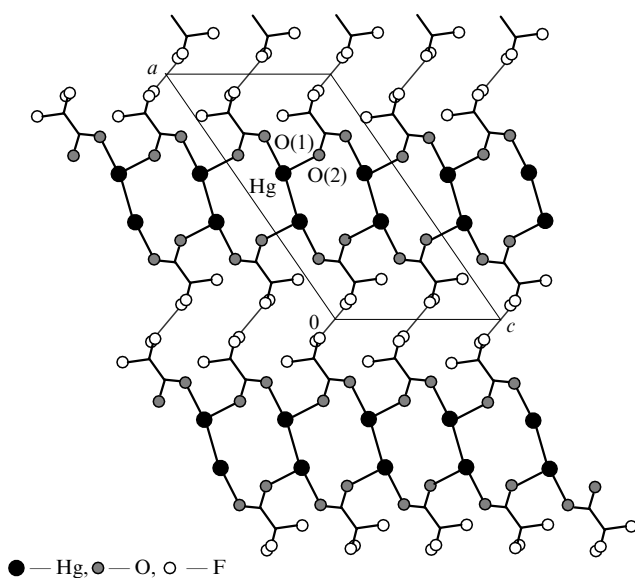


Figure 27. Crystal structure of $\text{Hg}_2(\text{CF}_3\text{CO}_2)_2$. The $\text{F}\cdots\text{F}$ contacts are indicated by dashed lines.

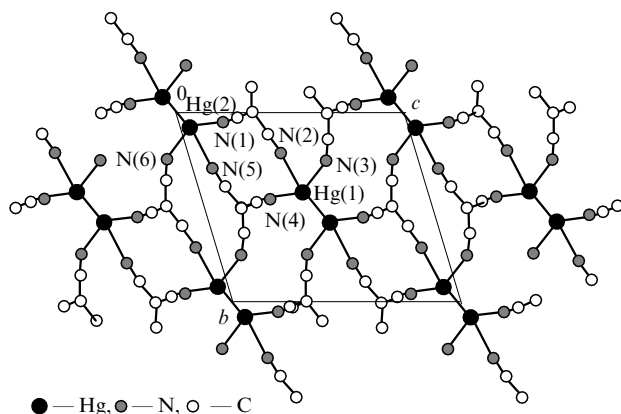


Figure 28. Projection of the crystal structure of $\text{Hg}_2[\text{C}(\text{CN})_3]_2$ onto the (100) plane.

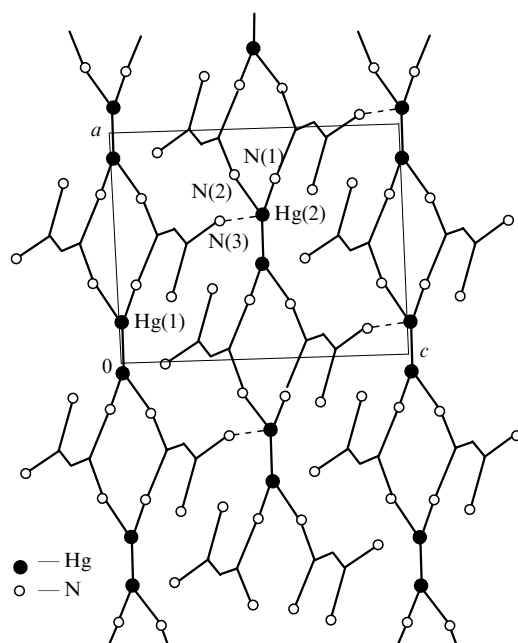


Figure 29. Layered structure of the $\text{Hg}_2(\text{C}_7\text{HN}_4)_2$ complex.

(2.515 Å) are located parallel to the b axis. The structure contains also distorted AlCl_4 tetrahedra. The shortest $\text{Hg}\cdots\text{Cl}$ distances are 3.10 and 3.12 Å.

Analysis of the $\text{Hg}-\text{Hg}$ and $\text{Hg}-\text{L}$ bonds in the monovalent mercury complexes with organic ligands demonstrates that there is no strict correlation between these parameters, as in inorganic compounds containing mercury in low oxidation states. The $\text{Hg}-\text{Hg}$ distances vary from 2.487 to 2.558 Å, which is in good agreement with the distances observed in the crystal structures of inorganic compounds. In the complexes of the $\text{Hg}_2\text{L}_n\text{X}_2$ type ($n = 2, 4$ or 6) with $\text{X} = \text{ClO}_4^-$ (see Refs 79–90), the anions have no substantial effect on the $\text{Hg}-\text{Hg}$ bond length and are involved only in nonbonded interactions with the metal atoms, whereas the oxygen atoms of the anions in the complexes with $\text{X} = \text{NO}_3^-$ (see Refs 91–97) complete the coordination about the mercury atoms of the $(\text{Hg}_2)^{2+}$ pairs ($\text{Hg}\cdots\text{O}$, 2.516–2.769 Å). In the $\text{Hg}_2(\text{L}^{15})_2(\text{H}_2\text{O})_2$ (see Ref. 98) and $\text{Hg}_2(\text{L}^{17})_2(\text{H}_2\text{O})_2$ (see Ref. 99) complexes, the water molecules are involved only in formation of additional bonds with the mercury atoms of the $(\text{Hg}_2)^{2+}$ pairs or in hydrogen bonding with the atoms of the ligands, whereas inorganic aqua complexes contain the aqua $[\text{H}_2\text{O}-\text{Hg}-\text{Hg}-\text{OH}_2]^{2+}$ cations. In the molecular complexes of the Hg_2L_2 type, the $\text{Hg}-\text{Hg}$ bond lengths vary from 2.500 to 2.519 Å.^{99–104} The complexes are linked in chains and layers through additional $\text{Hg}\cdots\text{L}$ contacts, as in inorganic monovalent mercury compounds. The coordination environment about the mercury atoms is formed primarily by atoms of organic ligands. In most compounds, anions are not coordinated to the metal atoms (the coordination number of the mercury atoms is 2).^{79–83} When the coordination number of Hg increases to 3 or 4 taking into account the contacts with the anions, the structures can be described as chain, layered⁹ and framework.^{4–102, 104, 105}

VI. Mercury-containing transition metal clusters

Presently, the data on a series of mercury-containing transition metal clusters containing either $(\text{Hg}_2)^{2+}$ pairs or more complicated cluster Hg_n groups are available. The principal crystallographic and crystal-chemical data for selected mercury-containing clusters are given in Table 1. In this section, we consider the mercury-containing clusters with the $\text{Hg}-\text{Hg}$ bond lengths varying in the range of 2.65–3.27 Å.

The structure of the $\text{Hg}_2\text{Co}_2[\text{N}(\text{CH}_2\text{CH}_2\text{PPh}_2)_3]_2(\text{THF})$ cluster consists of the discrete $\{[\text{N}(\text{CH}_2\text{CH}_2\text{PPh}_2)_3]\text{Co}(\text{Hg}-\text{Hg})\text{Co}[\text{N}(\text{CH}_2\text{CH}_2\text{PPh}_2)_3]\}$ molecules and the tetrahydrofuran molecules located between the complex molecules. Two $\text{Co}[\text{N}(\text{CH}_2\text{CH}_2\text{PPh}_2)_3]$ fragments are linearly bonded through the $(\text{Hg}_2)^{2+}$ ion (Fig. 30) so that the four metal atoms of the $-\text{Co}-\text{Hg}-\text{Hg}-\text{Co}-$ fragment are coplanar (the $\text{Co}-\text{Hg}-\text{Hg}$ angles are 179.7 and 178.4°).¹⁰⁶ The two-coordinate mercury atoms are shielded from additional bonding with the Ph rings of the $[\text{N}(\text{CH}_2\text{CH}_2\text{PPh}_2)_3]$ ligands. The $\text{Hg}-\text{Hg}$ distance (2.651 Å) is somewhat larger than those in the dimercury complexes with organic ligands. The shortest contact between the carbon atoms of the Ph rings and the mercury atoms is 3.48 Å.

The study of the compound $\{\text{Hg}_2\text{Pt}_6[\text{Ph}_2\text{P}(\text{CH}_2)_6\text{PPh}_2]_3\cdot(\text{C}_8\text{H}_9\text{NC})_6\}\cdot 2\text{C}_6\text{H}_6$ demonstrated that the $(\text{Hg}_2)^{2+}$ pair is inserted into the trigonal antiprismatic cage of the platinum atoms.¹⁰⁷ Two Pt_3 triangles are tightened by three $[\text{Ph}_2\text{P}(\text{CH}_2)_6\text{PPh}_2]$ ligands. Six isocyanide molecules act as bridging ligands in each triangular unit. The $\text{Hg}-\text{Hg}$ distance (2.872 Å) is larger than the analogous distances in monovalent mercury compounds with organic ligands but is somewhat shorter than the distances between the metal atoms in metallic mercury.⁶⁹

The structural studies of mercury-containing metal carbonyl compounds demonstrated that, as in compounds containing linear Hg_n chains ($n = 3$ or 4), the $\text{Hg}-\text{Hg}$ distances are in the range of 2.5–2.8 Å. This is indicative of a strong covalent bond, which is formed due to the overlap of the linear sp -hybridised orbitals. In the cases where other atoms, for example, transition

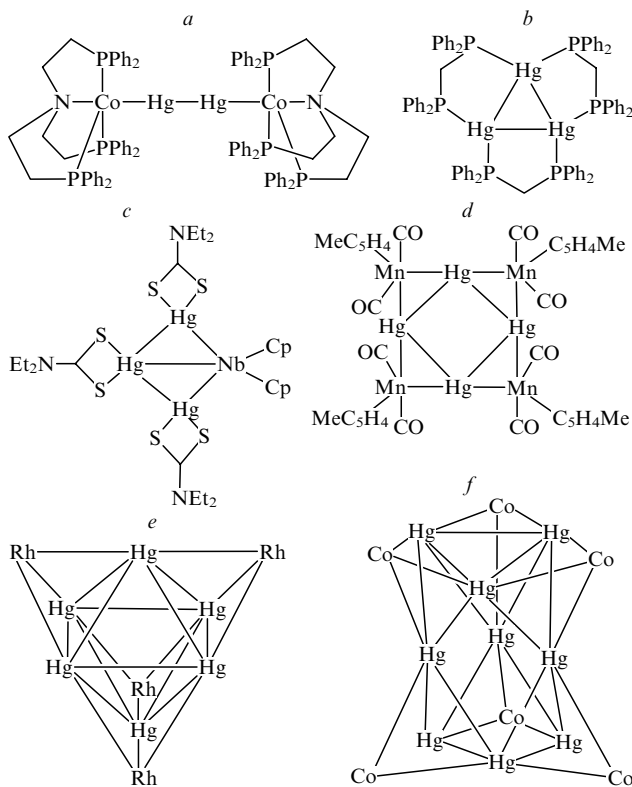


Figure 30. Schemes of the structures of mercury-containing transition metal clusters: (a) $\text{Hg}_2\text{Co}_2\text{N}(\text{CH}_2\text{CH}_2\text{PPh}_2)_3(\text{THF})$; (b) $\{\text{Hg}_3[(\text{Ph}_2\text{P})_2\text{CH}_2]_3\}(\text{SO}_4)_2 \cdot 1.5\text{H}_2\text{O}$; (c) $[\text{Nb}(\eta\text{-C}_5\text{H}_5)_2\{\text{HgS}_2\text{CN}(\text{C}_2\text{H}_5)_2\}_3] \cdot (\text{C}_2\text{H}_5)_2\text{S}_3$; (d) $[(\eta^5\text{-CH}_3\text{C}_5\text{H}_4)\text{Mn}(\text{CO})_2\text{Hg}]_4$; (e) $[(\text{C}_{12}\text{H}_{36})_3\text{Rh}]_4\text{Hg}_6$; and (f) $[\text{Hg}_9\text{Co}_6(\text{CO})_{18}] \cdot 2(\text{C}_3\text{H}_6\text{O})$.

metals (M), are involved in the Hg—Hg bond, the distances in the clusters increase to 3.2 Å.

In the $[(\text{Ph}_3\text{P})_2\text{N}]_2[\text{Hg}_2\text{Os}_{18}(\text{CO})_{42}\text{C}_2]$ cluster, the vertices of the Os triangles are linked through the mercury atoms to form the $\text{Os}_9\text{C}(\text{CO})_{21}$ units.¹⁰⁸ The molecule is centrosymmetrical with respect to the midpoint of the Hg—Hg bond. The Hg—Hg distance is 2.744 Å, whereas the Hg—Hg bond in the $[(\text{Ph}_3\text{P})_2\text{N}]_4[\text{Hg}_2(\text{Os}_{18}(\text{CO})_{42}\text{C}_2)(\text{CH}_2\text{CH}_2)]$ cluster,¹⁰⁹ which contains the framework of the metal atoms with a similar structure, is somewhat longer (2.820 Å).

The triangular $(\text{Hg}_3)^{4+}$ cluster containing the mercury atoms in the oxidation state of +4/3 was found in the $\{\text{Hg}_3[(\text{Ph}_2\text{P})_2\text{CH}_2]_3\}(\text{SO}_4)_2 \cdot 1.5\text{H}_2\text{O}$ compound.¹¹⁰ Each mercury atom is bound to the bridging $(\text{Ph}_2\text{P})_2\text{CH}_2$ ligands. In addition, two SO_4^{2-} anions form weak contacts with the mercury atoms. The Hg—Hg distances are 2.763, 2.764 and 2.802 Å, which are comparable with the analogous distances in the triangular groups observed in terlinguaite,⁴⁴ kuznetsovite⁶⁰ and $\text{Hg}_9\text{As}_4\text{O}_{16}$.⁶²

In the $[(\text{Ph}_3\text{P})_2\text{N}]_2[\text{Ru}_{18}\text{Hg}_3(\text{C})_2(\text{CO})_{42}] \cdot \text{CH}_2\text{Cl}_2$ cluster, the mercury triangle links two tricapped octahedral $[\text{Ru}_9(\text{CO})_{21}\text{C}]$ fragments (Hg—Hg, 2.919 and 2.922 Å; Hg—Ru, 2.640–2.734 Å).¹¹¹ It should be noted that the Hg—Hg distances are virtually equal to the corresponding distances in metallic mercury.⁶⁹ In the solid state, the $[\text{Ru}_{18}\text{Hg}_3(\text{C})_2(\text{CO})_{42}]^{2-}$ dianion has the symmetry C_3 . The average angle of rotation of the central Hg_3 triangle with respect to the two adjacent Ru_3 triangles is 30°. The short Hg...C_{CO} contacts (the average length is 2.64 Å) are present in the structure.

An analogous Hg_3 unit links two $[\text{Os}_9(\text{CO})_{21}\text{C}]$ fragments in the $[(\text{Ph}_3\text{P})_2\text{N}]_2[\text{Hg}_3\text{Os}_{18}(\text{CO})_{42}\text{C}_2] \cdot \text{CH}_2\text{Cl}_2$ cluster, the mercury triangle (Hg—Hg, 2.919–2.931 Å) being disordered.¹¹² Note that the Cd_3 triangle with the average Cd—Cd bond length of 2.980 Å

was found in the structurally related $[\mu_3\text{-Co}(\text{CO})_3]\text{Cd}_3\{\mu_3\text{[(CO)}_9\text{Co}_3(\mu_3\text{-CCO}_2)]_3(\text{THF})_3\}$ cluster.¹¹³

A series of Hg-containing metal clusters containing the heteronuclear triangular MHg_2 fragment were studied. The $\text{Hg}_2\text{Ag}[(\text{Ph}_2\text{P})_2\text{CH}_2]_3(\text{CF}_3\text{SO}_3)_3$ cluster contains the Hg_2Ag triangle all vertices of which are bound to the $[(\text{Ph}_2\text{P})_2\text{CH}_2]$ bridging ligands.¹¹⁴ The Hg—Hg (2.660 Å) and Hg—Ag (2.805 and 2.853 Å) distances are close to those found in AgHg_2PO_4 .³² The mercury and silver atoms have an approximately planar-square coordination formed by two metal atoms and two phosphorus atoms.

In the examples of mercury-containing transition metal clusters considered below, the Hg—Hg bonds (2.883–3.274 Å) approximate the distances in metallic mercury. Therefore, the mercury—transition metal bonds in these clusters prevail.

The rather unusual nearly planar Hg_3Nb unit, which is located in the equatorial plane of the wedge-shaped Cp_2Nb sandwich, was found in the organometallic $[\text{Nb}(\eta\text{-C}_5\text{H}_5)_2\{\text{HgS}_2\text{CN}(\text{C}_2\text{H}_5)_2\}_3]$ cluster.¹¹⁵ The dihedral angle between the $\text{NbHg}(1)\text{Hg}(2)$ and $\text{NbHg}(2)\text{Hg}(3)$ triangles in this complex is $\sim 5^\circ$. The Hg—Hg bond lengths (2.883 and 2.901 Å) are indicative of a rather strong interaction between the adjacent mercury atoms. The Hg—Nb distances vary from 2.777 to 2.808 Å. The cluster molecules are linked in dimeric units through the weak Hg...S bonds [$\text{Hg}(2)\text{—S}(11)$, 3.39 Å].

The organometallic $[(\eta^5\text{-CH}_3\text{C}_5\text{H}_4)\text{Mn}(\text{CO})_2\text{Hg}]_4$ compound¹¹⁶ contains the eight-membered Mn_4Hg_4 metallocycle in which four mercury atoms form a planar square with the Hg—Hg distances of 2.888 Å. The four-membered virtually planar Hg_4 ring (the Hg—Hg—Hg bond angle is 90°) was also found in the $[(\eta^5\text{-C}_5\text{H}_5\text{Re}(\text{CO})_2\text{Hg})_4]$ cluster with an analogous structure.¹¹⁷ The rhenium atoms are alternately located above and below the plane of the mercury square. The average angle of bend of the angular HgReHg fragments is 19.0° . The slight shortening of the Hg—Hg bonds (2.92 Å) compared to the distances in metallic mercury (2.99 Å) is indicative of the metal—metal interaction in the Hg_4 ring of the cluster. The authors believed that the distortion of the linear coordination of the mercury atoms (the Re—Hg—Re angle is 158.8°) is also evidence in favour of the Hg—Hg interaction. The observed eight-membered ring system is similar to that found previously in $[(\eta^5\text{-CH}_3\text{C}_5\text{H}_4)\text{Mn}(\text{CO})_2\text{Hg}]_4$.¹¹⁶ It should be noted that the Hg—M bonds are substantially shorter than the Hg—Hg distances in the above-described compounds [2.64 Å (Mn) and 2.74 Å (Re)].

The octahedra of six mercury atoms were observed in two clusters, viz., in $[(\text{C}_{12}\text{H}_{36})_3\text{Rh}]_4\text{Hg}_6$ (see Ref. 118) and $[(\text{C}_8\text{H}_{18})_2\text{Pt}]_4\text{Hg}_6$ (see Ref. 119). In the molecular structures of both compounds, the Rh and Pt atoms act as ‘caps,’ which complete the faces of the Hg_6 octahedra to form the heteroatomic Hg_6M_4 tetrahedron. The Hg—Hg bond lengths in the nearly regular mercury octahedra are in the ranges of 3.129–3.149¹¹⁸ and 3.081–3.274 Å.¹¹⁹ The Hg—Rh and Hg—Pt distances are in the ranges of 2.690–2.724 and 2.671–2.876 Å, respectively.

In the $[\text{Hg}_9\text{Co}_6(\text{CO})_{18}] \cdot 2(\text{C}_3\text{H}_6\text{O})$ cluster,¹²⁰ the structural unit containing nine mercury atoms was found. The framework of the metal atoms can be described as a distorted Co_6Hg_9 trigonal prism with the cobalt atoms occupying all vertices and the mercury atoms being located in the midpoints of the edges. The distances between the mercury atoms located in the centres of the triangular bases of the prism vary from 3.065 to 3.138 Å, whereas the distances from these atoms to the mercury atoms located in the midpoints of the edges of the prism, which link two bases, are somewhat longer (3.086–3.198 Å). The authors¹²⁰ believed that the Hg—Co interaction (2.521–2.609 Å) is the governing factor in the formation of the framework of the metal atoms.

The nature of the Hg—Hg interactions in the clusters of this type is still unclear. In the review,¹²¹ the structures of transition metal clusters with mercury atoms were considered and an attempt was made to explain the nature of the Hg—Hg and Hg—M bonds. The structural studies of transition metal clusters

revealed the existence of the linear $M-Hg-M$ units containing two-coordinate mercury atoms. The clusters can be divided into two types, *viz.*, two-dimensional clusters in which mercury atoms form polygons {for example, a triangle in $(C_{36}H_{30}NP_2)_2 \cdot [Hg_3Os_9(CO)_{21}C_2] \cdot CH_2Cl_2$ (see Ref. 112) or a square in $[(\eta^5-CH_3C_5H_4)Mn(CO)_2Hg]_4$ (see Ref. 116)}, and three-dimensional clusters in which mercury atoms form polyhedra {for example, an octahedron in $[(C_{12}H_{36})_3Rh]_4Hg_6$ (see Ref. 118) and $[(C_8H_{18}P)_2Pt]_4Hg_6$ (see Ref. 119) or a tricapped trigonal prism in $[Hg_9Co_6(CO)_{18}] \cdot 2(C_3H_6O)$ (see Ref. 120)}. The mercury atoms in these clusters are characterised by the linear *sp* configuration of the metal-metal bonds and the involvement in the secondary $Hg \cdots Hg$ interactions (2.89–3.15 Å). Note that in the compounds considered in Refs 115–120, the bonds between the mercury atoms and the transition metal atoms are, apparently, determining. The $Hg-Hg$ bond lengths (2.65–3.27 Å) are intermediate between the shortened bond lengths found in inorganic and complex compounds of monovalent mercury (2.46–2.59 Å) and the van der Waals $Hg^{2+} \cdots Hg^{2+}$ contacts (3.41 Å), which exist, for example, in polymercurated organic derivatives $R(HgX)_n$.^{122–124}

VII. Conclusion

In the present review, the data on the crystal structures of inorganic and complex compounds of mercury in low oxidation states and on some mercury-containing transition metal clusters containing the $(Hg_2)^{2+}$ pairs and the Hg_n groups are summarised. The $Hg-Hg$ and $Hg-X$ bonds ($X = O, N, S$ or Se) are analysed and the modes of coordination of the mercury atoms in the mercury pairs and cluster groups are considered.

The crystal chemistry of monovalent mercury compounds is similar to the crystal chemistry of divalent mercury compounds. The ability of the mercury atom to form linear $X-Hg-X$ fragments is retained. However, the *sp*-bonds in the $X-Hg-Hg-X$ groups are not necessarily exactly collinear. Interestingly, the bonds between the mercury atoms of the $(Hg_2)^{2+}$ pair and the X atom are longer (the average length is 2.14 Å) than the $Hg-X$ distances in divalent mercury compounds (the average length is 2.06 Å). The environment about the mercury atoms in the $(Hg_2)^{2+}$ pairs is generally formed by two X atoms. However, the coordination of the pair may be completed by atoms located at larger distances. The instances of the nonlinear coordination about the atoms of the $(Hg_2)^{2+}$ dimers by three X atoms ($X = O$ or N) with the longer $Hg-X$ bonds are mentioned. The $Hg-Hg$ bond lengths in inorganic and complex compounds of formally monovalent mercury vary from 2.46 to 2.59 Å. An increase in the $Hg-Hg$ bond length is observed in the linear $(Hg_4)^{2+}$ groups (2.59–2.63 Å), infinite Hg_n chains (2.64–2.67 Å), $(Hg_3)^{4+}$ triangles (2.60–2.70 Å) and transition metal clusters containing $(Hg_2)^{2+}$ pairs, $(Hg_3)^{4+}$ triangles and Hg_n groups.

In mixed-valence compounds, the tendency of mercury-oxygen groups to polymerisation, which is typical of divalent mercury, is retained. Pairs of formally monovalent mercury atoms form linear $O-(Hg_2)^{2+}-O$ groups, which, in turn, form 10-, 12-, 14-, 16- and 22-membered rings in combination with each other and with the linear $O-Hg^{2+}-O$ fragments. The rings are linked in different fashions to form two-dimensional planar or corrugated networks, layers or frameworks. The structures with the 14-membered $\{[(Hg_2)^{2+}]_2(Hg^{2+})_4O_6\}$ rings are of frequent occurrence.

In compounds containing polyatomic groups of mercury atoms, the description of the coordination polyhedra about individual mercury atoms is arbitrary because these polyhedra are substantially distorted due to the presence of the strong $Hg-Hg$ bond. In these cases, it is worthwhile from the crystal-chemical standpoint to consider this series of structures as containing the overall complex Hg_n cations ($n = 2$ or 3) with the coordinates of the geometric centres of the complexes and to describe the coordination environment about the Hg_n^{x+} cation as a whole.

In the structures of mercury compounds with fluorine and MF_6^- anions, the relationships between the value of the averaged formal charge on the mercury atom, the shortest $Hg-F$ distances, the structure of the Hg_n^{x+} cation and the $Hg-Hg$ distance in this cation are found. As the charge on the mercury atom decreases from +1 to +0.33, the $Hg-F$ distance increases from 2.13 in Hg_2F_2 to 3.2 Å in Hg_3NbF_6 and the sizes of the Hg_n^{x+} cations increase in the series from the finite nearly linear groups to infinite Hg_n chains and planar close-packed layers of mercury atoms. The $Hg-Hg$ distances in these cations vary from 2.51 to 2.90 Å.

Analysis of the structures of inorganic monovalent mercury compounds revealed no substantial effect of the mercury atoms of the $(Hg_2)^{2+}$ pair on the bond lengths in the anions, such as ClO_4^- , SO_4^{2-} , SeO_4^{2-} , PO_4^{3-} and NO_2^- , whereas an elongation of one of the bonds with the participation of the oxygen atom, which is bound to the mercury atom of the $(Hg_2)^{2+}$ pair, is observed in compounds with the AsO_4^{3-} and BrO_3^- anions. The NO_3^- anion rather often completes the coordination environment about the mercury atom through contacts of 2.45–2.88 Å and can act as a bridging ligand. In monovalent mercury complexes with organic ligands, the ClO_4^- anions are involved only in nonbonded interactions with the mercury atoms of the $(Hg_2)^{2+}$ pairs, while the function of the NO_3^- anions is analogous to that in inorganic monovalent mercury compounds.

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Transformations of organic compounds under the action of mechanical stress

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Abstract. Transformations of organic compounds (monomeric and polymeric) under the action of mechanical stress are considered. Two types of processes occur under these conditions. The first type involves disordering and amorphisation of crystal structure and conformational transformations as a result of rupture of intermolecular bonds. The second type includes mechanochemical reactions activated by deformation of valence bonds and angles under mechanical stress, namely, the rupture of bonds, oxidation and hydrolysis. Data on the organic mechanochemical synthesis of new compounds or molecular complexes are systematised and generalised. It is demonstrated that mechanical treatment ensures mass transfer and the contact of reacting species in these reactions. Proteins are especially sensitive to mechanical stress and undergo denaturation; enzymes are inactivated. The bibliography includes 115 references.

I. Introduction

Mechanical treatment of a substance can induce numerous transformations, which include, firstly, rupture and formation of valence bonds and deformation of bond angles, and, secondly, both destruction and generation of weaker intermolecular interactions (disordering, amorphisation of the crystal structure, conformational transitions and polymorphic transformations).

Mechanochemistry started to develop in the 1940–1950s, based on the results of applied studies dealing with polymer processing (plasticisation and rolling of elastomers, grinding of glassy polymers) (see, for example, Refs 1–5). Later, substantial progress has been attained in the mechanochemistry of inorganic compounds (metals, salts, oxides);^{6–13} the influence of high pressure combined with shear strain on the rate of solid-state transformations of low-molecular-mass organic compounds has been studied;^{14–17} the occurrence of mechanochemical reactions in high-energy mills has been discovered;^{18–21} mechanochemical transformations of coals have been studied;²² free radical reactions induced by mechanical stress have been considered;^{23, 24} and

experimental studies and theoretical calculations for mechanochemical reactions involving cleavage of C–C bonds^{25–27} and oxidation and hydrolysis reactions have been performed.^{28–30} (The vast majority of these studies were concerned with solid-phase processes.)

A new and fairly promising line of research representing technology of the future, nanotechnology, is closely related to mechanochemistry. A non-traditional application of atomic force and tunnelling microscopes has been reported;³¹ it was proposed to use them for micro-manipulation, *i.e.*, for positioning atoms and molecules at distances required to initiate a chemical reaction between them (molecular design).

Despite the fact that mechanochemistry of organic compounds has been successfully developing in recent years (most of the studies in this field were carried out by Russian scientists), the results obtained have not been surveyed; the reasons and the mechanisms of the influence of mechanical stress on chemical processes have not been analysed. The purpose of this review is to fill this gap and to present mechanochemistry (in particular, mechanochemistry of organic compounds) as a field of science developing at the border between chemistry and physics.

II. Rupture of intra- and inter-molecular bonds upon mechanical treatment

Organic compounds, both polymeric and monomeric, contain bonds of two types, namely, strong interatomic (covalent) bonds within the molecules and relatively weak (van der Waals, hydrogen) intermolecular bonds. Naturally, the weaker intermolecular bonds should be the first to split under the action of mechanical stress; this results in disordering or loosening of the structure of substances. The degree of disordering depends on the type of mechanical treatment, the amount of energy supplied and the substance structure. Crystalline materials undergo amorphisation and polymorphic transformations under mechanical stress; polymers undergo conformational transitions. It should be noted that in the case of polymers, mechanical treatment induces rupture of both types of bonds, because intermolecular bonds are formed along the whole length of polymer chains and the total energy needed to cleave them becomes commensurable with the energy of valence bonds.

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1. Rupture of intermolecular bonds

a. Amorphisation of molecular crystals and polymorphic transformations[†]

During fine disintegration of a substance, after the substance particles have reached a particular size, the new surface no longer forms and plastic flow of the substance starts. In some cases, further mechanical treatment results in the particle aggregation. As a rule, the specific surface area (S_{sp}) of the initial organic crystals falls in the range of $0.1\text{--}1\text{ m}^2\text{ g}^{-1}$; after grinding, it increases several-fold depending on the dose of mechanical energy delivered, the structure of the substance, the presence of moisture, impurities, *etc.* In some cases, exceptionally high S_{sp} values have been attained. Thus the specific surface areas attained on grinding of cortisone acetate and saponic acid (based on gas adsorption data) were as high as $130\text{ m}^2\text{ g}^{-1}$ (see Ref. 32) and $400\text{ m}^2\text{ g}^{-1}$ (see Ref. 33), respectively. These unusually high S_{sp} values point to extensive disordering (loosening) of the structures of these materials.

As a rule, grinding causes a decrease in the degree of crystallinity and sometimes complete amorphisation, which was confirmed by X-ray diffraction patterns and IR spectra recorded for various crystals — ampicillin trihydrate, digoxin, sodium prasteron sulfate,³³ sulfanilamides,^{34,35} phthalylsulfathiazole,³⁶ sulfathiazole,³⁷ *etc.* Analysis of the X-ray diffraction patterns of sulfamonomethoxine (Fig. 1a) allowed the researchers cited³⁴ to conclude that the observed broadening of diffraction lines is due to both a decrease in the size of crystallites (to $\sim 100\text{ Å}$) and an increase in the lattice micro-distortions (2–2.5-fold).

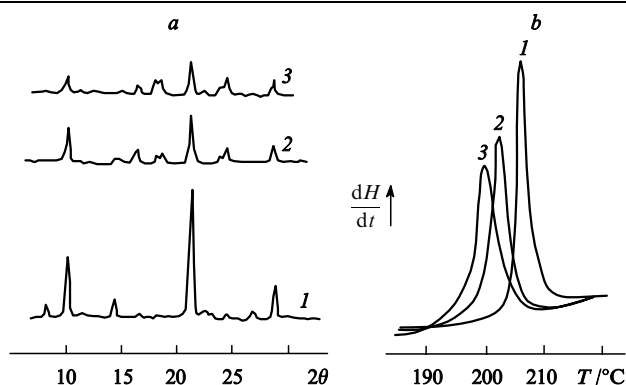


Figure 1. X-Ray diffraction patterns ($\text{CuK}\alpha$ radiation) (a) and differential scanning calorimetry curves (b) of sulfamonomethoxine powders after grinding in a jet mill.³⁴

The initial sample (1) and the samples having been passed four (2) and six (3) times through the jet mill.

Amorphisation increases the rates of dissolution and solubility of compounds;^{33,34} it decreases the melting points and heats of melting of crystals and extends the temperature ranges of melting.³³

Fig. 1b presents the variation of the melting point and the heat of melting of sulfamonomethoxine powders as functions of the degree of disintegration found from the data of differential scanning calorimetry (DSC).³⁴ The values for the change in free energy (ΔG) calculated in two ways, namely, from the decrease in the melting point and the heat of melting and from the increase in the solubility of sulfamonomethoxine on grinding, agree with each other and reach $0.8\text{--}0.9\text{ kJ mol}^{-1}$ (see Ref. 34).

[†] The data on the influence of mechanical treatment on the properties of low-molecular-mass organic crystals, presented in the review, have been mainly taken from publications devoted to the technology of drugs, which often includes various types of mechanical treatment, for example, grinding or pressing.

In some cases, for instance, for fullerene, the peak corresponding to a phase transition ($\sim 260\text{ K}$) completely disappears from the thermograms.³⁸

For most of the organic crystal studied, disordering of the crystal structure is associated with disturbance of the system of intermolecular hydrogen bonds, which is confirmed by IR spectra.^{33,34,39}

Some organic crystals, for example, barbiturates, streptocid, sulfathiazole, theophylline, cortisone acetate, *etc.*^{32,33,37} undergo polymorphic transformations on grinding, as indicated by X-ray diffraction, calorimetric and spectroscopic data. In the case of sulfathiazole, mechanically induced reversible transition of the form stable at room temperature into a metastable form occurs (the latter is usually produced by heating the stable form at $\sim 174^\circ\text{C}$).³⁷ In the case of cortisone acetate, a structure with $P2_1$ point group of symmetry passes into a structure with $P2_12_12_1$ group of symmetry.³² It was found³¹ that under the action of anisotropic compression forces, C_{60} fullerene is transformed into known carbon phases (diamond, graphite) and into some metastable crystalline and amorphous modifications.

During the polymorphic transformations induced by mechanical treatment, one form does not pass directly into another; this occurs *via* a disordered non-crystalline state. Upon prolonged mechanical treatment, the new phase arising also becomes amorphised.^{32,37}

The changes in the physico-chemical properties of substances induced by pressing are similar to those occurring on grinding. Normally, pressing causes a decrease in the degree of crystallinity and polymorphic transformations.³³ This has been detected for streptocid, phenylbutazone, chloropropionamide, ephedrine hydrochloride, libexin, noxyron, *etc.* However, the rate of dissolution of some substances can decrease upon pressing due to the aggregation of powder particles.

b. Structure disordering and conformational transitions in polymers

As in the case of molecular crystals, the mechanical dispersion of polymers in mills at low temperatures ($\sim 80\text{ K}$) results in substantial disordering (loosening) of their structure caused by loss of the intermolecular van der Waals contacts. This is indicated, for example, by the sharp increase in the adsorption of inert gases by polymers. The specific surface area of dispersed poly(methyl methacrylate) (PMMA) calculated from argon sorption isotherms is $600\text{--}800\text{ m}^2\text{ g}^{-1}$ (see Ref. 11), and that of poly(methyl silsesquioxane) (PMSO) is $400\text{ m}^2\text{ g}^{-1}$ (see Ref. 40) under the same conditions.

During unfreezing of a PMMA sample, the disordered structure relaxes even at 120 K and the specific surface area diminishes to a value of several square meters per gram. However, in the case of PMSO, the disordered state is retained during heating of the samples to 500 K . This can be explained by the specific chemical structure of PMSO; mechanical dispersion of this polymer is accompanied by free radical reactions giving valence cross-links, which stabilise the arising disordered state.⁴⁰

Crystallisation of solutions (melts) of polymers and separation of liquid phases on exposure to an external mechanical field are phenomena long known in the physical chemistry of polymers.^{41,42} This is due to the fact that under tensile or shear stress, macromolecular coils are untwisted, the number of contacts between macromolecules increases, and, as a consequence, the degrees of their aggregation and orientation increase.

A mechanical action (static compression under $75\text{--}100\text{ kbar}$ combined with shear deformation) on crystalline polyoxymethylene (POM) induces conformational transitions of various types.^{43,44} In particular, a broad range of rotational isomers of chains were found and a phase transition of the hexagonal modification into an orthorhombic one was detected in POM crystals with straightened chains which had been subjected to hydrostatic compression. Evidently, even under conditions of only hydrostatic compression, tangential stresses and micro-

shears may appear due to the anisotropy of the mechanical properties of the crystals.

During mechanical grinding and pressing of proteins, cleavage of hydrogen bonds and disturbance of hydrophobic and electrostatic interactions occur, resulting in changed conformations of protein molecules and their denaturation. Mechanically induced denaturation of proteins and inactivation of enzymes are considered in Section V.

2. Rupture of valence bonds

a. Models of mechanical rupture

Rupture of a valence bond on stretching (the simplest mechanochemical reaction) can be represented as follows.³¹ Two atoms forming a bond are spaced by distance r_0 and are connected by springs to the walls of the surrounding structure. The energy of bond breakage U_{br} can be represented as the sum of the potential energy of the bond U_{bond} and the elastic strain energy U_{el} of the structure to which the atoms belong. The latter parameter varies as a function of the displacement of atoms from the position where they form the bond towards the equilibrium position with respect to the structure to which they are linked (corresponds to a certain positive value of bond rigidity $k_{s, str}$)

$$U_{el} = \frac{1}{2} k_{s, str} (\Delta d - \Delta r)^2,$$

$$U_{br}(\Delta r, \Delta d) = U_{bond}(\Delta r) + U_{el}(\Delta r, \Delta d).$$

Here $\Delta r = r - r_0$ and $\Delta d = d - d_0$ are the differences between the atom coordinates in the stressed and unstressed states, respectively; d_0 is the distance between the ends of the spring in the non-stretched state.

Figure 2 shows the variation of the potential energy of a C—C bond as a function of Δr for various Δd values. The model parameters used in the calculation have been reported.³¹ It can be seen from the Figure that as Δd increases, two potential wells appear instead of one well and subsequently they are again replaced by one potential well. As $k_{s, str}$ increases, the potential barrier decreases and finally it entirely vanishes.

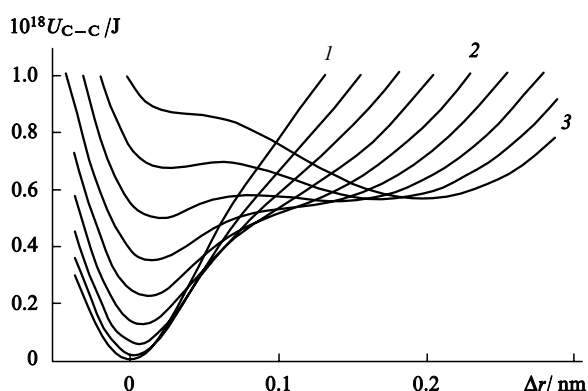


Figure 2. Potential energy of the C—C bond as a function of the distance.³¹ Δd / nm: (1) 0, (2) 0.1, (3) 0.2.

Figure 3 presents plots for the height of the potential barrier $U^\ddagger$ vs the rigidity of bonds of various types for equal depths of the wells.³¹ When $k_{s, str} > 90 \text{ N m}^{-1}$ and the characteristic times for bond rupture are $\geq 10^{-7} \text{ s}$, energy dissipation is small with respect to kT for all types of bonds. In the case of C—C bonds, the requirements to the rigidity are less stringent; it is sufficient that $k_{s, str} > 60 \text{ N m}^{-1}$. In the case of weaker bonds, C—Si and Si—Si, the requirements are even lower.

The kinetic theory of the strength of solids, apart from the purely mechanical rupture of interatomic valence bonds induced by an external force, takes account of the destructive role of thermal motion, *i.e.* cleavage of interatomic bonds is caused by

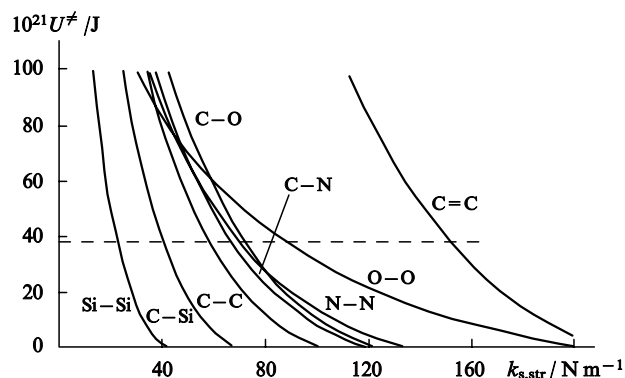


Figure 3. Height of the potential barrier for the stretching of bonds vs their rigidity.³¹

energy fluctuations arising due to the thermal motion of atoms rather than by the external force itself.⁴⁵ According to a concept developed in a publication⁴⁵ (thermofluctuation mechanism), two elementary stages should be distinguished in the bond rupture, namely, (1) force perturbation of interatomic bonds in a loaded body, which decreases the energy barrier to the bond cleavage and (2) splitting of stressed bonds upon thermal fluctuations.

The rate constant for the bond rupture k can be calculated from the equation

$$k = k_0 \exp \left(\frac{E_a - \sigma v_a}{RT} \right),$$

where k_0 and E_a are the preexponential factor and the activation energy for the thermal bond rupture, respectively, σ is the mechanical stress and v_a is the unit activation volume.

The rupture of valence C—C bonds in polymers has been studied most comprehensively (both theoretically and experimentally). The deformation of valence bonds in stretched samples of oriented linear polymers (polypropylene, polyamide, polytetrafluoroethylene, *etc.*) has been observed by IR spectroscopy.⁴⁵ The absorption bands corresponding to stretching vibrations of the C—C bonds in the polymer backbones shift to lower frequencies upon stretching. The band contours for stressed (stretched) samples also change. According to estimates,⁴⁵ the maximum loads of individual bonds in polymers attained on stretching are 10–20 GPa. The thermofluctuation elementary events of destruction occur within small activation volumes (commensurable with the volume of atoms) upon great overstress.

It has been assumed^{46–48} that not only rupture of stretched bonds can be induced by thermofluctuations in a stressed polymer but also self-ionisation of macromolecules accompanied by ejection of electrons. A calculation of the electronic spectrum of a macromolecule with stretched C—C bonds showed⁴⁷ that the elongation of a bond gives rise to a local electron level; its energy for a factor of two elongation is $\sim 4\text{--}5 \text{ eV}$, which is close to the energy of charge separation in a polymer.

The electrons having been liberated under the action of mechanical stress can be captured by traps (molecules with large electron affinity, structure defects) and are again released when the traps have been destroyed; this accounts for the mechanical emission of electrons, which has been found to accompany stretching of films and grinding of some polymers [polyethylene (PE), polyethylene terephthalate] and organic crystals.^{46, 48, 49}

The decrease in the ionisation potential of molecules subjected to mechanical stresses has been described by quantum-chemical methods.^{27, 30} Figure 4 shows the calculated plot for the variation of the ionisation potential I as a function of bond angles in the propane molecule.²⁷ It can be seen that an increase in the deformation of the molecule results in lower I values.

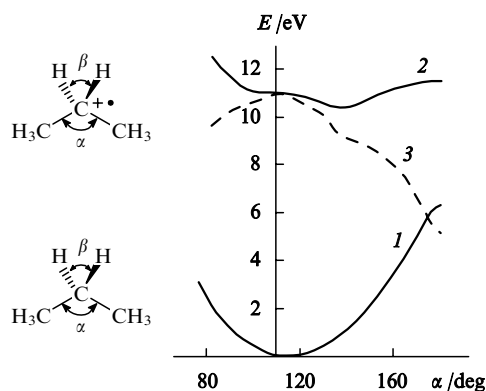


Figure 4. Quantum-chemical calculation for the change in the ionisation potential upon deformation of bond angles α and β ($\alpha = \beta$) in the propane molecule.²⁷

Curves (1) and (2) show the potential energy (E) of propane and its radical cation, respectively; curve (3) is the difference between curves (2) and (1).

Apart from the mechanical emission of electrons, some other experimental results cannot either be interpreted in terms of the thermofluctuation mechanism. Firstly, the compositions of the molecular products of thermally and mechanically induced destructions are different.^{25, 26, 45} The products of mechanical destruction contain no heavy fragments of polymer chains, which are typically present in the case of thermal degradation. The formation of light products on mechanical destruction indicates that the vibrational energy is distributed non-uniformly, being located in regions with a size of not more than 10 Å. Secondly, mechanical destruction of some polymers (PMMA, the three-dimensional epoxy polymer based on diglycidyl ether of resorcinol and *meta*-phenylenediamine, and ebonite) has been found to give high-energy molecular products.^{25, 26} The kinetic energy of these species was estimated using the time-of-flight mass spectrometer equipped by a device for high-speed detection of molecules. The velocity of the flight of the molecular products formed was used to calculate the translation temperature, which amounted to 2000–5400 K for the above-mentioned polymers.

The appearance of vibrationally excited states upon destruction of a PMMA sample was confirmed by thermal radiation spectra.⁵⁰ It can be seen from Fig. 5 that radiation consists of two components — Planck's radiation and a characteristic narrow emission band at 8.3 μm , which appears 10–60 μs after the sample fracture; this band is related to deactivation of the vibrationally excited centres, which arise during destruction of the sample and whose nature is unknown. Analysis of the spectra

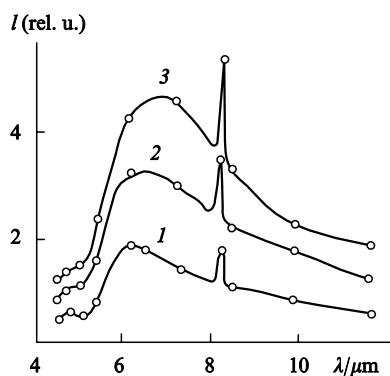


Figure 5. Heat radiation spectra recorded during fracture of a PMMA sample.⁵⁰

Time elapsed after the onset of destruction 10 (1), 20 (2) and 30 μs (3).

obtained led to the conclusion that the average warming of the sample during the polymer fracture does not exceed 200 °C.

In a series of publications (see a review²⁵ and the studies cited therein), the destruction of a stretched chain of atoms has been studied by methods of molecular mechanics. Studies^{25–27} on mechanodestruction of one-dimensional models of polymer chains consisting of 50 and 100 carbon atoms led the researchers to the conclusion that solitons play the crucial role in mechanodestruction. Over a long period (~ 10 ps) after the rupture of a stretched chain, the elastic energy stored in the chain is not thermalised and no thermal fluctuations (in the generally accepted sense⁴⁵) occur. It was shown that movement of high-energy solitons may be accompanied by the formation of C–C double bonds and by discharge of the side-chain atoms. It was shown that rupture of one chain may yield several high-energy molecular products capable of inducing destruction of the adjacent polymer chains; thus, chain branching is possible.

All the models for bond rupture known to date are one-dimensional and are restricted to the views of classical mechanics. Only the first attempts to pass from one-dimensional to two-dimensional models have been undertaken.⁵¹

Nevertheless, the one-dimensional chains considered above can be accepted as a satisfactory approximation to real linear macromolecules. Description of the mechanically induced bond rupture in three-dimensional systems (cross-linked polymers and low-molecular-mass crystals) is a more complicated task, none of the models presented being suitable for this purpose.

b. Formation of free radicals

Free radicals resulting from the rupture of valence bonds during mechanically induced destruction of many polymers and some low-molecular-mass compounds have been detected by EPR.^{23, 24, 52} The appearance of 'mechanical' macroradicals was observed on stretching of films and fibres and on grinding of linear and three-dimensional polymers in a mortar, in a mill, *etc.* The EPR spectra of 'mechanical' macroradicals have been thoroughly studied, which permitted identification of the type of bond being cleaved in each polymer; it was found that the covalent bonds in the polymer backbones and cross-links (or bridges) undergo homolytic cleavage. Thus vinyl polymers [PE, polypropylene, poly(methyl acrylate), PMMA, polystyrene (PS), *etc.*] and polypeptides [poly(amino acids), proteins] undergo cleavage of C–C bonds; in the case of carbon-and-oxygen polymers [polyformaldehyde, poly(ethylene oxide), polyesters and three-dimensional polyesteracrylate], C–C and/or C–O bonds are split; for ladder and three-dimensional network organosilicon polymers [PMSSO and polyphenylsilsesquioxane (PPSSO)], rupture of the Si–O bonds is observed, and in some polypeptides (trypsin, insulin, serum albumin), cleavage of C–C and C–S bonds occurs.

When polymers are subjected to mechanical treatment in a mill, the rate of accumulation of macroradicals (dR/dt) in the beginning of the process is constant and then it gradually decreases and approaches zero; thus, the concentration of macroradicals reaches a limiting value. The kinetics of radical accumulation are described by the equation²⁴

$$\frac{dR}{dt} = W_d - W_r, \quad (1)$$

where W_d is the rate of bond rupture, equal to $k_d[M]$; W_r is the rate of the decay of radicals upon interaction with one another, equal to $k_r[R]^2$; $[M]$ is the concentration of bonds that can be cleaved; $[R]$ is the concentration of macroradicals; k_d and k_r are effective rate constants for these reactions in the solid phase (see below).

At the beginning of the mechanical grinding when $W_d \gg W_r$, $(dR/dt)_0 \approx W_d$, *i.e.* when the intensity of the mechanical energy supply is constant, the rate of destruction depends only on the polymer nature. The rate of destruction in laboratory vibrational mills with energy input of 1–10 W g^{−1} at temperatures of 100–300 K amounts to 10¹⁴–10¹⁶ g^{−1} s^{−1}. The steady-state concentration of free radicals $[R]_{\text{lim}}$ (for $dR/dt = 0$) in linear

flexible-chain polymers is $(1-5) \times 10^{18} \text{ g}^{-1}$ and that for rigid-chain (especially three-dimensional) polymers is $10^{19}-10^{20} \text{ g}^{-1}$.

The relative rates of destruction of various polymers during grinding under identical conditions are compared in Table 1. The rate of bond rupture is determined, first of all, by the rigidity of the structure. It increases on passing from flexible-chain PE to more rigid PS and then to polypeptides, the structures of which are noted for special rigidity owing to the presence of peptide bonds in the backbone and a dense network of hydrogen bonds. The maximum destruction rates were detected for three-dimensional polymers (glyceromaleate, α,ω -diethylene glycol phthalatedimethacrylate).

Table 1. Relative rates of mechanical destruction of polymers at $T \approx 100 \text{ K}$.²⁴

Polymer	M_w	M_n	$(dR/dt)_{\text{rel}}$ (see ^a)
PE	290 000	—	1
PS	300 000	—	17
PPSSO	450 000	—	20
PEM ^b	—	—	120
Collagen	—	290 000	30
Subtilisin	—	27 000	55
Serum albumin	—	67 000	45
Trypsin	—	24 000	40
Insulin	—	5 733	6
Gramicidin	—	1 140	1.5

^a The rate of destruction of PE was taken to be unity.

^b PEM is a cross-linked polymer of α,ω -diethylene glycol phthalatedimethacrylate.

The rate of mechanical destruction and, hence, of the formation of free radicals decreases with a decrease in the molecular mass of the polymer. Thus the rate of formation of radicals in insulin, which has the lowest molecular mass among the series of proteins studied, is 7–9 times lower than those in other proteins.

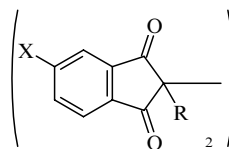
The question of the limiting molecular mass M_{lim} or the limiting degree of polymerisation n_{lim} below which the mechanical destruction of covalent bonds is terminated and only weak intermolecular bonds are broken has arisen repeatedly in the mechanochemistry of polymers.^{1,24} The n_{lim} value depends on the chemical structure of the polymer and the relationship between the strengths of valence and intermolecular bonds and can be roughly estimated from the expression

$$U = n_{\text{lim}} U_{\text{coh}}, \quad (2)$$

where U is the strength of a valence bond being cleaved and U_{coh} is the cohesion energy for a monomer unit. Expression (2) does not take into account the structural inhomogeneity of a real polymeric material and the stress gradient.

The cohesion energy is especially large for polymers which contain hydroxy, carboxy, amino and other groups which form intermolecular hydrogen bonds (for polypeptides U_{coh} reaches $40-50 \text{ kJ mol}^{-1}$ per amino-acid residue). For these polymers, low n_{lim} and M_{lim} values should be expected. Indeed, for polyethylene $n_{\text{lim}} \approx 100$, while in the case of polypeptides, $n_{\text{lim}} \approx 6$. Therefore, free radicals have been detected after mechanical treatment of relatively low-molecular-mass cyclopeptides containing only ten (gramicidin) and twelve (bacitracin) amino-acid residues in the ring.⁵²

Free radicals are formed when some low-molecular-mass organic compounds are subjected to high pressure together with shear deformation. To detect the radicals, a special resonator has been designed for an EPR spectrometer, which acts simultaneously as one of the anvils.^{16,17,53} Thus in arylindandione dimers



$X = \text{H, Cl, NMe}_2$; $R = p\text{-Me}_2\text{NC}_6\text{H}_4$

destruction involves the $C_\alpha-C_\alpha$ bond, the strength of which ($U \approx 70 \text{ kJ mol}^{-1}$) is comparable with the U_{coh} value. It was found that hydrostatic pressure (up to 0.7 GPa) without shear strain does not induce the formation of radicals, *i.e.* it is the shearing component of the mechanical stress that causes the bond rupture.

Fig. 6 shows the dependence of the yield of free arylindandione radicals (in relative units) on the angle of rotation of the anvils at a constant pressure.¹⁶ When the angles of rotation are small, the yield of radicals rapidly increases (curves 1, 2, the linear section), *i.e.* the radical generation process predominates. An increase in the angle decreases the yield of radicals and their recombination starts to predominate. Ultimately, as in the case of mechanodestruction of polymers (see above), the concentration of radicals reaches a limiting value.

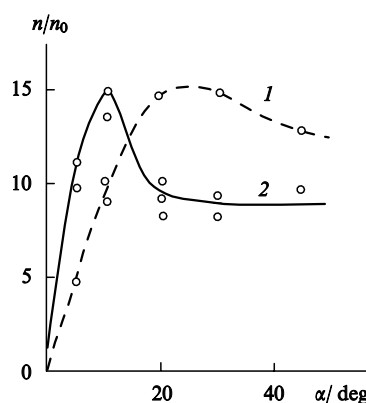
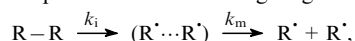


Figure 6. Yield of arylindandione radicals vs angle of rotation of the anvils α at a pressure of 7 (1) and 12 kbar (2);¹⁶ n_0 is the initial concentration and n is the current concentration of reacting species.

Under the same conditions, the EPR spectrum of C_{60} fullerene was found to exhibit a signal which was assigned to the carbon radicals formed upon destruction of the C_{60} molecules.⁵³ The rate of generation of these radicals is comparable with the rate of generation of arylindandione radicals ($\sim 10^{16} \text{ g}^{-1} \text{ s}^{-1}$).

Indirect evidence pointing to the cleavage of valence bonds to give free radicals has been obtained under the action of an indenter, shock waves and vibratory grinding of the crystals of some nitro compounds.⁴⁹ For example, minor concentrations (10^{16} g^{-1}) of $\dot{\text{N}}\text{O}_2$ radicals were detected by EPR spectroscopy upon vibratory grinding of pentaerythritol tetranitrate or cyclotrimethylenetrinitramine. It was suggested⁴⁹ that in this case, the formation of paramagnetic centres is related to the effect of the radiation which arises upon the fraction of crystals. To elucidate the reasons for the appearance of paramagnetic species more precisely, further studies are required.

Mechanical destruction in the solid phase can be represented as a sequence of the following stages:^{54,55}



and the effective rate constant for the destruction, k_d , can be represented as follows:

$$k_d = \frac{k_m k_i v}{k_m + k_i} \quad (3)$$

The first stage is a reaction characterised by the rate constant k_i and resulting in the formation of $(R^{\bullet} \cdots R^{\bullet})$ radicals, which occur in unit volume or in cage v . The k_m constant characterises departure of the radicals from the cage. The molecule in the pre-rupture state is stretched, and after bond cleavage, the radicals are removed from each other and leave the unit volume. The rupture of the bond rather than the emergence of the radicals from the cage is the limiting step in the destruction, *i.e.*, $k_i \ll k_m$.

III. Free-radical reactions

The free radicals having formed upon the mechanical destruction enter into ordinary free-radical reactions — recombination, decomposition, addition and substitution. The reactions occurring in the field of mechanical stress should be distinguished from those proceeding after the field has been removed (post-effect). The former type of reaction would involve most likely mechanically activated species. In addition, mechanical treatment causes plastic deformation of the material and migration of particles. In the latter type of reaction, the role of mechanical action reduces mostly to the generation of radicals, while the subsequent free-radical processes obey the rules inherent in them.

Virtually all of the mechanochemical free-radical reactions described to date occur in the solid phase; therefore, the specific features of the kinetics of solid-phase reactions should be taken into account.

1. Recombination

The elementary step of radical interaction (recombination) in the solid phase is preceded by the step in which they approach each other. This can occur either as chemical migration of a free valence or as physical migration of the reacting species.^{23,24} In the former case, recombination is a complex process consisting of separate elementary steps. (Some of these reactions are considered below.) In the latter case, recombination kinetics are determined by the mobility of radicals. The decay of macroradicals in a polymer matrix having been subjected to mechanical grinding occurs near the glass transition temperature T_g .²⁴ At this temperature, the segmental mobility of the polymer chains is unfrozen and the radicals become able to move large distances and meet one another.

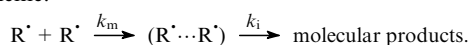
The decay of radicals in the field of mechanical stress, *i.e.* under conditions of forced mobility of reacting species, is a specific case. The effective rate constants for recombination of free radicals during grinding in a mill can be estimated from the kinetics of accumulation of free radicals.^{24,54}

When $dR/dt = 0$, the rate constant for recombination k_r has the form [see Eqn (1), Section II.2.b]

$$k_r = \frac{W_d}{[R]_{\text{lim}}^2}.$$

Depending on the nature of the polymer and the energy input of the mill, the k_r values at 100–300 K range from 10^{-24} to $10^{-21} \text{ cm}^3 \text{ s}^{-1}$.

Radical recombination can be represented by the following scheme:



In the step characterised by the constant k_m , the radicals approach each other under the action of plastic deformation caused by mechanical stress. Using Eqn (3) provided that $k_m \ll k_i$, we obtain $k_r = k_m v$. The volume of a cage v is approximately $5 \times 10^{-22} \text{ cm}^3$, and the frequency of the translation of radicals during mechanical treatment of the material in the mill (80–100 K) is 10^{-3} to 1 s^{-1} .

Recombination of radicals in the solid phase is characterised by a distribution of rate constants with the boundary values k_{max} and k_{min} . This may be due to the fact that the local reaction conditions — the size of the cage, mutual orientation of the reacting species, the closest environment, *etc.* — are different.^{16,53,56–58} Species interacting in any system can be characterised at any instant by the distribution function $n(k,t)dk$, which determines the number of species that react in unit volume at instant t with a rate constant k ($k_{\text{min}} \leq k \leq k_{\text{max}}$). Since species can migrate between various fractions of the distribution function (*i.e.*, between states with different k), it becomes ‘intermixed’. The form of ‘intermixing’ of the distribution function is determined by the processes that induce the changes in the kinetic properties of the reacting species. In particular, mechanical dispersion brings about ‘mechanical intermixing’ of the distribution function.⁵⁸

If mechanical intermixing results in the reaction rate constant k becoming equal to k_{max} , this means that the reaction occurs under kinetically controlled conditions. However, a different regime when $k_{\text{min}} \ll k \ll k_{\text{max}}$ and the reaction is controlled by diffusion is more frequently encountered in practice.

The post-effect recombination can be described satisfactorily by equations of polychronous kinetics.^{16,53}

$$\frac{n}{n_0} = \left(\ln \frac{k_{\text{max}}}{k_{\text{min}}} \right)^{-1} (-\ln k_{\text{min}} - \ln n_0 t).$$

The difference between k_{max} and k_{min} for arylindandione radicals reaches five orders of magnitude. The k_{max} value depends only slightly on the pressure applied and on the angle of shear and is approximately $5 \times 10^{-20} \text{ cm}^3 \text{ s}^{-1}$. Thus, shear strain and pressure scarcely influence the rates of the fastest reactions but do influence the rates of the slowest ones.

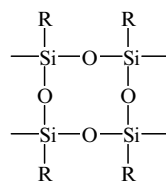
Obviously, the formation of free space and creation of a favourable arrangement of radicals are the limiting steps for radical recombination.

2. Radical decay

It is known^{24,59} that mechanical treatment of polymers is accompanied by decay of macroradicals. In macroradicals, the bond located in the β -position to the unpaired electron is weakened; the activation energy for the rupture of this bond in hydrocarbon radicals in the gas phase is about 100–120 kJ mol⁻¹ and in some cases [*e.g.* in the $-\text{CH}_2\dot{\text{C}}\text{MeX}$ radicals in PMMA ($\text{X} = \text{CO}_2\text{Me}$) and polyisobutylene ($\text{X} = \text{Me}$)], it decreases to 50–70 kJ mol⁻¹.

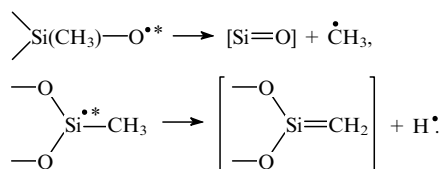
Mechanodestruction of polyformaldehyde, polyisobutylene and polyorganosiloxanes at low temperatures, *i.e.* under conditions when the thermal decay of macroradicals occurs at an extremely low rate, has been found to give light volatile products.^{24,60}

Thus the light products of mechanodestruction obtained by grinding of PMSSO in a mill at temperatures of $\leq 200 \text{ K}$ include mostly hydrogen, methane and ethane; those in PPSSO consist of hydrogen and benzene.⁶⁰



$\text{R} = \text{Me}$ (PMSSO), Ph (PPSSO).

The compositions and the conditions of formation of products imply that hydrogen atoms and $\dot{\text{C}}\text{H}_3$ and $\dot{\text{C}}_6\text{H}_5$ radicals are formed during the mechanodestruction. Presumably, the mechanical destruction of polymers gives rise to vibrationally excited macroradicals, which then decompose to yield low-molecular-mass radicals. Thus destruction of PMSSO involves the following processes:



The formation of hydrogen atoms was proved experimentally.

Figure 7 *a* shows the kinetic curves for the formation of H_2 and CH_4 and for the accumulation of free radicals ($\text{R}^{\bullet}$) during destruction of PMSSO. The diffusion of light species ($\text{H}^{\bullet}$ and $\dot{\text{C}}\text{H}_3$) results in migration and decay of the free valence; therefore, the amount of macroradicals observed in the destruction of PMSSO is always lower than the amount of monomeric products (per g of the polymer). The evolution of hydrogen and the formation of CH_4 , C_2H_6 and $\text{R}^{\bullet}$ are compared in Fig. 7 *b*; the plot was constructed using the results of a large number of experiments, in which the intensity of destruction of PMSSO varied by a factor of up to 50 (various conditions of mechanical treatment — duration of grinding, design of the working vessel, *etc.*, were used). Irrespective of the destruction intensity and dispersion conditions, the total amount of the volatile products evolved in the PMSSO destruction exceeds ~ 4.5 -fold the number of free radicals observed. The overall rate of formation of low-molecular-mass radicals ($\text{H}^{\bullet}$ and $\dot{\text{C}}\text{H}_3$) is higher than the rate of formation of macroradicals by a factor of 8–9. These data attest to a very high (~ 0.9) probability of decomposition of ‘hot’ macroradicals.

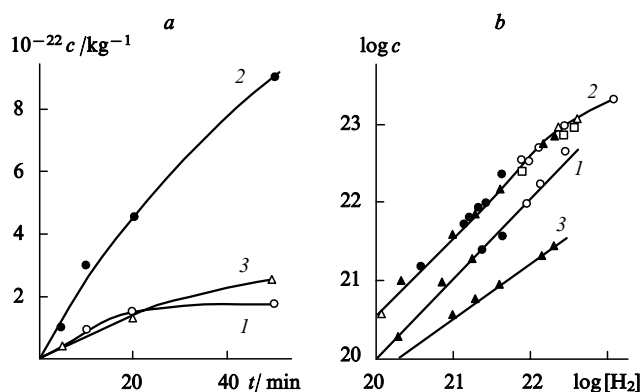


Figure 7. Kinetics of accumulation of radical and molecular products (*a*) of the mechanical destruction of PMSSO and comparison of their concentrations (*b*);⁶⁰

(*a*) (1) $[\text{R}^{\bullet}]$, (2) $[\text{CH}_4]$, (3) $[\text{H}_2]$; (*b*) (1) $[\text{R}^{\bullet}]$, (2) $[\text{CH}_4]$, (3) $[\text{C}_2\text{H}_6]$ (different designations refer to different rates of formation of hydrogen and different conditions of mechanical destruction).

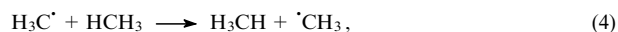
In the case of PPSSO, the rates of formation of volatile products and free radicals are commensurable and the total rate of formation of low-molecular-mass radicals ($\text{H}^{\bullet}$ and $\dot{\text{C}}_6\text{H}_5$) is twice as high as the rate of formation of macroradicals; the probability of decomposition of ‘hot’ radicals for PPSSO is about 0.6–0.7.

The mechanical treatment of polymers yields internal macroradicals, *i.e.* radical products of interaction of the primary terminal macroradicals with surrounding macromolecules (see Section III.3). It has been assumed that the internal macroradicals decompose during mechanodestruction to give terminal radicals and unsaturated compounds; after that, the terminal radicals interact with macromolecules to give internal macroradicals, *i.e.* a chain reaction occurs.⁶¹ However, experiments with polyethylene samples containing high concentrations of internal radicals, prepared by exposure of the samples to radiation, demonstrated that the role of mechanically induced destruction of internal

radicals is relatively insignificant, recombination being the main pathway for the decay of these radicals.⁶² This may be due to the non-uniform distribution of elastic energy among individual bonds in an amorphous solid; as a consequence, the ratio between the rates of rupture of weakened bonds (in the internal radicals) and normal bonds in macromolecules is determined by the probability of energy localisation on these bonds rather than by the ratio of their strengths.

3. Hydrogen atom transfer

The influence of mechanical stress on the free-radical transfer of a hydrogen atom has been considered theoretically using the model of the symmetrical process



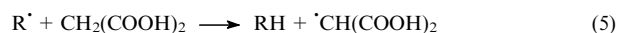
which occurs under normal conditions with a high activation energy ($\approx 60 \text{ kJ mol}^{-1}$).³¹ The calculation of the influence of methane compression on the height of the barrier to reaction (4) showed that within the framework of this model (extended LEPS potential and *ab initio* calculation methods), at a compression force of 3.6 nN, $U^{\ddagger} = 0$. However, at room temperature, there is no need to diminish the barrier to zero. Thus at a compression force of 1 nN, $U^{\ddagger} \approx 18 \text{ kJ mol}^{-1}$ and the reaction proceeds at room temperature at a plausible rate.

The influence of tensile stress on the rate of hydrogen atom transfer is considered in Section IV in relation to the reaction of ozone with polyolefins.

The following method proved to be fruitful for studies of low-temperature free-radical reactions:²⁴ solutions of polymers frozen at 80–100 K were subjected to mechanical dispersion in a vibratory mill; the role of mechanical treatment reduced mainly to the generation of free radicals and ensuring the mass transfer and the contact between the reacting particles. It was found that reactions proceed both during treatment of mixtures in the mill and after the mill has been switched off and the temperature has increased. A series of reactions involving carbon-centred and peroxy radicals (which are readily formed when carbon-centred radicals contact with atmospheric oxygen) have been found.

For instance,²⁴ it was shown that at low temperatures ($\sim 100 \text{ K}$), macroradicals abstract hydrogen atoms from various types of bonds, O–H (phenol), N–H (primary and secondary amines), S–H (benzenethiol and phenylmethanethiol) and C–H (alkylbenzenes, acetonitrile, malonic acid). The C–H bonds are especially strong and reactions involving these bonds are characterised by high activation energies ($> 30 \text{ kJ mol}^{-1}$). The rate constants were found to be 4–6 orders of magnitude greater than those calculated from the data obtained for the liquid phase at elevated temperatures.

The kinetics of the reaction of the macroradicals formed upon destruction of PS, polyvinyl acetate, *etc.*, with malonic acid



was studied²⁴ over a broad temperature range (100 to 200 K) (Fig. 8). It can be seen from the Figure that at 100–150 K, the reaction rate scarcely depends on the temperature; at $T > 150 \text{ K}$, it sharply increases and at $T > 200 \text{ K}$ the reaction rate cannot be measured because it is too high.²⁴

The experimental rate constants for hydrogen atom transfer are in good agreement with those calculated with allowance for the tunnelling of hydrogen through the potential barrier.

The hydrogen atom transfer determines the migration and stabilisation of radical states in polymers. Thus it is known^{23,24} that the radical products of mechanical destruction of polymers contain, even at low temperatures ($\sim 80 \text{ K}$), internal macroradicals, resulting from abstraction of hydrogen atoms from polymer chain units.

Yet another example of hydrogen atom transfer in polymers is provided by the reaction of peroxy radicals with macromolecules, which is the rate-determining step in the low-temperature oxidation of polymers.⁵⁸

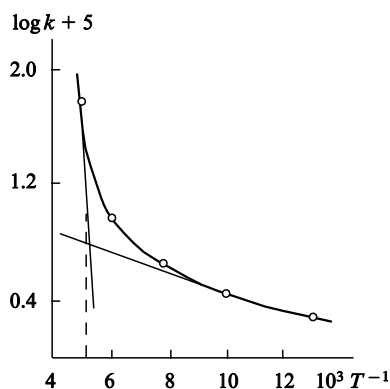
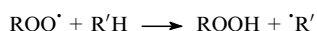


Figure 8. Temperature dependence of the rate constant for reaction (5).²⁴ The circles show the experimental results and the curve is based on calculations with application of the tunnelling correction.



This reaction was studied for PMMA and PS over a wide temperature range *in vacuo* after termination of mechanical treatment. As for other reactions occurring in the solid phase, in this case, too, kinetic non-equivalence of the reacting species was discovered; the distribution function of the 'mechanical' peroxy radicals in PMMA and PS over rate constants at 210–300 K has a hyperbolic shape⁵⁸ (see also Section III.1). For instance, in polystyrene, the rate constants for individual fractions of the distribution function can differ by ten orders of magnitude:

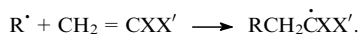
$$k_{\max} = 3.8 \times 10^8 \exp\left(-\frac{43}{RT}\right) \text{ and } k_{\min} = 1.3 \times 10^{12} \exp\left(-\frac{88}{RT}\right)$$

(the activation energy is expressed in kJ mol⁻¹).

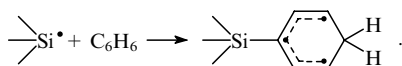
Thus, study of mechanochemical reactions of hydrogen atom transfer resulted in the elucidation of interesting specific features of the reaction kinetics, namely, tunnelling of a hydrogen atom at low temperatures, non-equivalence of the reacting species in the solid phase and 'mechanical intermixing' of the distribution function. However, no influence of mechanical stress on the activation energy for the hydrogen atom transfer was found.

4. Addition

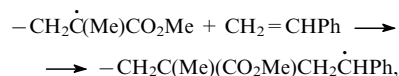
A study of mechanical treatment of mixtures of polymers with monomers in a vibratory mill provided experimental data on the addition of free radicals to C=C bonds.²⁴ It was found that at 80–100 K, the $-\text{CXX}'\dot{\text{C}}\text{H}_2$ and $-\text{CH}_2\dot{\text{C}}\text{XX}'$ macroradicals (X = H, Me; X' = Ph, CO₂Me, OCOMe) readily enter into the reaction



Under the same conditions, carbon-centred and silyl macroradicals add to benzene and its derivatives to give radicals of the cyclohexadienyl type,^{63,64} for example,



The kinetics of the reaction



which occurs on mechanical treatment of the initial compounds in a vibrational mill, has been studied in the 80–143 K temperature range.²⁴ At 80 K, the reaction does not proceed, and at 113–143 K the dependence of the rate constant on the temperature obeys the Arrhenius equation. The activation energy for the

reaction (21 kJ mol⁻¹) is close to the activation energy for the same reaction in the liquid phase at 280–330 K.

Thus, no mechanochemical effects were found in the studies of addition reactions with relatively low activation energies. Apparently, these effects could be found for reactions with higher activation energies.

The role of mechanical stress in free-radical reactions studied to date is to initiate the formation of macroradicals and to ensure mass transfer (to let the reagents meet each other). No influence of mechanical treatment on the activation energy of these reactions was found.

IV. Oxidation and hydrolysis

The influence of mechanical stress on the potential barriers can be clearly followed for some reactions (oxidation, hydrolysis). Acceleration of oxidation under tensile stress was discovered by Kuz'minskii *et al.* back in 1953 (oxidation of elastomers by atmospheric oxygen).⁶⁵

Krisyuk *et al.*^{28,30} carried out oxidation of polyolefins by ozone.



The oxidation (sorption of ozone and formation of free radicals) of oriented polypropylene films is accelerated 2–5-fold when a tensile stress σ ranging from 33 to 145 GPa is applied.

Mechanical stress accelerates hydrolysis of polyamides; this was first observed by Bershtein⁶⁶ and then studied by Krisyuk *et al.*^{29,30} Both the oxidation of polyolefins with ozone and the hydrolysis of polyamides are accelerated on stretching of these polymers according to an exponential pattern (in the temperature range of 328 to 369 K)

$$\ln \frac{k}{k_0} = \frac{\alpha \sigma}{RT}, \quad (6)$$

where k_0 is the rate constant for the reaction (k) in the absence of tensile stress σ . The constant α characterises the sensitivity of the reaction to stress and depends on the polymer structure. This constant is defined by the equation

$$\alpha = \phi(l^\ddagger - l_0)s, \quad (7)$$

where ϕ is the overstress coefficient, which depends on the structure of the polymer material, $l^\ddagger$ and l_0 are the lengths of the reaction fragment in the transition and initial states, respectively, and s is the cross-section of the molecule.

Experimental data on the acceleration of oxidation of polypropylene by ozone are presented in Fig. 9a, and the data for the hydrolysis of polycapraamide are shown in Fig. 9b; these results confirm the validity of Eqn (6).

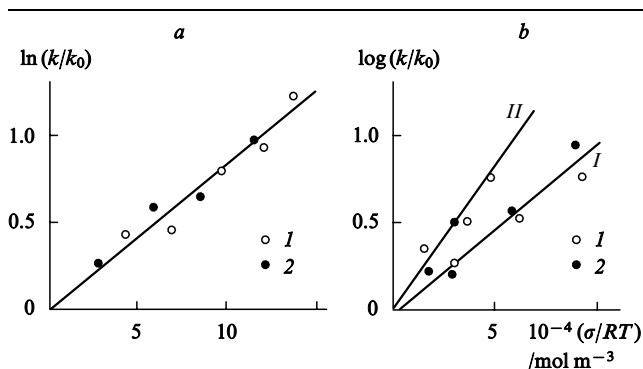


Figure 9. Rate constants for ozonisation of polypropylene (a) at 291 (I) and 313 K (2) and for hydrolysis of polycapraamide (b) at 393 (I) and 113 K (2) vs mechanical stress.³⁰ The stretching ratio of the samples is 6 (I) and 3 times (II).

It has been shown²⁸ that an increase in the rate of polyolefin oxidation cannot be explained either by the change in the diffusion and sorption parameters, or by the change in the molecular mobility, or by destruction of polymer chains. The change in the reactivity of the C–H bonds in polymer chains is caused by stretching and is similar to the situation with the abstraction of hydrogen atoms from strained rings.⁶⁷

When a hydrogen atom is eliminated, the sp^3 hybridisation of the carbon atom changes to sp^2 , resulting in a greater bond angle. This brings the structure closer to a transition state and, as a consequence, accelerates the reaction.

The acceleration of hydrolysis of polyamides can be interpreted at a qualitative level in a similar way. The C–N bonds in polyamide are strengthened due to delocalisation of the π electrons of the carbonyl groups, which interact with the nitrogen p orbitals. On stretching, the interacting orbitals move apart, the conjugation is violated and hydrolysis occurs faster. The effect of stretching resembles the influence of substituents in conformity with the Hammett–Taft equation.

Quantum-chemical calculation³⁰ for the cross-section of the potential energy surface for some monomers modelling polymer chains (methane, propane, butane) has shown that stretching of molecules weakens the C–H bonds. When the molecule is stretched, the energy of the initial state increases to a greater extent than the energy of the transition state, resulting in a lower activation energy for the reaction. Thus, the calculation showed that the C–H bond is actually activated and that the sensitivity of a reaction to deformation increases with an increase in the strength of this bond and with a decrease in the activity of the hydrogen acceptor.

The change in the activation energy of a reaction under the influence of a force f is described by the equation

$$\Delta E_a = f(l^\ddagger - l_0). \quad (8)$$

It follows from Eqns (6)–(8) that stretching of molecules would accelerate those reactions in which the formation of the transition complex is accompanied by elongation of the reactive fragment. Conversely, processes accompanied by a decrease in the length of this fragment should be retarded on stretching.

V. Mechanochemistry of proteins and polypeptides

The necessity of developing the mechanochemistry of proteins and polypeptides can hardly be overstated; indeed, study of the mechanochemical transformations provides a key for the understanding of some phenomena occurring in living cells and organisms. During preparation of food, medicines, *etc.*, proteins undergo various types of mechanical treatment (grinding, pressing); this can change their structures and properties.

The main mechanochemical processes occurring in proteins include rupture of covalent bonds in polypeptide chains, mechanically activated hydrolysis of peptide bonds and destruction of weak intermolecular bonds. Mechanical treatment can also change the catalytic activity of protein enzymes.

1. Mechanical destruction of covalent bonds

Mechanical treatment (grinding, stretching) of samples of poly(amino acids) (polyalanine, polyleucine, polyvaline), fibrillar proteins (collagen, silk), globular proteins (trypsin, subtilisin, serum albumin), oligopeptides (gramicidin, bacitracin) has been found (EPR data) to yield free radicals,^{24, 52, 68–70} the EPR spectra in gelatin, collagen, silk, serum albumin, *etc.* having much in common despite the different amino-acid composition of the proteins. The experimental data accumulated by now permitted determination of the structure of the resulting free radicals and the type of bond being cleaved.

Based on the analysis of spectral characteristics of the radicals resulting from mechanical treatment of polypeptides at ~ 80 – 100 K and their transformations on heating to

200–250 K⁵² and on exposure to light,⁶⁹ one can conclude that the C–C bonds are cleaved predominantly.



Initially, this affords reactive terminal radicals, which then react with polypeptide chains to give internal radicals.⁵²



The abstraction of hydrogen from the carbon atom in the α -position with respect to the CO group is accompanied in some cases (*e.g.* in polyleucine) by its transfer from side substituents to give $-NHCH(CH_2\dot{C}Me_2)C(O)-$.⁵²

In the case of trypsin, albumin and insulin, the mechanically induced cleavage of the polypeptide backbones is accompanied by rupture of the C–S bonds.⁵² The C–S bonds are weaker than the C–C bonds and are destroyed more rapidly. The proportion of sulfur-centred radicals, $\dot{R}_S$, ranges from 14% to 20% of the total number of radicals formed.

In the presence of atmospheric oxygen, carbon-centred radicals (both terminal and internal) are oxidised, being thus converted into peroxy radicals. Sulfur-centred radicals are stable and are retained unchanged up to 340–360 K, when they become sufficiently mobile to recombine.

The rate of formation of free radicals in proteins is higher than that in linear synthetic polymers (see Section II.2.b and Table 1). The rate of mechanical destruction of collagen was calculated from the rate of accumulation of free radicals and compared with the rate of decrease in the molecular mass of this protein calculated from electrophoresis data.⁷⁰ The rates of rupture of the covalent C–C bonds in collagen dispersed in a micromill (80–90 K) or in a vibratory mill (100–150 K) amount to 1.5×10^{15} and 8.0×10^{15} bonds $g^{-1} s^{-1}$, respectively (EPR data) or 1.8×10^{15} and 9.6×10^{15} bonds $g^{-1} s^{-1}$, respectively (electrophoresis data); *i.e.* the values found by two independent methods are in satisfactory agreement with each other.⁷⁰

The above data confirm the assumption that homolytic cleavage of the polypeptide chain is the main source of free radicals during the mechanical grinding of proteins.

2. Mechanically activated hydrolysis

As shown above (see Section IV), polyamides readily undergo mechanically activated hydrolysis. The possibility of this type of hydrolysis in proteins was demonstrated in relation to trypsin;⁷¹ the sample obtained by mechanical dispersion of this compound at 295 K was found to contain hydrolysis products, namely, *N*-terminal amino acids (glycine, tyrosine, serine and glutamic and aspartic acid). When trypsin was dispersed at a low temperature (~ 80 K), amino acids were not formed.

3. Breaking of weak intermolecular contacts

The breaking of weak intermolecular contacts (hydrogen bonds and hydrophobic and electrostatic interactions) brings about conformational transitions and disordering of the protein structure; in our opinion, this is the main reason for mechanical denaturation (both reversible and irreversible). The conformational transitions have also been studied for globular proteins (trypsin, subtilisin)^{71, 72} and for fibrillar proteins with rod-like molecules (collagen).⁷³

Curves 1 and 2 of Fig. 10 show the decrease in the intrinsic viscosity $[\eta]$ of collagen upon mechanical destruction.⁷³ Curve 1 was constructed using experimental data and curve 2 was calculated from the equation

$$[\eta] = 1.23 \times 10^{-9} M^{1.8},$$

where M is the molecular mass of the polymer after mechanical destruction. It was assumed that the change in the viscosity of a

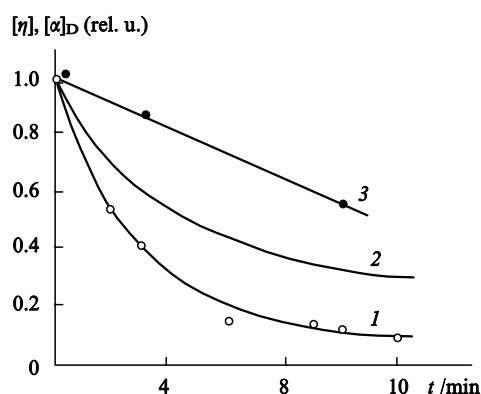


Figure 10. Variation of some properties of collagen during mechanical grinding;⁷³ (1) and (2) decrease in the intrinsic viscosity $[\eta]$ (1 is experimental curve, 2 is calculated curve); (3) decrease in the specific optical rotation $[\alpha]_D$.

solution of collagen is entirely due to the decrease in the size of macromolecules caused by the rupture of covalent bonds during grinding, while the shape of the molecules remains unchanged. However, the experimental values are much smaller than the calculated ones, which might imply that the rod-like shape of macromolecules has changed.

One more piece of evidence for the change in the shape of collagen macromolecules is the substantial decrease in the specific optical rotation $[\alpha]_D$ for large degrees of grinding (see Fig. 10, curve 3).^{73, 74}

A clear representation of the change in the rod-like shape of collagen molecules (the appearance of concave molecules, spherical particles and associates of various shapes and sizes) is provided by electron photomicrographs⁷³ of dilute solutions of collagen samples subjected to mechanical treatment.

Thus, experimental data obtained for collagen indicate that the rupture of covalent bonds in the macromolecule to give free radicals is accompanied by the rupture of weak intermolecular contacts. This results in disordering (loosening) of the protein structure, the change in the macromolecule conformation and in 'mechanical' denaturation. At extensive stages of the process, collagen acquires the properties of flexible-chain gelatin;⁷³ in dilute solutions, it forms molecular coils and associates composed of several macromolecules held together by new intermolecular bonds, which arise randomly.

A water-insoluble fraction has been found in the samples of globular proteins, trypsin and subtilisin subjected to mechanical dispersion, the proportion of this fraction increasing with an increase in the duration of grinding.⁷¹ However, its appearance is not related to covalent cross-linking, because this fraction dissolves on heating. Apparently, dispersion leads to a change in the conformation of the protein molecules, resulting in their association, referred to as 'mechanical' denaturation.

The conformational changes in trypsin molecules have also been observed by circular dichroism.⁷¹ The decrease in the amplitude of the Cotton effect in the 250–310 nm range points to appreciable changes in the tertiary structure of the protein, which affect the local environment of chromophore groups, in particular, tryptophan.

4. The change in the catalytic and biological activity of proteins

It has been found^{75–77} that on stretching a polyamide thread, the enzyme activity of trypsin or chymotrypsin immobilised on it decreases 3–6-fold. However, after termination of stretching and subsequent relaxation, the enzyme activity is restored, *i.e.* in this case, reversible deactivation of the enzyme occurs. Thus, by subjecting immobilised enzymes to mechanical treatment, one

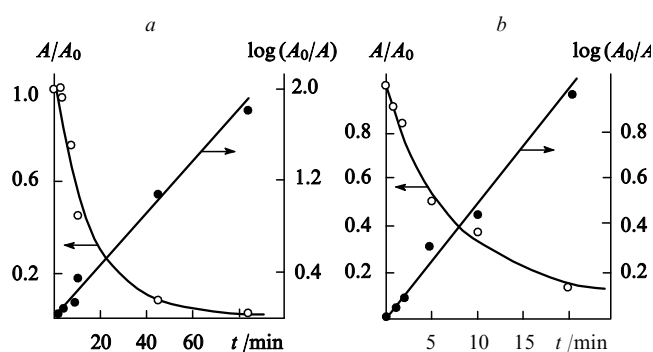


Figure 11. Kinetics of the decrease in the activity (A) of subtilisin (*a*) and trypsin (*b*) during mechanical treatment in a mill at 80 K; A_0 is the activity of the enzymes before the treatment.⁷²

can change their conformations and control the catalytic properties.

Irreversible inactivation of enzymes was observed upon pressing (pressure ≤ 550 MPa)⁷⁸ and mechanical grinding of some proteases.^{71, 72} Experimental data for trypsin and subtilisin are presented in Fig. 11. Apparently, mechanical strain leads to the change in the enzyme conformation and in the microenvironment of the active site. It was found that some of the enzyme molecules completely lose their catalytic activity, and some molecules start to 'operate' at a lower rate than the molecules of the native enzyme.⁷²

The influence of mechanical treatment on the thymalin — a polypeptide complex with immunomodulating properties — has been studied.^{79, 80} After mild mechanical treatment in a mill, the biological activity of the preparation increases in both *in vitro* and *in vivo* experiments, which is highly important regarding the increase in its efficiency. The reasons for this phenomenon have not been elucidated yet.

VI. Mechanochemical synthesis

1. Solid-phase mechanochemical synthesis

The importance of mechanochemical synthesis among other methods of synthesis is constantly increasing. In particular, in recent years, substantial progress has been attained in the solid-phase mechanosynthesis using planetary activator mills and Bridgman anvils.

The first studies along this line were concerned with reactions in polymer–monomer and polymer–polymer systems, resulting in modification of the initial macromolecules and formation of block and graft copolymers, which are used successfully for practical purposes. Mechanical treatment of these systems was carried out in masticators, extruders, mills, bending rolls, *etc.* More detailed description can be found in monographs.^{1, 3, 4}

In this Section, we summarise the examples of solid-phase mechanochemical synthesis based on low-molecular-mass compounds carried out over the last decade.^{14, 15, 18–20, 36, 81–87} The syntheses were carried out using various equipment ranging from simple mortars to planetary activator mills⁸ and the Bridgman anvils.¹⁴ Planetary mills operate in pulse mode; the pressure created by these devices is normally about several Gigapascals. The Bridgman anvils create a constant stress field with a pressure of up to ~ 10 GPa, and the pressure in specially designed diamond anvils can reach 550 GPa.³¹

The role of mechanical treatment is mainly to provide forced transfer of the reacting particles and to ensure their contact, although other mechanisms also contribute to the reactions.

It was found¹⁴ that the degree of transformation of monomers into polymers in the Bridgman anvils depends on the angle of rotation of the anvils (Fig. 12). Plastic deformation ensures mass

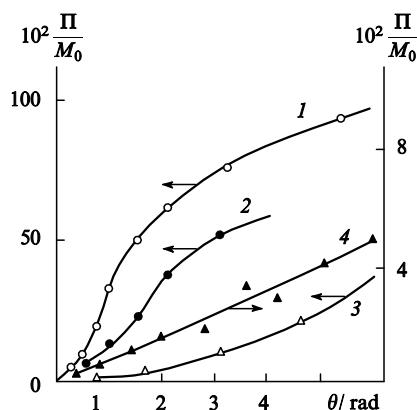


Figure 12. Yield of the polymer (Π/M_0) vs angle of rotation of the anvils (θ) (2000 MPa, 293 K);¹⁴ (1) acrylamide, (2) methacrylamide, (3) maleic anhydride, (4) trioxane (1000 MPa).

transfer and mixing of reactants and removes the reaction products from the reaction area.

Solid-phase mechanochemical reactions occurring under conditions of explosion induced by strong uniaxial compression have been found;⁸¹ the characteristic times of these reactions are only 10^{-5} – 10^{-7} s.

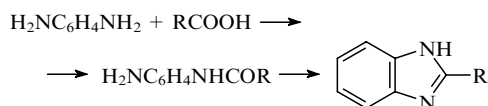
Two mechanisms of mechanochemical reactions are most likely: (1) under the action of mechanical stress, intermixing at the molecular level occurs and (2) the product is formed on the surface of macroscopic reacting species. However, in the case of explosion reactions, the high rates cannot be explained in terms of either of these mechanisms. It has been suggested⁸² that an explosive chemical reaction is initiated by a shock wave, which loosens the lattice of reacting particles for the period of the relief of elastic stress and thus makes the system quasi-homogeneous.

Several examples of mechanochemical syntheses carried out under various conditions are presented below.

Diels–Alder reaction. The action of shear stress on solid cyclopentadiene and cyclobutadiene (2–5 GPa, ~150 K) gives rise to dicyclopentadiene and vinylcyclohexene, respectively.⁸³

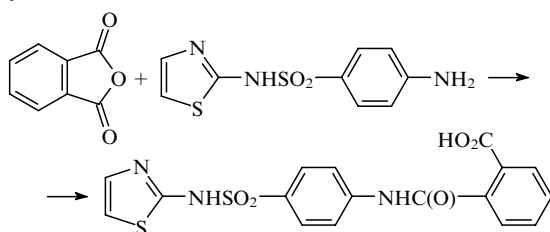
Synthesis of amides (acylation). Solid mixtures of aromatic amines with carboxylic acids react (pressure up to 8 GPa, rotation angle of anvils up to 720° , temperature 200–300 K) to give amides.⁸⁴ The yields reach 50% or even more; the rates of the transformations are greater than the rates of the same processes in the liquid phase by factors of hundreds of thousands.

In the case of *ortho*-phenylenediamine, cyclisation of the resulting amides yields the corresponding benzimidazoles.



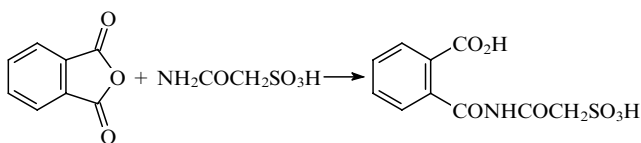
The cyclisation is accelerated by mechanical stress to a lesser extent than acylation.

Mechanochemical synthesis of phthalylsulfathiazole has been accomplished¹⁸ by combined mechanical treatment of phthalic anhydride and sulfathiazole.



The product (formed in a nearly quantitative yield) is not contaminated by phthalazoleimide or phthalates, which are normally produced in the liquid-phase synthesis.

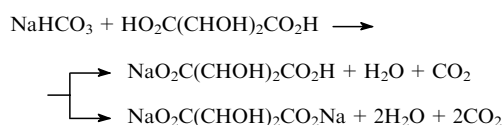
Generally, phthalic anhydride readily enters into solid-phase mechanochemical reactions. Thus its pressure-initiated reaction with sulfacetamide gives rise to *N*-phthalylsulfacetamide.⁸⁵



It should be noted that reactions with phthalic anhydride do not stop after termination of mechanical treatment.

Synthesis of polypeptides. The action of high shearing pressure on amino acids gives peptides. As in the case of amides, the reaction affords predominantly linear products rather than cyclic compounds (dioxopiperazines), which are usually formed in these reactions carried out in solutions and melts.⁸⁷

Synthesis of metal carboxylates. A mixture of sodium hydrogen carbonate with tartaric acid has been found⁸⁸ to react under elevated pressures (1–15 kPa) yielding sodium tartrates



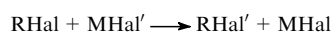
The action of high pressure in combination with shear strain under conditions of explosion induces the reactions



giving salts of organic acids in 70%–80% yields.

The reaction of sodium carbonate with benzoic or salicylic acids was carried out in a planetary activator mill.⁸⁹ The process has obvious advantages over the conventional liquid-phase synthesis—it occurs over one technological stage instead of standard six or seven stages, does not require the use of water, *etc.*

Halogen exchange



Hal = Br, I; Hal' = F, Cl, I; M = Li, Na, K, Cs

occurs both with aromatic^{20,21} and aliphatic ($\text{R} = \text{Me}, \text{Et}, \text{Pr}^n$) compounds.⁹⁰

Synthesis of organometallic compounds. It has been shown that mechanochemical synthesis of organometallic and coordination compounds is, in principle, possible.^{91–93} Cyclopentadienyl, dicarbonyl, β -diketonate and other organometallic derivatives were synthesised.

2. Mechanochemical synthesis and nanotechnology

One task of molecular nanotechnology, which has been developing successfully over the last 10–15 years, is the assembling of complex chemical structures. It has been shown³¹ that a chemical reaction can, in principle, be carried out under conditions when it is controlled by forced mechanical migration of individual reacting species (atoms, molecules, free radicals). The work on the transfer of species is done by molecular mills and manipulators such as an atomic force microscope (AFM), scanning tunnelling microscope (STM) and some other devices. Using these instruments, atoms or molecules can be placed (positioned) into a definite position with respect to each other (with allowance for the distance between them and orientation needed for the reaction to be initiated). For example, AFM permits the surfaces to be positioned in relation to one another with an accuracy of ~0.01 nm with a compression force of up to 0.01 nN. STM was used to position xenon atoms (4 K) on the surface of a nickel single crystal, which resulted in the formation of a linear heptamer.⁹⁴ The capacities and prospects for the development of the 'posi-

tional' mechanosynthesis have been described in detail by Drexler.³¹

The positional mechanosynthesis is carried out *in vacuo* and differs substantially from the conventional gas- and liquid-phase syntheses. As for solid-phase reactions, the notion of concentration (the number of molecules of a given type in unit volume) is absolutely inapplicable to this type of mechanosynthesis. A certain role in the positional mechanosynthesis is played by local steric and electronic effects; however, mechanical positioning has the crucial influence on the reaction rate.

The force F acting on the particles and the 'activation' length $\Delta l^\ddagger$ are related by the expression³¹

$$\Delta l^\ddagger = -kT \left(\frac{d}{dF} \ln k_{\text{react}} \right)_T,$$

where k_{react} is the rate constant for the reaction. Normally $\Delta l^\ddagger \simeq -0.1$ nm and possible compression forces reach 5 nN, which corresponds to $E_a \sim 300$ kJ mol⁻¹. More realistic estimates of the decrease in the activation energy due to the action of mechanical force are presented in the discussion dealing with the rupture of valence bonds (II.2.a) and free-radical substitution (III.3).

Within the one-dimensional model and the theory of transition state, the condition for the occurrence of a reaction is given by the expression

$$\Delta U^\ddagger \leq kT \left(\frac{t_{\text{react}} f_{\text{TST}}}{-\ln P_{\text{err}}} \right),$$

where $\Delta U^\ddagger$ is the height of the potential barrier, t_{react} is the time of the reaction, f_{TST} is the frequency factor (for a mechanochemical reaction with a relatively rigidly fixed arrangement of the reacting species, $f_{\text{TST}} \geq 10^{12}$ s⁻¹) and P_{err} is the probability of an error in a mechanochemical operation. At 300 K, assuming that $t_{\text{react}} = 10^{-7}$ s and $P_{\text{err}} = 10^{-15}$, $\Delta U^\ddagger \leq 20$ kJ mol⁻¹.

The positional mechanosynthesis has several advantages. Thus, unlike the conventional (diffusion mechanosynthesis), in this case, side reactions can be avoided, which is especially desirable for the synthesis of complex molecules containing a large number of functional groups. In the positional mechanosynthesis, non-planned collisions of molecules cannot occur and, hence, undesirable reactions are excluded.

However, among other factors, the applicability of this method is restricted by the fact that such mechanosynthetic systems are usually sensitive to thermal destruction; therefore, only reactions proceeding at room temperature, *i.e.* those having relatively low activation energy, can be carried out by positional mechanosynthesis.

Mechanical positioning ensures the transformation of the mechanical energy into chemical energy. It allows one to choose between alternative reaction pathways, to diminish the activation energy and to increase the effective concentration of the reactants because they are placed in the most favourable positions with respect to each other.

Presumably,³¹ positional mechanosynthesis would be used for the construction of complex molecules, for example, diamond-like structures. A number of properties of diamond-like materials (strength, hardness, relatively low specific weight, *etc.*) permit them to be used in nanomechanical systems in order to perform positional mechanosynthesis of other complex molecules.

Diamond-like structures consist of polycyclic organic molecules composed of sp^3 -hybridised carbon atoms.⁹⁵ Some planes, (110) and (100), contain strained reactive alkene groups, which provide for the ability of diamond-like structures to participate in synthetic transformations. The (111) plane in diamond is usually hydrogenated, which opens up the way for its chemical modification.

One modification route is based on the abstraction of a hydrogen atom, which plays an important role in the synthesis of diamonds.⁹⁵ The hydrogen abstraction can be achieved by virtue of free radicals of various structures. However, to enable posi-

tional mechanosynthesis, they should comply with definite requirements, namely, they should (a) have a very high hydrogen affinity, (b) contain no bulky groups in the structure, (c) represent a fragment of a structure that can be attached to the AFM or STM tip and used as the holder during positioning; (d) possess mechanical and chemical stability during positioning and (e) be readily generated and regenerated.^{31,95}

Under the action of anisotropic compression forces (~ 20 GPa) at room temperature, fullerene can be converted into diamonds (see II.1.a); therefore, it might be a suitable substance for positional mechanosynthesis of diamond-like materials.

3. Polymerisation

The mechanochemical polymerisation was first discovered on grinding of acrylic and methacrylic acid derivatives (acrylamide, methacrylamide and sodium and potassium salts of these acids) in the presence of some salts, metals and oxides, which serve as initiators.¹

High pressures ($\sim 10^3$ MPa) combined with shear stress induce polymerisation of compounds containing C=C bonds (ethylene, styrene, methylstyrene, *etc.*), C≡C bonds (acetylene derivatives), conjugated double bonds (butadiene, cyclopentadiene, *etc.*), aromatic rings (benzene, naphthalene, anthracene, *etc.*) and heterocycles (pyridine, thiophene, *etc.*) even at the temperature of liquid nitrogen.¹⁴

In principle, high pressures in combination with shear strain can cause reactions that do not occur under ambient conditions. For example, the activation energy for ethylene dimerisation is about 200 kJ mol⁻¹; however, under the action of pressure and shear strain, the π bond in the ethylene molecule can be cleaved. The resulting biradical³¹ can either dimerise to give cyclobutane or initiate polymerisation.

It can also be claimed that the aromatic rings in benzene, pyridine, polynuclear compounds, *etc.*, can be cleaved in a similar way, although real mechanisms of these transformations are rather complex.¹⁴

In some cases, mechanical stress sharply accelerates polymerisation. Thus the rate constants for the mechanically initiated polymerisation of styrene, acrylamide and other monomers are 2–5 orders of magnitude greater than the corresponding constants found for these reactions in the liquid phase.¹⁴

Several groups of researchers^{96–99} have discovered polymerisation of frozen monomers, which occurred at very high rates at low temperatures (≤ 77 K). The influence of mechanical stress was found to be the main driving force of these processes. It has been shown⁹⁶ that local mechanical treatment (a needle prick) of frozen cyclopentadiene (77 K), prepared by the method of molecular beams, causes its chain polymerisation; similarly, a local treatment with a pin of γ -irradiated solid acetaldehyde initiates its cryopolymerisation even at 4.2 K.⁹⁹

It was shown⁹⁹ that the local mechanical action on a frozen sample induces the formation of a primary crack, which initiates spontaneous propagation over the sample of a narrow area densely covered by an extensive network of freshly formed cracks. The chemical reaction occurs on the surface of cracks (or near them) and, in turn, create conditions for further destruction in the neighbouring area of the matrix. The solidity of the sample can be violated, for example, due to the temperature or density gradients, arising during the reaction and creating stresses, which destroy the sample. Thus, the matrix undergoes layer-by-layer dispersion under the influence of the running field of mechanical stress, and the reaction wave propagates spontaneously over the sample.

The relationship between the reactivity and mechanical stresses arising in the reaction has been studied by EPR for the unfreezing of organic crystals of diacyl peroxides having been subjected to photolysis at ~ 15 K.¹⁰⁰ Radical pairs and CO₂ molecules are formed in the system and create a high local pressure. The mechanical stress thus arising relaxes as a result of movement of these molecules towards the surface.

4. Formation of molecular complexes

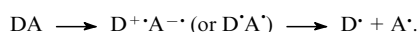
Mechanical treatment of two-component systems gives rise to various types of molecular complexes — charge transfer complexes, inclusion compounds and complexes formed due to acid–base interactions, hydrogen bonds or simply van der Waals forces.

Complexation of the acid–base type between phenols and amines has been found for a mixture of hexamethylenetetramine (urotropin) and resorcinol.^{101,102} The reaction proceeds both during explosion initiated by compression¹⁰¹ and under relatively mild conditions, namely, in a disintegrator;¹⁰² the yields are nearly quantitative in both cases.

It has been shown that interpolymer complexes (polymeric compounds stabilised by bonds of the ionic type) can be prepared by mechanochemical synthesis under high pressure combined with shear stress.¹⁰³ Polymethacrylic acid (polymeric acid) and PMMA or polymethylvinyltetrazole (polymeric base) were used as the initial compounds.

Combined mechanical grinding of polyvinylpyrrolidone (PVP) with some additives (Ad) (chloranil, phenothiazine, hydroquinone, acridine, *etc.*) gives charge transfer complexes of the $n-\pi$ and $\pi-\pi$ types, for example, PVP^+Ad^- (with chloranil) or PVP^-Ad^+ (with phenothiazine).¹⁰⁴

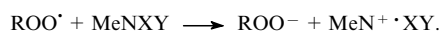
The samples obtained upon trituration in a mortar of two substances able to form stable radicals, one of which being an electron donor (D) (phenols, catechols, porphyrins, *etc.*) and the other being an electron acceptor (A) (*e.g.*, quinones) have been studied by EPR spectroscopy.¹⁰⁵ The researchers were able to record the EPR spectra of the primary reaction products, biradical triplet complexes or radical pairs, and secondary products — free radicals.



The triplet molecular complexes or radical pairs generated by mechanical treatment are much more stable than those prepared by photolysis of the same donor–acceptor solid mixtures. Apparently, once formed, they are quickly incorporated into the new crystal lattice arising upon mechanical treatment.

Electron transfer has also been detected on exposure of mixtures of organic compounds, electron donors and acceptors, to elastic acoustic waves.¹⁰⁶

Yet another example of electron transfer is represented by mechanochemical reactions of peroxy macroradicals with compounds containing a tertiary amino group (phenothiazine and pyrazolone derivatives), which have been studied by EPR.⁶³



The reaction occurs during mechanical grinding of a mixture of a polymer (PS, polyvinyl acetate, *etc.*) and a substance with electron-donating properties.

Combined mechanical grinding of α - and β -cyclodextrins with acetylsalicylic, benzoic or *p*-hydroxybenzoic acid yields inclusion compounds.¹⁰⁷ Their formation proceeds *via* a stage of amorphisation of polymers and low-molecular-mass crystals followed by dissolution of crystals in the amorphous medium. Hungarian researchers³⁸ prepared inclusion compounds by grinding γ -cyclodextrin with fullerene and thus attained solubilisation of the latter substance.

The vast majority of studies dealing with the synthesis of molecular complexes are associated with new methods for the development of drugs aimed at increasing their therapeutic activity, which depends on bioavailability. It is known^{33,108} that bioavailability of drugs poorly soluble in water is determined by the rate of dissolution. It was found that combined grinding of drugs with polymers of various structures leads to distribution (to a molecular level) of the drug in the polymer matrix to give molecular complexes (in the literature devoted to the technology of drugs, these systems are normally referred to as solid dispersions³³). As a rule, this combined grinding makes it possible to increase the solubility and the rate of dissolution of hydrophobic compounds in aqueous media.^{33,108,109} Meanwhile, by appropri-

ate selection of the initial pair consisting of a polymeric carrier and a drug, the liberation of the drug from the molecular complex can also be retarded (prolonged-action preparations). Preparations of this type have been obtained, for example, by joint grinding of some substance of the benzimidazole series with microcrystalline cellulose.¹¹⁰

The polymeric matrices used for this purpose are usually natural polymers, namely, cellulose and its derivatives, starch, cyclodextrins, proteins, chitin, chitosan and pectin and some synthetic polymers [poly(ethylene oxide) or polyvinylpyrrolidone].

The majority of drugs are low-molecular-mass organic compounds containing functional groups capable of forming intermolecular hydrogen bonds ($\text{C}=\text{O}$, OH , NH , *etc.*). During mechanical grinding of mixtures of drugs with polymers, the intermolecular hydrogen bonds are destroyed and new hydrogen bonds with macromolecules are formed (IR-spectroscopy data¹⁰⁸). Thus the molecules of benzoic, salicylic and acetylsalicylic acids, hexobarbital, *etc.* form hydrogen bonds of the $>\text{C}=\text{O}\cdots\text{HOR}$ type with cellulose and oligosaccharide molecules. Derivatives of barbituric acid form in addition $\text{NH}\cdots\text{O}(\text{H})\text{R}$ bonds with hydroxy groups of polymers. In the inclusion compounds described above, obtained by grinding of cyclodextrins with acetylsalicylic, benzoic and *p*-hydroxybenzoic acids, hydrogen bonds link the OH groups of cyclodextrin to the $\text{C}=\text{O}$ groups of acids.

The redistribution of hydrogen bonds during grinding of acetylsalicylic acid (Aspirin) with some fillers (cellulose, alumina) has been studied fairly comprehensively by IR spectroscopy.³⁹ Aspirin is responsible for an absorption band with a maximum at 1695 cm^{-1} , due to the stretching vibrations of the $\text{C}=\text{O}$ group in the dimer. Grinding of the sample results in broadening of this band and displacement of the ν_{CO} vibration frequency of the dimer to $1700\text{--}1710\text{ cm}^{-1}$, indicating the appearance of a monomeric species with an intramolecular hydrogen bond. The conversion of the dimer into the monomer is also confirmed by optical diffuse reflection spectra.³⁹ The formation of molecular complexes of Aspirin with fillers (vibration frequency $\nu_{\text{CO}} = 1749\text{ cm}^{-1}$) was not detected in the study cited,³⁹ although it had been observed previously.¹¹¹

Upon grinding of isobutylphenylpropionic acid (ibuprofen) with poly(ethylene glycol), hydrogen bonds between the carboxy groups of the acid and the hydroxy groups of the polymer (IR-spectroscopy data) and van der Waals interactions between the polymer molecules and the aromatic rings of ibuprofen (electronic absorption and luminescence spectra) were detected.¹¹¹

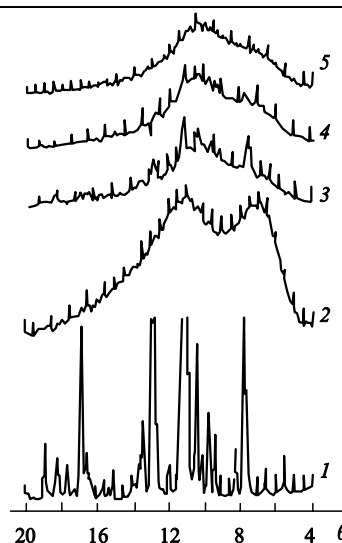


Figure 13. X-Ray diffraction patterns of sulfathiazole (1), polyvinylpyrrolidone (2) and their mixtures (3–5) after mechanical treatment for 3 (3), 6 (4) and 12 min (5).¹¹²

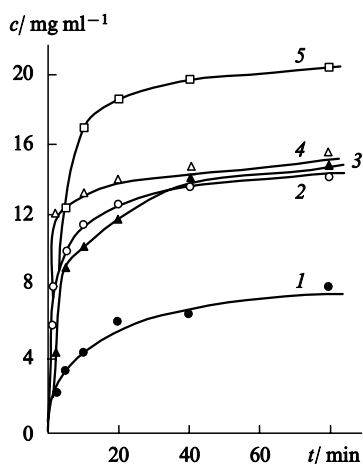


Figure 14. Change in the rate of dissolution of griseofulvin after mechanical treatment of its mixtures with polymers;¹⁰⁹ (1) a mixture of griseofulvin with gelatin without mechanical treatment, (2) gelatin, (3) chitin, (4) polyethylene glycol, (5) chitosan.

After grinding of a drug–polymer mixture, peaks characteristic of the drug usually disappear from the X-ray diffraction patterns (an example is shown in Fig. 13).

The initial rate of dissolution of a drug after its combined grinding with polymers can increase by a factor of tens (an example is shown in Fig. 14). The increase in the solubility is especially pronounced when the mechanical treatment yields a new polymorphic modification with a higher solubility. For instance, in the case of grinding of sulfathiazole with polyvinylpyrrolidone in a planetary mill, the solubility of the drug increases almost 10-fold.¹¹²

Thus, the whole set of data described above, both direct (optical spectra) and indirect (the decrease in the melting point and heat of melting, the increase in the solubility and in the rate of dissolution), point to the formation of molecular complexes stabilised mostly by hydrogen bonds.

The practical importance of the molecular complexes with drugs (in particular, for increasing the bioavailability of the drug) becomes obvious from the results of bioassays, which are few in number but convincing.^{33, 108, 113, 114}

VII. Conclusion

The review shows that mechanical stress induces numerous physical transformations and chemical reactions in organic compounds. They are based on the rupture of bonds, generation of free radicals, decrease in the activation energies of reactions, provision for the transport of reacting species, etc.; in some cases, some of the above-listed processes predominate, while in other cases, they occur and act simultaneously.

The practical potential of the mechanochemistry has been appreciated and adopted by investigators engaged in diverse branches of science. Solid-phase mechanochemical syntheses of various compounds have been performed by now. The yields in mechanochemical reactions are sometimes higher than those in similar reactions conducted in the liquid phase.

The advantages of mechanochemical synthesis include the possibility of performing it at low or room temperatures, environmental cleanness (no solvents are involved) and the simplicity of the process technology.

A mechanochemical process carried out in a reactor mill includes three main stages (a) grinding of the material in order to attain the optimum size of particles; (b) mixing of the reactants in order to attain the maximum contact between the particles (c) the reaction itself. At present, all the three stages occur simultaneously in the same device, although they require differ-

ent levels of delivered energy. Apparently, for industrial implementation of mechanochemical synthesis, it would be expedient to separate the stages, i.e. to carry out each stage of the process in a separate specially designed reactor.¹¹⁵

Mechanochemical methods have been recognised in the technology of drug manufacture and are used to control the rate of drug dissolution and to increase their therapeutic activity.

The new promising line in mechanochemistry, positional mechanosynthesis, is closely related to the molecular nanotechnology and is regarded as technology of the XXIst century. Although the development of this line of research is only at its beginning and is now held up due to the absence of necessary equipment, there seems to be no conceptual obstacles to the design of mechanosynthetic machines.

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N-Fluoro amines and their analogues as fluorinating reagents in organic synthesis

G G Furin, A A Fainzilberg

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Abstract. The data on the synthesis and application in organic synthesis of fluorinating compounds containing N–F bonds are surveyed and systematised. The reagents are classified into two categories, *viz.*, neutral (perfluoro-*N*-fluoropiperidine, *N*-fluoro-2-pyridone, *N*-fluorosulfonamides, *N*-fluoro-*N*-alkylamides, *N*-fluorobis(trifluoromethyl)sulfonylamine, *N*-fluorobenzo-1,3,2-dithiazole 1,1,3,3-tetroxide, *N*-fluoro sultams) and ionic reagents (*N*-fluoropyridinium, *N*-fluoroquinuclidinium and 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts). A comparative analysis of the fluorinating activity of the reagents depending on their structure and the nature of the solvent is carried out taking into account theoretical calculations. The possibility of fluorination of various classes of organic compounds is discussed. The mechanisms of fluorination with N–F compounds are analysed using kinetic data. The advantages and disadvantages of *N*-fluoro amines in comparison with elemental fluorine, xenon difluoride and other fluorinating reagents are considered. The influence of the nature of the solvent on the fluorinating activity of *N*-fluoro amines and their analogues is discussed. The bibliography includes 245 references.

I. Introduction

Over almost a century, fluorination of organic and inorganic substrates with elemental fluorine has been used as the basis for the synthesis of fluorine-containing compounds. Fluorine is known to be a highly potent fluorinating reagent. However, being a strong oxidant, fluorine is aggressive against numerous organic substrates and solvents and thus does not manifest the high selectivity required in fine organic synthesis. Other plausible fluorinating reagents, such as xenon difluoride and perchloryl

fluoride ($FClO_3$), have not received wide acceptance in fluoroorganic chemistry, primarily because of their high cost, although their pilot-plant syntheses have already been carried out. For example, the synthesis of $FClO_3$ is being carried out at the Russian Research Centre 'Applied Chemistry'.

The situation in this area has changed radically in the past decade. The ever increasing application of fluorine-containing compounds as biologically active compounds (first of all, of medicinal drugs) has given a strong impetus to the synthesis of a wide range of new electrophilic fluorinating reagents (fluorine 'carriers'), *viz.*, the so-called *N*-fluoro reagents and fluoro compounds (*O*-fluoro reagents).

Undoubtedly, *N*-fluoroamines and their analogues belong to the most representative class of fluorine 'carriers' as regards their number, previous experience and application. A chemist engaged in synthesis will always be able to select a reagent complementary to the substrate to be fluorinated in its physical and chemical characteristics.^{1–6}

N-Fluoro reagents surpass *O*-fluoro and *S*-fluoro reagents in stability, reliability, safety, ecological friendliness and handling convenience.^{7–16}

In considering the wealth of knowledge concerning the chemistry of *N*-fluoro amines and their analogues, we thought it more reasonable to classify these fluorinating reagents into two groups according to the type of the fluorine–nitrogen bond in their molecule. The first group includes the so-called neutral compounds of the type R_2NF , *i.e.*, the reagents in which the fluorine atom is bound to the uncharged nitrogen atom. The second group includes the reagents in which the fluorine atom is bound to the positively charged nitrogen atom.

The most popular neutral compounds are perfluoro-*N*-fluoropiperidine, *N*-fluoro-2-pyridone, *N*-fluoro carboxamides, *N*-fluoro sulfonamides, *N*-fluoro sulfonylamines (including perfluorinated compounds), *N*-fluoro(diphenylsulfonyl)amine, *N*-fluoro alkanesulfonimides, *N*-fluoro benzenesulfonimide and *N*-fluoro sultams. The most popular quaternary compounds include *N*-fluoropyridinium, *N*-fluoroquinuclidinium and 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts.

Only a few *N*-fluoro-reagents are commercially available. The data on these compounds are summarised in the review by Lal *et al.*⁶

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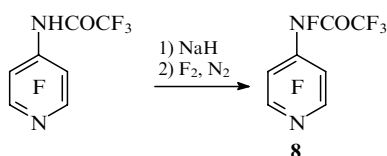
3. The use of *N*-fluoro carboxamides and *N*-fluoro sulfonamides

N-Fluoro carboxamides and *N*-fluoro sulfonamides are obtained by fluorination of the corresponding amides or sulfonamides with elemental fluorine or other fluorinating reagents. Thus fluorination of alkylamides with CF₃OF results in the corresponding *N*-fluoroalkylamides in high yields.³¹

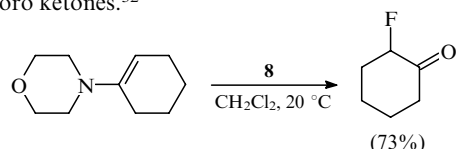


R ¹	R ²	Yield (%)
Me(CH ₂) ₁₆	Me	30
Me		60
4-FC ₆ H ₄	Me	13
H	Me	85
H		71

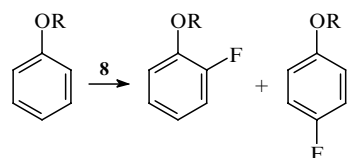
Direct fluorination of sodium *N*-(perfluoro-4-pyridyl)trifluoroacetamide with elemental fluorine was used to obtain the selective fluorinating reagent, *viz.*, (*N*-fluoro-*N*-perfluoro-4-pyridyl)trifluoroacetamide (**8**).^{32–34}



The reagent **8** fluorinates diethyl phenylmalonate (NaH, THF, from –10 to 20 °C) to give the fluoro derivative **6** in 66% yield.³² The reaction with enamines results in the corresponding α-fluoro ketones.³²

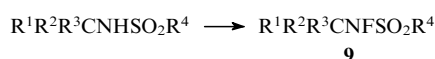


The reactions with phenol (MeOH, 20 °C) and anisole (MeCN, 20 °C) yield mixtures of *ortho*- and *para*-isomers (in 1 : 1 and 7 : 3 ratios, respectively).³²



R = H (91%), Me (81%).

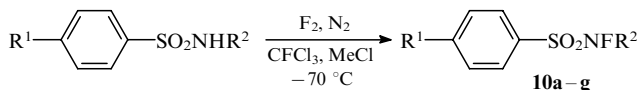
Fluorination of sulfonamides with F₂ in the presence of KF or with a FClO₃–NaH mixture gives the corresponding *N*-fluoro derivatives of the type **9** (yield ~ 60%). Fluorination of *O*-acetyl-*N*-tosyl- and *N*-mesylphenylglycinol gives the corresponding *N*-fluoro derivatives in 52% and 13% yields, respectively.^{35, 36}



R ¹	R ²	R ³	R ⁴
Ph	H	CO ₂ Et	4-MeC ₆ H ₄ , Me, F ₃ C
Me	Bn	CO ₂ Et	4-MeC ₆ H ₄
Ph	H	CH ₂ OAc	4-MeC ₆ H ₄
Pr ⁱ	H	CO ₂ Et	4-MeC ₆ H ₄ , Me, F ₃ C
Ph	H	Me	4-MeC ₆ H ₄ , Me, F ₃ C

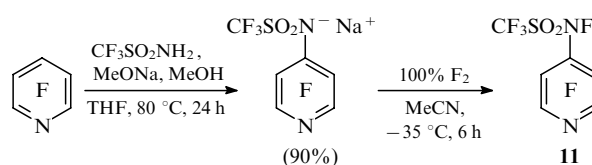
Compounds **9** possess fluorinating ability and can be used for the synthesis of α-fluorocarbonyl derivatives from enolates (Table 1).^{35, 36}

Normally, fluorination of *N*-alkyl(aryl)sulfonamides is performed in a CFCl₃–CHCl₃ mixture (1 : 1) using 1%–5% F₂ in N₂, MeOF or CF₃OF as fluorinating reagents. *N*-Fluoro sulfonamides **10a–g** were synthesised in this way.^{37–47}



Compound 10	R ¹	R ²	Yield (%)	Ref.
a	Me	Bu ^t	14	37
b	Me	Me	59	37
c	Me	Bu ^t CH ₂	57	37
d	Me		47	37
e	Me		71	37
f	Me		11	37
g	H	Bu ^t	—	47

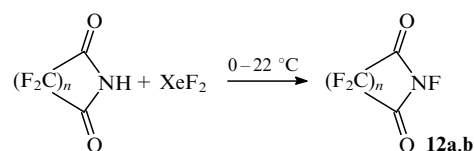
Sulfonamide derivatives are preferably fluorinated as the corresponding salts.^{48–50} Thus the fluorination of sodium perfluoro-*N*-(4-pyridyl)methanesulfonamide with elemental fluorine results in perfluoro-*N*-fluoro-*N*-(4-pyridyl)methanesulfonamide (**11**) in 89% yield.⁴⁹



N-Perfluoroquinolyl-, -isoquinolyl and -naphthylsulfonamides were also introduced into the reaction.⁴⁹

It is noteworthy that *N*-*tert*-butyl-*N*-fluoro-*p*-toluenesulfonamide **10a** can be obtained in 69% yield by fluorination of sodium *N*-*tert*-butyl-*p*-toluenesulfonamide with cesium fluoroxysulfate in MeCN at 0–5 °C.⁵¹

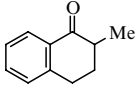
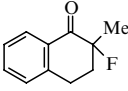
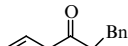
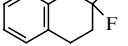
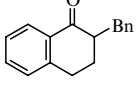
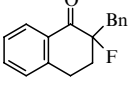
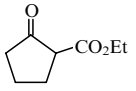
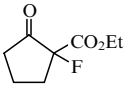
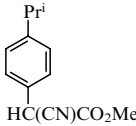
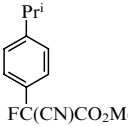
Perfluorosuccinimide and -glutarimide react with xenon difluoride to give the corresponding *N*-fluoro imides **12a,b** in good yields.^{52, 53} The fluorination is performed at 0–20 °C in the absence of the solvent or at 0 °C in dichlorodifluoromethane for 24 h. These compounds represent easily distillable liquids, which are stable upon 24-h storage in quartz glassware under nitrogen. The fluorination of sodium phthalimide with cesium fluoroxysulfate in acetonitrile gives *N*-fluorophthalimide in 48% yield.⁴⁵

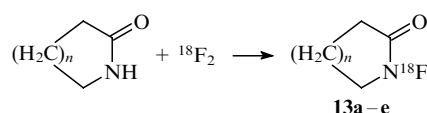


n = 2 (**a**, 55%–65%), 3 (**b**, 50%–60%).

Satyamurthy *et al.*⁵⁴ used the reaction of solutions of lactams with 100% fluorine for the synthesis of *N*-fluoro lactams **13** labelled with ¹⁸F. However, the yields of *N*-fluoro lactams **13a–c** are rather low. Higher yields could be obtained by fluorination of solutions of lactams in Freon with fluorine diluted with neon.⁵³

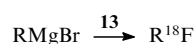
Table 1. Fluorination of organic compounds with *N*-fluorosulfonamides in THF.^{35, 36}

Substrate	Fluorinating reagent 9				Reaction conditions		Reaction product	Yield (%)	Enantio- meric excess (%)
	R ¹	R ²	R ³	R ⁴	base	T / °C			
	Ph	H	Me	4-MeC ₆ H ₄	LDA ^a	−40 to −20		10	40
	Ph	H	Me	4-MeC ₆ H ₄	KHMDS ^b	−40–0		46	46
	Ph	H	Me	Me	LDA	−40–0		11	20
	Ph	H	Me	4-MeC ₆ H ₄	LDA	−4 to −20		3	46
	Ph	H	Me	Me	LDA	−40–0		4	6
	Ph	H	Me	4-MeC ₆ H ₄	NaH	0–20		20	14
	Ph	H	Me	Me	NaH	0		6	30
PhCOCH(Me)CO ₂ Et	Ph	H	Me	4-MeC ₆ H ₄	NaH	0	PhCOCF(Me)CO ₂ Et	21	18
	Ph	H	Me	Me	NaH	0	PhCOCF(Me)CO ₂ Et	21	6
	Pr ⁱ	H	CO ₂ Et	Me	NaH	20		6	6

^a LDA is lithium diisopropylamide; ^b Potassium bis(trimethylsilylamide).

Compound 13	<i>n</i>	Yield (%)	Radiochemical yield (%)
a	1	76	41
b	2	61	33
c	3	79	42
d	4	71	48
e	5	33	19

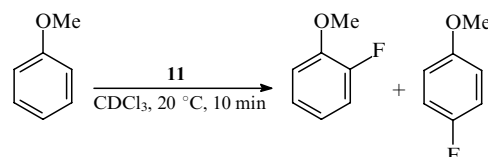
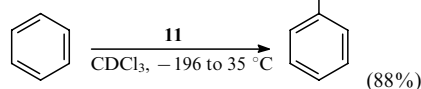
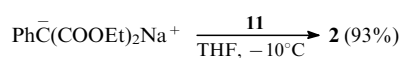
N-Fluorolactams **13** can be used for the synthesis of fluoro derivatives labelled with ¹⁸F. They react with the Grignard reagents, however, the yields of the reaction products are low.⁵⁴



Reagent	13a	13b	13c	13c	13c	13c	13d
R	Ph	Ph	Ph	4-MeC ₆ H ₄	1-naphthyl	cyclo-C ₆ H ₁₁	Ph
Yield (%)	1–2	8	20	30	51	19	19

Controlled fluorination of aromatic compounds and derivatives of malonic acid with *N*-fluoro lactams of the type **13** and with *N*-fluoro sulfonamides **10** and **11** can be used for the synthesis of aromatic fluoro derivatives and fluorinated malonates.

Thus sulfonamide **11** fluorinates sodium diethyl phenylmalonate, benzene and anisole (a mixture of *ortho*- and *para*-fluoroanisoles is formed in 3:1 ratio and in 98% yield).⁴⁹ *N*-Fluorobenzenesulfonamide reacts with anisole (4 h, 150 °C) to yield a mixture of 57% 2-fluoroanisole and 37% 4-fluoroanisole.^{53, 54}



The data on fluorination of several compounds with substituted *N*-fluorotoluenesulfonamides **10a, c, d** are presented in Table 2.³⁷

The halogen atoms in alkenyl iodides can be selectively substituted by the fluorine using *N*-fluorobenzenesulfonamide, *via* intermediate lithium derivatives. The yields of the resulting fluorides are rather high, although in some cases alkenes are formed in large amounts. The results of fluorination of alkenyl iodides are presented in Table 3.⁴⁷

(a) Bu^tLi, THF–Et₂O–C₅H₁₂ (4:1:1), −120 °C;(b) PhSO₂NFBu^t, from −120 to 20 °C.

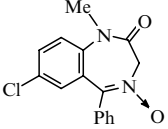
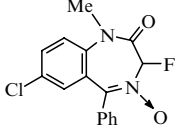
4. Fluorinating reagents based on *N*-fluoro sulfonylamines

N-Fluoro imides have found much wider application in organic synthesis than *N*-fluoro amides. The methods for preparing *N*-fluorobis[alkyl(aryl)sulfonyl]amines are based on direct fluorination of the corresponding bisalkyl(aryl)sulfonylamines (1%–3% F₂ in Ar or XeF₂). Fluorinated products are obtained in up to 70% yields.⁵⁵

N-Fluorodisulfonylamines of the type CF₃SO₂NFSO₂R (R is perfluoroalkyl, cycloalkyl, aralkyl or aryl) are obtained by fluorination of the corresponding imides with elemental fluorine at −20 °C.^{56–64} Thus treatment of (CF₃SO₂)₂NH with F₂ at 22 °C gives *N*-fluorobis(trifluoromethylsulfonyl)amine (**14a**) in 95% yield. *N*-Fluorodisulfonylamines **14b–e** and imides **15** were synthesised in a similar way.⁵⁹

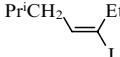
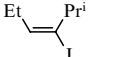
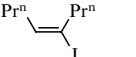
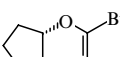
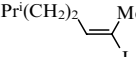
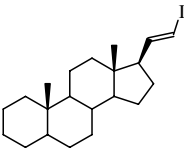
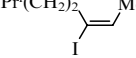
The fluorination is performed with elemental fluorine diluted with nitrogen in solvents (CHCl₃, CFC₃, HF, fluorohydrocarbons, MeCN) at 80–135 °C in the presence of NaF or CaF₂.

Table 2. Fluorination of organic compounds with *N*-fluorosulfonamides **10**.³⁷

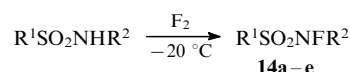
Substrate	Base	Reagent	Solvent	<i>T</i> / °C	Reaction product	Yield (%)
PhCH(COOEt) ₂	NaH	A	THF	20	PhCF(COOEt) ₂	81
MeCH(COOEt) ₂	NaH	A	PhMe, THF	20	MeCF(COOEt) ₂	53
PhMgCl		B	Et ₂ O	20	PhF	50
Me ₂ CHNO ₂	Bu ⁿ ₄ N ⁺ OH [−]	B	PhMe, PhH	−20	Me ₂ CFNO ₂	83–87
	KH	B	THF	20		60
	KH	B	PhMe, THF	−50		52
PhCOCH ₂ CHMe ₂	KH	C	Et ₂ O	20	PhCOCHFCHMe ₂	81
Me(CH ₂) ₁₃ MgBr		C	PhMe, Et ₂ O	−78	Me(CH ₂) ₁₃ F	15
Ph ₂ CHCOOH	Bu ⁿ Li	C	PhMe, THF	−50	Ph ₂ CFCOOH	69
	Bu ⁿ Li	C	PhMe, THF	20		24
	KH	C	PhMe, THF	−50		81
	KH	C	PhMe, THF	−50		31
	MeLi	C	PhMe, THF	−20		35
Me-  -SO ₂ NHBu ^t	Bu ⁿ Li	C	PhMe, THF	20	Me-  -SO ₂ NHBu ^t	55

Note. A, *N*-fluoro-*N*-neopentyl-*p*-toluenesulfonamide (**10c**); B, *N*-*tert*-butyl-*N*-fluoro-*p*-toluenesulfonamide (**10a**); C, *exo*-*N*-fluoro-2-norbornyl-*p*-toluenesulfonamide (**10d**).

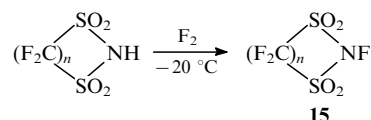
Table 3. Fluorination of alkenyl iodides with *N*-*tert*-butyl-*N*-fluorobenzenesulfonamide.⁴⁷

Alkenyl iodide	Yield (%)		Alkenyl iodide	Yield (%)	
	fluor- ide	alk- ene		fluor- ide	alk- ene
n-C ₆ H ₁₃ CH=CHI	71	15		88	7
PhCH=CHI	76	10		83	7
	85	3		74	8
	75	12		80	13
	75	12			

Syvret *et al.* have proposed to use lithium derivatives instead of free imides.⁶²

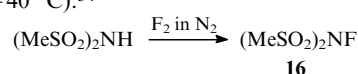


R¹ = CF₃; R² = SO₂CF₃ (**a**, 95%), SO₂C₄F₉ (**b**, 96%), SO₂C₆F₁₃ (**c**, 93%), Me (**d**, 11%); R¹ = C₄F₉, R² = SO₂C₆F₁₃ (**e**, 88%).



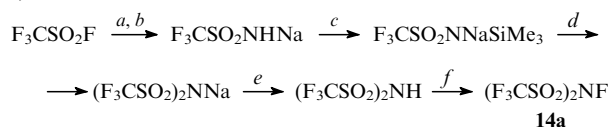
n = 2 (77%), 3 (61%), 4 (86%).

N-Fluorobis(methylsulfonyl)amine (**16**) was obtained in 90% yield by fluorination of bis(methylsulfonyl)amine with elemental fluorine (F₂:N₂ = 1:9) in acetonitrile in the presence of NaF (−40 °C).³⁴



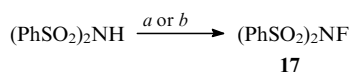
Other *N*-fluorobis[alkane(arene)sulfone]amides^{33,64,65} and *N*-fluorobenzo-1,3,2-dithiazine 1,1,3,3-tetroxide [commonly referred to as *N*-fluoro-*o*-benzodisulfonimide (NFOBS)]^{66,67} have been synthesised in a similar way. Water or water–organic solvent mixtures can be used as a reaction medium.⁶⁴ The best results are attained through the use of sodium salts of the corresponding sulfonimides.^{34,65,67}

The reagent **14a** obtained by the scheme given below (total yield 76% with respect to trifluoromethanesulfonyl fluoride) is the most reactive among other *N*-fluorodisulfonylamines.⁵⁹ This compound has a boiling point at 90–91 °C, is thermally stable, can be stored in glassware and is a highly efficient fluorinating agent which has many applications. The same scheme was used to obtain the reagent **14a** labelled with ¹⁸F (45% radiochemical yield).⁶⁸



(a) NH₃ (liquid), –78 °C; (b) NaOMe, MeOH (95%); (c) (Me₃Si)₂NH, Δ (92%); (d) F₃CSO₂F, THF, 100 °C, autoclave (98%); (e) H₂SO₄, sublimation *in vacuo* (93%); (f) 100% F₂, metal tube, from –196 to 22 °C (95%).

N-Fluorobis(phenylsulfonyl)amine (**17**) often referred to as *N*-fluorobenzenesulfonamide was obtained in 70% yield by fluorination of bis(phenylsulfonyl)amine with fluorine diluted with nitrogen, in acetonitrile or in a CHCl₃–CFCl₃ mixture in the presence of sodium fluoride at –40 °C.^{69–71} The structure of compound **17** was confirmed by X-ray diffraction analysis.⁷¹

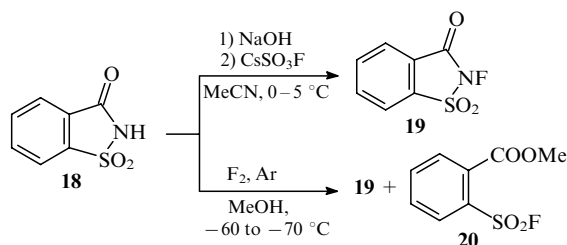


(a) 10% F₂ in N₂, NaF, MeCN, –40 °C; (b) 10% F₂ in N₂, NaF, CHCl₃–CFCl₃ (1 : 1), –40 °C.

N-Fluorobis(phenylsulfonyl)amine (**17**) is a white crystalline powder, which is soluble in the majority of organic solvents (ether, THF, CH₂Cl₂, MeCN, PhMe). It is convenient in handling, non-hygroscopic and storage-stable. This reagent can be used for fluorination of carbanions, enolates and enol esters as well as for the preparation of fluorinated intermediates used in the production of medicinal drugs.

Fluorination of the sodium salt of saccharin **18** with cesium fluorosulfate in acetonitrile at 0–5 °C gives the *N*-fluoro derivative **19** in 69% yield. Treatment of compound **18** with fluorine in methanol at –60 °C (–70 °C) gives methyl *o*-fluoro-sulfonylbenzoate **20** formed by the opening of the heterocycle and the fluoro derivative **19**.⁴⁰

An analogue of compound **19**, 3-fluorobenzo-1,2,3-oxathiazin-4-one 2,2-dioxide (**21**), is prepared by treatment of sodium salt

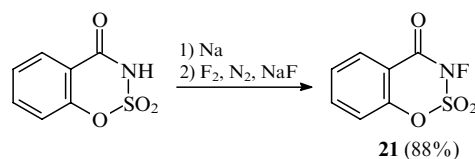


of benzo-1,2,3-oxathiazin-4(3*H*)-one 2,2-dioxide in acetonitrile with dilute fluorine in the presence of sodium fluoride (–40 °C).^{33, 34, 63} The reagent **21** is a rather stable crystalline compound, which manifests high fluorinating ability and is used for fluorination of various compounds including carbanions, steroids and aromatic compounds.^{34, 63} Examples of these reactions are given in Table 4.

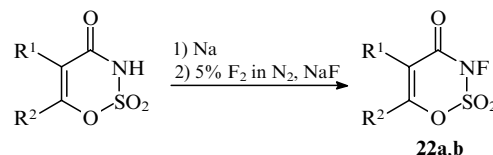
Table 4. Fluorination of organic compounds with 3-fluorobenzo-1,2,3-oxathiazin-4-one 2,2-dioxide (**21**).³⁴

Starting compound	Reaction conditions ^a			Reaction product	Yield (%)
	solvent	<i>T</i> / °C	<i>t</i> / h		
PhMgBr	THF	20	4	PhF	5
PhC(CO ₂ Et) ₂ Na ⁺	THF	20	4	PhCF(CO ₂ Et) ₂ (2)	52
	THF	20	0.5		77
	n-C ₆ H ₁₄	65	8		66
	MeCN	20	4		59
PhOMe	MeCN	150	5		77 ^b

^a Sodium bis(trimethylsilyl)amide (NaHMDS) was used to generate the enolates and salts. ^b The *ortho* : *para* ratio is 56 : 44.

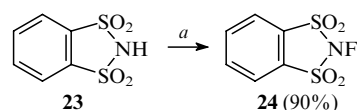


Substituted *N*-fluoro-1,2,3-oxathiazin-4-one 2,2-dioxides **22a, b** are prepared in a similar way.⁶⁵



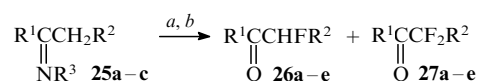
R¹ = H, R² = Me (**a**); R¹ = Me, R² = Me (**b**).

Treatment of benzo-1,3,2-dithiazole 1,1,3,3-tetroxide (**23**) with nitrogen-diluted fluorine at –40 °C gives *N*-fluorobenzo-1,3,2-dithiazole 1,1,3,3-tetroxide (**24**)^{66, 67, 72} as a white crystalline powder. Its structure was confirmed by X-ray diffraction analysis.⁷¹



(a) 10% F₂ in N₂, NaF, CFCl₃–CHCl₃, –40 °C.

Electrophilic fluorination of imines **25a–c** with *N*-fluorobis(trifluoromethylsulfonyl)amine (**14a**) yields mono- (**26a–e**) and difluoroketones (**27a–e**); the imine anions were generated by treatment with bases.⁷³



(a) **14a**, CH₂Cl₂, Na₂CO₃, 22 °C; (b) H₃O⁺.

Direct fluorination of imines with (CF₃SO₂)₂NF (**14a**) gives α-monofluoro and α,α-difluoro ketones without preliminary generation of anions.^{74–76} The results of fluorination are listed in Table 5.⁷³ Enamines react in a similar way. Thus 1-morpholino-1-

Table 5. Synthesis of fluoro ketones by fluorination of imines **25** with the reagent **14a**.⁷³

Compo- unds 25–27	R ¹	R ²	R ³	14a : 25 Ratio	Yield of 26 (%)	Yield of 27 (%)
a	Ph	H	Pr ⁿ	2.4 : 1	0	82
				1 : 3	33	15
b	4-MeC ₆ H ₄	H	Pr ⁿ	2.4 : 1	0	83
				1 : 3	36	16
c	Ph	Me	Pr ⁿ	2.4 : 1	0	58
				1 : 3	38	17
d	4-MeOC ₆ H ₄	H	Bu ⁿ	2.4 : 1	0	70
				1 : 3	26	17
e	4-BrC ₆ H ₄	H	Bu ⁿ	2.4 : 1	0	78
				1 : 3	30	16

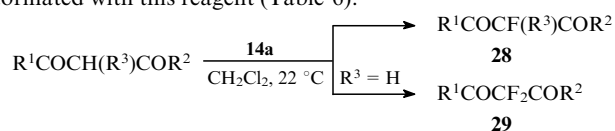
phenylpropene reacts with compound **14a** to give α -fluoro-propiophenone after hydrolysis. Fluorination of imines and enamines with the reagent **14a** can be regarded as an alternative route to α -fluoro ketones, which are usually synthesised from the corresponding enolates. Mild reaction conditions and high yields of the final products make this procedure very promising.

The reagent **14a** proved to be efficient in fluorination of lithium enolates of esters, amides, ketones, β -diketones and β -oxo esters (enolates are prepared by treatment with lithium diisopropylamide in THF). The fluorination is fairly selective at 22 °C and results in monofluoro derivatives.⁷⁵

$\text{R}^1\text{R}^2\text{CHCOX} \xrightarrow[2) \text{14a, THF, 22 } ^\circ\text{C}]{1) \text{LDA}} \text{R}^1\text{R}^2\text{CFCOX}$			
X	R ¹	R ²	Yield (%)
OCH ₂ Ph	H	H	76
OEt	H	OEt	63
OEt	H	Ph	71
OEt	Me	Ph	83
OEt	Et	Ph	70
NPr ₂ ⁱ	H	Ph	87
NPr ₂ ⁱ	Me	Ph	85
NPr ₂ ⁱ	Et	Ph	70
Ph	H	H	86
Me	Ph	Ph	81

The synthesis of α,α -difluoro derivatives requires 2 equiv. of the reagent **14a** and more drastic conditions.^{60, 66, 75–77}

The nature of substituents at the carbonyl group of ketones has no appreciable influence on the yields of the monofluorinated derivatives, which are normally high. Esters are also smoothly fluorinated with this reagent (Table 6).⁷⁶



Lithium diethyl 2-nitromalonate is fluorinated with high yield in the treatment with (CF₃SO₂)₂NF (**14a**) in THF.^{60, 76}

The fluorination of β -diketones, β -oxo esters and β -oxo amides with the reagent **14a** in non-polar solvents results in the formation of α -monofluoro or α,α -difluoro derivatives. Thus ethyl 2-chloroacetoacetate,⁷⁴ ethyl 2-acetoxyacetoacetate⁷⁸ and 3-chloro-2,4-pentanedione⁷⁹ are fluorinated with the reagent **14a** in chloroform in quantitative yields. Fluorination of benzoylacetone in CH₂Cl₂ gives 90% of 1-benzoyl-1,1-difluoroacetone, whereas in a CH₂Cl₂–H₂O system the monofluoro derivative is obtained in 93% yield (see Table 6).⁷⁶

Fluorination of α -oxo esters can also occur in the absence of bases. These compounds generate fluoro derivatives with practi-

Table 6. Fluorination of 1,3-dicarbonyl compounds [R¹COCH(R³)COR²] with the reagent **14a**.⁷⁶

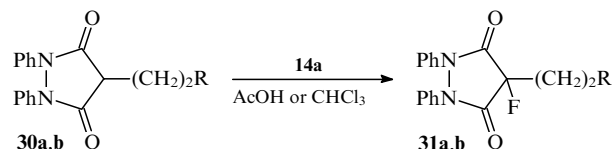
R ¹	R ²	R ³	Reagent : substrate ratio	Solvent	t /h	Yield (%) ^a	
						28	29
Me	Me	Me	1 : 1	CH ₂ Cl ₂	7	91	
Me	Me	OEt	1 : 1	CH ₂ Cl ₂	7	83	
Me	Me	H	2 : 1	CH ₂ Cl ₂	3		54
Me	OEt	H	2 : 1	CH ₂ Cl ₂	20		80
Ph	Me	H	2 : 1	CH ₂ Cl ₂	24		90
Ph	Me	H	2 : 1	CH ₂ Cl ₂ –H ₂ O	11	93	
Ph	OEt	H	2 : 1	CH ₂ Cl ₂	24		96
Me	OEt	H	1.5 : 1	CH ₂ Cl ₂ –H ₂ O	8		86
<i>p</i> -NO ₂ C ₆ H ₄	OEt	H	1.5 : 1	CH ₂ Cl ₂ –H ₂ O	11		94
Pr ⁱ	OEt	H	1.3 : 1	CH ₂ Cl ₂ –H ₂ O	14		91
OMe	OMe	H ^b	1 : 1	THF	5		78
OEt	OEt	Ph ^b	1 : 1	THF	3		92

^a After separation by chromatography on SiO₂. ^b Sodium enolate was used.

cally quantitative yields upon treatment with equimolar amounts of the reagent **14a**.⁷⁴

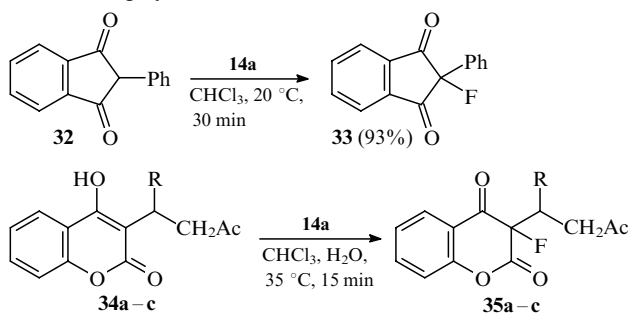
$\text{R}^1\text{R}^2\text{CHCOCOOR}^3 \xrightarrow{\text{14a}} \text{R}^1\text{R}^2\text{CFCOCOOR}^3$			
R ¹	R ²	R ³	Yield (%)
Me	Me	Et	95
Me	Et	H	95
H	Me	H	95

4-Substituted *N,N*-diphenylpyrazolidine-3,5-diones **30a,b** are fluorinated with 1 equiv. of the reagent **14a** in acetic acid or in CHCl₃ to give 4-*n*-butyl-4-fluoro-1,2-diphenylpyrazolidine-3,5-dione (**31a**) and 4-fluoro-1,2-diphenyl-4-[(2-phenylsulfinyl)ethyl]pyrazolidine-3,5-dione (**31b**).⁷⁷



R = Et (**a**, 95%), SPh (**b**, 90%).

The fluorination of 2-phenylindane-1,3-dione (**32**) with the reagent **14a** in acetic acid at 20 °C gives 2-fluoro-2-phenylindane-1,3-dione (**33**).⁴² In fluorination of substituted 4-hydroxycoumarins **34a–c** with the reagent **14a**, the fluorine atom also occupies the α -position relative to the carbonyl group to give compounds **35a–c** in high yields.⁴²



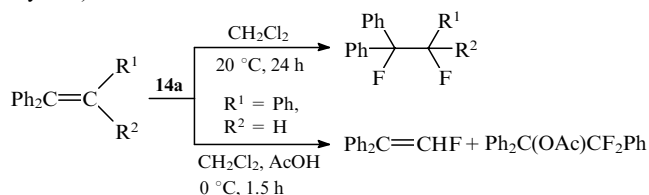
R = H (**a**, 91%), Ph (**b**, 92%), 4-ClC₆H₄ (**c**, 90%).

The fluorination of 4-hydroxy-3-(3-oxobutyl)coumarin **34a** in a chloroform–water mixture (5 min, 35 °C) gives the corresponding fluoro derivative **35a** (which represents a mixture of diastereomers) in a quantitative yield.⁵⁸ 3-Fluoro-3-(1-phenyl-3-oxobutyl)-

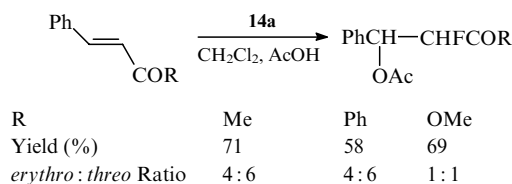
2*H*-benzopyran-2,4-dione and 3-fluoro-3-[1-(4-chlorophenyl)-3-oxobutyl]-2*H*-benzopyran-2,4-dione are prepared in a similar way. The highly selective fluorination of heterocyclic compounds with the reagent **14a** is better carried out in polar solvents, *e.g.*, 2,2,2-trifluoroethanol or nitromethane.⁷³

N-Fluorobis(trifluoromethylsulfonyl)amine (**14a**) reacts with some activated aromatic compounds such as toluene, anisole and acetanilide, resulting in the *ortho*- and *para*-substituted products.⁶⁵ Monofluoro derivatives are predominantly formed at the ArH : **14a** ratio of 2 : 1. As for nitrobenzene, chlorobenzene or acetophenone, they cannot be introduced into this reaction.^{59, 65, 69, 70}

The reagent **14a** is effective in reactions with alkenes to give addition products of fluorine at the multiple bond. If a CH₂Cl₂–acetic acid mixture is used, the latter enters into the reaction to give acetoxy and hydroxyfluoro derivatives (these reactions were described, *e.g.*, with styrene and *trans*-β-methylstyrene).⁸⁰

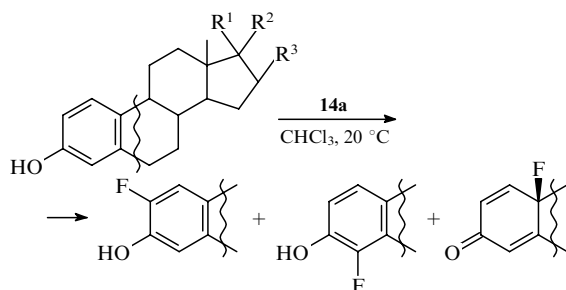


The reagent **14a** reacts with α,β-unsaturated carbonyl compounds in AcOH to give β-acetoxy α-fluoro ketones.⁸⁰

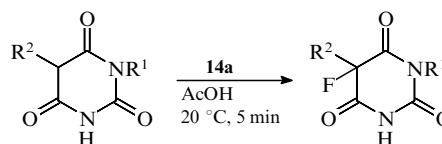


Uracil does not react with (CF₃SO₂)₂NF (**14a**) at 22 °C in AcOH, presumably due to its poor solubility, whereas at 45 °C this reaction is completed in 12 h to give a difluoro derivative.⁸⁰ 1,3-Dimethyluracil is much more reactive and gives a difluoro derivative in the reaction with 2 equiv. of (CF₃SO₂)₂NF (**14a**) at 22 °C (yield 85%); 1 equiv. of the reagent **14a** gives 1,3-dimethyl-5-fluorouracil.⁸⁰

N-Fluorodisulfonylamine (**14a**) is effective in fluorination of various steroids. Thus fluorination of estra-1,3,5-trien-3-ols in CHCl₃ gives *ortho*- and *para*-fluorinated products. If acetic acid is used as a solvent, fluorine selectively occupies the *para*-position to give 10β-fluoro-1,4-estradien-3-one derivatives in high yields.⁶¹



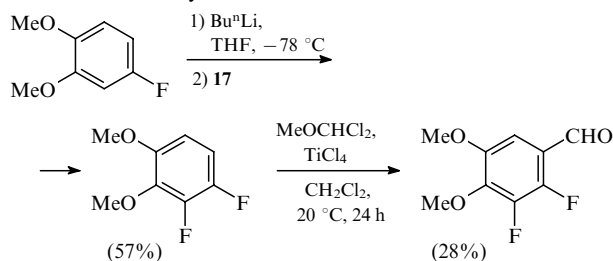
The fluorination of a suspension of 2,4,6-trihydroxypyrimidine in acetic acid with 1 equiv. of (CF₃SO₂)₂NF (**14a**) at room temperature results in a monofluoro derivative, whereas a 5,5-difluoro derivative is obtained in high yield with 2 equiv. of the reagent.⁷⁷ This method was used for the synthesis of a wide range of fluorinated pyrimidinetriones.⁷⁷



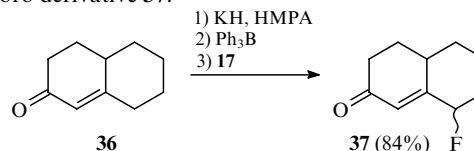
R ¹	H	Me	Et	Bu ⁿ	Ph	OMe	Me	Et	Ph
R ²	H	H	H	H	H	H	Me	Me	Me
Yield (%)	88	92	89	90	91	90	92	83	91

Along with reagent **14a**, other *N*-fluoro imides, *e.g.*, *N*-fluorobis(phenylsulfonyl)amine (**17**) or *N*-fluorobenzo-1,3,2-dithiazole 1,1,3,3-tetroxide (**24**) are used for fluorination of various classes of organic compounds. Some examples are given in Table 7.

The reagent **17** is more efficient than the reagent **24** in fluorination of organometallic compounds and highly stabilised anions (see Table 7). Under the action of the reagent **17** (100 °C, 18 h), acetanilide gives a mixture of isomeric fluoroacetanilides, the yields of the *ortho*- and *para*-isomers being 25% and 15%, respectively.⁶⁵ Fluorination of metallated aromatic and heteroaromatic compounds with the reagent **17**, which is accompanied by the formation of *ortho*-fluoro derivatives, is used in the synthesis of valuable biologically active compounds, *e.g.*, fluoro- and difluoroveratric aldehydes.^{74, 81, 82}



Base-catalysed formation of enolates, subsequent complexation with boron compounds and fluorination of the latter with the reagent **17** is a novel method for the synthesis of γ-fluorinated α,β-unsaturated ketones.^{83–85} Thus the reaction of the reagent **17** with a carbanion generated from 4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (**36**) in the presence of triphenylborane gave the fluoro derivative **37**.⁸⁴



The enolate prepared from 10-methyl-1(9)-octal-2-one upon treatment with KH in a HMPA–THF mixture in the presence of triphenylborane gives a fluoro derivative with the reagent **17** in the α : β ratio of 1 : 8.6 (yield 84%).⁸⁵

Yet another example of efficient fluorination with this reagent in the presence of 2-phenylbenzo[1,3,2]dioxaborol is the synthesis of γ-fluorinated steroid enones. Thus the fluoro derivative **39** was prepared from compound **38**.⁸⁴

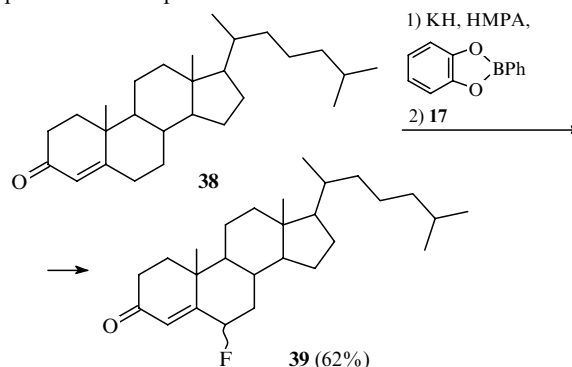


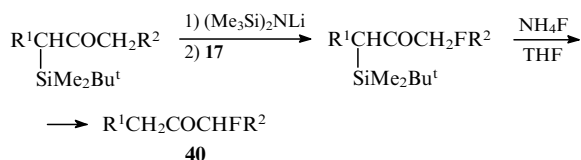
Table 7. Fluorination with the reagents **17** and **24**.

Substrate	Reagent	Reagent : substrate ratio	Temperature /°C	Time /h	Reaction product	Yield (%)	Ref.
	17	22 : 1	150	5		100 ^a	65
	17	1 : 1	100	24		33 ^a	65
	17	2 : 1	100	18		40 ^b	65
	17	50 : 1	100	216		19 ^c	65
	17	2 : 1	−78 ^d	6–7		56	74
	17	2 : 1	−78 ^d	6–7		62	74
	24	2 : 1	−78 ^d	6–7		0	74
	17	2 : 1	−40 ^d	6–7		74	74
	24	2 : 1	−40 ^d	6–7		70	74
	24	2 : 1	−40 ^d	6–7		71	74
	17	2 : 1	−78 ^d	6–7		74	74
	24	2 : 1	−78 ^d	6–7		30	74
	17	1 : 1	20	24		46	65
	17	1 : 1.2	−78	20		76	65
	17	1 : 3	105	20		40	65
	17	1 : 1.2	−78 ^e	20		47	65
	17	1 : 1.2	−78 ^e	20		85	65
	17	1 : 1.15	−95 ^e	20		50	65
	17	1 : 1.2	0 ^f	20		47	65
	17	1 : 1.3	−78 ^g	20		82	65

^a The *ortho* : *meta* : *para* ratio is 58 : 5 : 37. ^b The *ortho* : *para* ratio is 62 : 38. ^c The *ortho* : *meta* : *para* ratio is 65 : 7 : 28. ^d The organolithium derivative was generated previously by treatment with BuⁿLi in THF. ^e The lithium derivative was generated previously by treatment with LDA in THF. ^f The potassium derivative was generated previously by treatment with KH in Et₂O. ^g The potassium derivative was generated previously by treatment with KHMDS in THF.

The fluorination of lithium enolates of silylated ketones with the reagent **17** gives α-fluoro ketones **40** in high yields. The

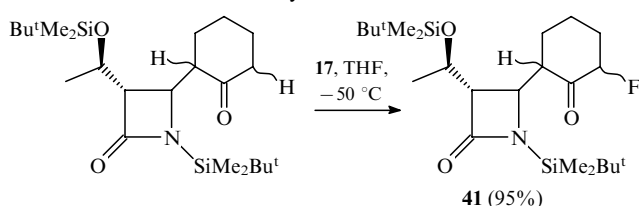
silyl group is eliminated by treatment with ammonium fluoride.⁸⁶



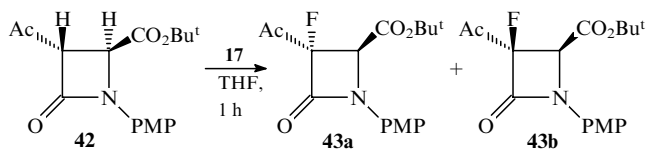
R ¹	R ²	Yield (%)	Configuration of 40
Et	Et	97	<i>S</i>
Pr	Pr	97	<i>S</i>
Et	PhCH ₂	95	<i>R</i>
	(CH ₂) ₃	99	<i>R</i>
	(CH ₂) ₄	99	<i>R</i>

Synthesis of α -fluoro ketones with the reagent **17** has also been described by Padova *et al.*⁸⁷

The fluorinating reagent **17** was used for introducing fluorine into a molecule containing an azetidinone fragment.⁸⁸ Compound **41** is an intermediate in the synthesis of new antibiotics.

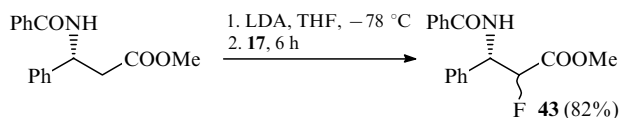


The fluorination of the azetidinone derivative **42** with the reagent **17** results in a mixture of stereoisomeric 3-fluoroazetidinones **43a,b** (yield 70%). The isomer ratio depends on temperature, *e.g.*, at 20 °C the **43a**:**43b** ratio is 85:15, whereas at -15 °C it is 95:5.⁸⁸



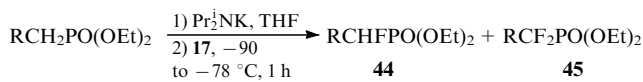
PMP is polymethylenepyridine.

Compound **17** is a very convenient reagent for diastereoselective fluorination of optically active substances. Thus the fluorination of a dianion generated from (-)-methyl 3-benzamido-3-phenylpropionate gives compound **43** with the *anti*:*syn* diastereomer ratio of 35:65.⁸⁹

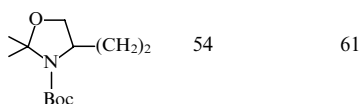


Treatment of methyl phenylacetate with *N*-fluorodisulfonylamine **17** in the presence of hexamethyldisilazane in THF (1 h, -78 °C) yields methyl difluorophenylacetate.⁹⁰

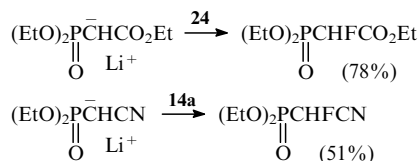
Fluorination of alkylphosphonate anions with the reagent **17** results in monofluoro **44** and difluoro derivatives **45**.^{78, 79, 91, 92}



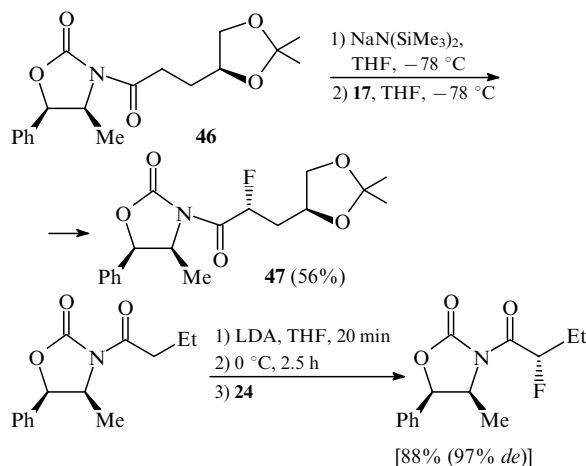
R	Yield of 44 (%)	Yield of 45 (%)
H	11	66
Bu	48	70
Me	45	66



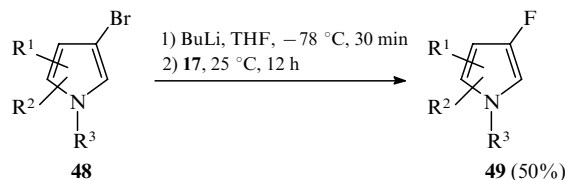
Other *N*-fluorinating agents can also be used for preparing monofluoro derivatives of alkylphosphonates.^{72, 91}



Sodium enolate obtained by treatment of compound **46** with sodium bis(trimethylsilyl)amide is fluorinated with the reagent **17** to give the monofluoro derivative **47**.⁹² This method was also used for the synthesis of other fluoro derivatives of oxazolidinone.⁹³

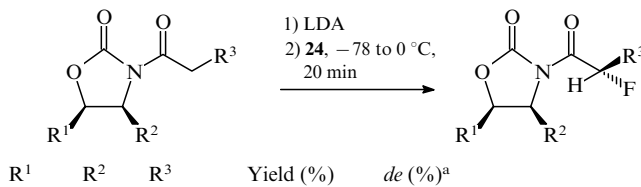


Treatment with the reagent **17** of lithium derivatives of functionalised pyrroles **48** prepared from bromides **48** results in the fluoro derivatives **49**.⁹⁴



R¹, R² = Ar, Alk, CN; R³ = CH₂OEt, SiPr₃.

N-Fluorobenzo-1,3,2-dithiazole 1,1,3,3-tetroxide (**24**) is effective in fluorination of enolates and carbanions (Table 8).⁷² It is also used for stereoselective fluorination of chiral lithium enolates.⁶⁶



R ¹	R ²	R ³	Yield (%)	<i>de</i> (%) ^a
Ph	Me	Bu ⁿ	88	97
H	Pr ⁱ	Bu ⁿ	85	96
Ph	Me	Bu ^t	86	96
H	Pr ⁱ	Bu ^t	80	97
Ph	Me	PhCH ₂	84	89
Ph	Me	Ph	86	86

^a The diastereomer ratio was determined on the basis of GLC and ¹H NMR data.

Fluorination of 1,3-dicarbonyl compounds with the imide **24** results in α -fluoro derivatives in yields up to 95%.⁷² The reaction of the imide **24** with anisole results in a mixture of 2-, 3- and 4-fluoroanisoles (total yield ~ 100%, the isomer ratio is 58:5:39, respectively).

Table 8. Fluorination of ketone enolates and carbanions with *N*-fluoro-benzo-1,3,2-dithiazole 1,1,3,3-tetroxide (**24**).⁷²

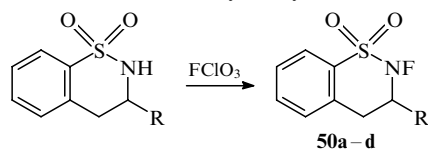
Substrate ^a	Time /h	Reaction product	Yield (%)
	1 ^b		80
	2 ^b		100
	2 ^c		87
	2 ^b		65
	4 ^c		60–65
	2 ^d		45
	4 ^c		60
PhMgBr	4 ^e	PhF	80

^a KHMDS, lithium bis(trimethylsilyl)amide (LiHMDS) and LDA were used to generate enolates and salts. ^b The fluorinating reagent was added to the enolate at 0 °C with subsequent warming to 20 °C. ^c After addition of the fluorinating reagent, the mixture was heated to 20 °C. ^d The fluorinating reagent was added to the enolate at –78 °C with subsequent warming to 0 °C. ^e The substrate was added to the fluorinating reagent at 0 °C.

5. The use of *N*-fluoro sultams

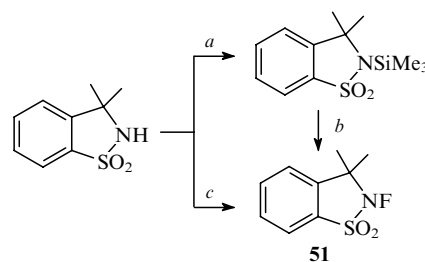
N-Fluoro sultams are obtained in high yields by the reaction of nitrogen-diluted fluorine (10% F₂ in N₂) with the corresponding sultams or their derivatives (direct fluorination in CHCl₃–CFCl₃ (1:1), 1 h, –40 °C, in the presence of NaF powder^{35,95–100}). *N*-Fluoro sultams are colourless crystalline compounds that are thermally stable and may be stored without decomposition for a sufficiently long period of time.

The fluorinating reagents **50a–d** were obtained by fluorination of the corresponding NH derivatives with FClO₃.¹⁰¹ Their structure was confirmed by X-ray diffraction analysis.⁷¹



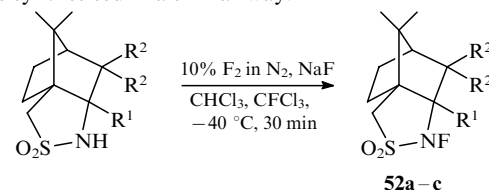
R = Prⁱ (**a**), Bu^t (**b**), cyclo-C₆H₁₁ (**c**), Ph (**d**).

Yet another effective fluorinating reagent of this type is *N*-fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (**51**).^{98–107} It is prepared using two main approaches, *viz.*, fluorination (10% F₂ in N₂) of *N*-trimethylsilyl-3,3-dimethyl-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (yield 49%¹⁰⁵) and direct fluorination of the NH derivative in the presence of NaF. In the latter case, the yield of compound **51** reaches 74%.¹⁰⁵



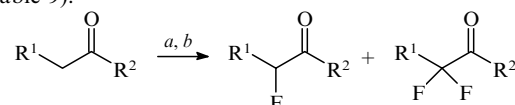
(a) (Me₃Si)₂NH, Δ, 95%; (b) 10% F₂ in N₂, CFCl₃, CHCl₃, –40 °C, 49%; (c) 10% F₂ in N₂, NaF, CFCl₃, CHCl₃, –40 °C, 74%.

N-Fluoro sultams **52a–c** on the basis of bicyclo[2.2.1]heptane are synthesised in a similar way.^{95–99}



Compound 52	R ¹	R ²	Configuration	Yield (%)
a	H	Cl	(+)	80
b	H	H	(–)	75
c	Me	H	(+)	80

N-Fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (**51**) is effective in fluorination of enolates and carbanions generated by strong bases.¹⁰⁵ The reaction is carried out in THF and yields a mixture of monofluoro and difluoro ketones (Table 9).



(a) B[–], THF, –78 °C; (b) **51**, THF, from –78 to 20 °C.

Table 9. Fluorination of carbonyl compounds with *N*-fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzothiazole 1,1-dioxide (**51**).¹⁰⁵

R ¹	R ²	Base	51 : substrate ratio	Mono: di-fluoro ketone ratio	Total yield (%)
Ph	MeO	LDA	(1.3–1.6):1	95:5	40
		LiHMDS	(1.3–1.6):1	>98:2	33
		NaHMDS	(1.3–1.6):1	70:30	36
		KHMDS	(1.3–1.6):1	53:47	27
		KHMDS	(1.3–1.6):1	64:36	23
Ph	MeO	KHMDS	(2.6–3.6):1	2:98	53
Me	Ph	LDA	1.1:1	97:3	53
		LiHMDS	1.1:1	95:5	66
		NaHMDS	1.1:1	78:22	56
		NaHMDS	1.1:1	>95:5	49
		KHMDS	1.1:1	50:50	40
		KHMDS	1.1:1	65:35	49
Me	Ph	KHMDS	(2.6–3.6):1	5:95	64
Me	PhCH ₂ O	LiHMDS	(1.3–1.6):1	>98:2	<10
		KHMDS	(1.3–1.6):1	90:10	58
		KHMDS	(2.6–3.6):1	33:67	27
Me	NPr ₂ ⁱ	LDA	(1.3–1.6):1	>98:2	20
		KDA ^a	(1.3–1.6):1	>98:2	47
		KDA ^a	(2.6–3.6):1	54:46	42

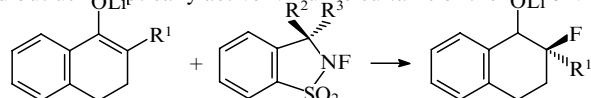
^a KDA is potassium diisopropylamide.

Table 10. Rate constants for fluorination of some organic nucleophiles with the *N*-fluoro sultam **51**.¹⁰⁸

Substrate	E°_{Nu} (see ^a)	Solvent	T /°C	k_{exp} /litre mol ⁻¹ s ⁻¹	k_{calc}^b /litre mol ⁻¹ s ⁻¹	Reaction product	Yield (%)
	1.6	Cl(CH ₂) ₂ Cl	60	$\ll 10^{-6}$ (see ^c)	6.3×10^{-24}		no reaction
	0.34	Et ₂ O	0	$> 8 \times 10^{-2}$	5×10^{-15}	MeC(F)(CO ₂ Et) ₂	94
	-0.39	THF	-78	3.2×10^{-2}	3×10^{-15}		80 ^d
	-0.34	THF	-75	1.9×10^{-2}	1.2×10^{-7}		72 ^d
	-0.29	THF, Et ₂ O	0	6.8×10^{-2}	1.4×10^{-7}	see ^c	17
	0	MeCN	0	1.3×10^{-3}	2×10^{-5}	see ^f	0

^a For the reagent **51**, $E^\circ = -0.12$. ^b Calculated for the SET process. ^c The reaction rate is too small to be measured. ^d No other reaction products were found. ^e 62% of naphthalene and 12% of naphthyltetrahydrofuran were isolated. ^f The fluorinated products were not characterised.

Enantioselective fluorination of lithium enolates can be carried out using optically active *N*-fluoro sultams of the type **51**.¹⁰³



$R^1 = \text{Me}$ (80% *ee*), Et (72% *ee*), Bn (86% *ee*); $R^2 = \text{Me}$, $R^3 = \text{Pr}^i$.

The rate of this reaction depends on the nature of the metal and the solvent. Thus propiophenone reacts with *N*-fluoro sultam **51** at -78°C , its sodium derivative reacts from -60°C to

-40°C , whereas the lithium derivative of propiophenone reacts only at temperatures above -40°C .

The rate constants of the fluorination of various compounds with the reagent **51** are listed in Table 10.¹⁰⁸

N-Fluoro sultams **52a–c** have found application as enantioselective fluorinating reagents (Table 11).^{95,96,99} The fluorination of enolates was carried out using 1.5 equiv. of the reagents **52a,b**. The ratio of enantiomers was determined by NMR spectroscopy with the use of a shift-reagent.^{95,96}

Table 11. Asymmetric fluorination of enolates with *N*-fluorosultams **52a,b**.^{95,96}

Substrate	Fluorinating reagent	Base	Solvent	T /°C	Reaction product	<i>ee</i> (configuration) (%)	Yield (%)
	52b	LDA	THF	-78 to 20		35	< 5
	52a	LDA	THF	-78		10(<i>S</i>)	49
	52a ^a	NaHMDS	THF	-78 to 0		67(<i>S</i>)	41
	52a ^a	NaHMDS	THF	-78		65(<i>S</i>)	40
	52a	NaHMDS	THF	-78 to 0		75(<i>R</i>)	40
	52a	NaHMDS	THF	-78		65(<i>R</i>)	50
	52b	NaH	Et ₂ O	0 to 20		25	28
	52a	NaH	Et ₂ O	0 to 20		46	> 95
	52a	NaHMDS	THF	-78 to 0		26	57
	52b	NaH	Et ₂ O	0 to 20		70	63
	52a	NaH	Et ₂ O	-78 to 0		34	59
PhCH(Me)CO ₂ Et	52b	LDA	THF	-78 to 20		35	< 10
	52a	LDA	THF	-78		29	62
	52a	NaHMDS	THF	-78		33	54

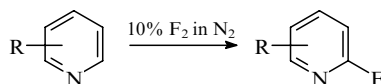
^a 0.8 Equiv. of the reagent **52a** was used.

III. Highly efficient fluorinating reagents based on heterocyclic compounds containing a fluorine atom at the charged nitrogen atom

Synthesis of fluorinating reagents in which the fluorine atom is bound to the charged nitrogen atom of a heterocycle is one of the most fruitful ideas in the chemistry of organofluorine compounds. Two groups of reagents are mainly used, *viz.*, *N*-fluoropyridinium and *N*-fluoroquinuclidinium derivatives. This type of compounds (they are commonly referred to as charged or quaternary) are characterised by high reactivity which surpasses that of neutral reagents of the type R_2NF . The interest in these compounds is also due to the possibility to vary their structures to match a specific synthetic problem. Therefore, these reagents can be used for fluorination of a vast variety of substrates. It is not accidental that only charged fluorine 'carriers' have rapidly found industrial application.

1. Fluorination with *N*-fluoropyridinium salts

N-Fluoropyridinium salts are structurally the simplest and most readily available fluorine carriers of the type $(R_3NF)^+X^-$. Direct fluorination of pyridine and its derivatives with nitrogen-diluted fluorine (10% F_2 in N_2) in $CF_2ClCFCl_2$ results mainly in 2-fluoropyridines.¹⁰⁹

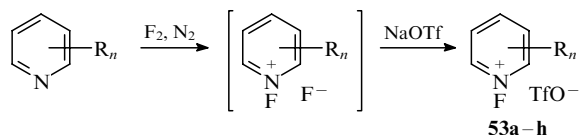


Substrate	$T/^\circ C$	Reaction product	Yield (%)
4-MeC ₅ H ₄ N	-25	2-F-4-MeC ₅ H ₃ N	31
4-EtC ₅ H ₄ N	-25	2-F-4-EtC ₅ H ₃ N	32
4-PrC ₅ H ₄ N	-25	4-F-4-PrC ₅ H ₃ N	47
4-PhCH ₂ C ₅ H ₄ N	-25	2-F-4-CH ₂ PhC ₅ H ₃ N	25
3,5-Me ₂ C ₅ H ₃ N	0	2-F-3,5-Me ₂ C ₅ H ₂ N	37
3,5-Cl ₂ C ₅ H ₃ N	25	2-F-3,5-Cl ₂ C ₅ H ₂ N	46
4-AcC ₅ H ₄ N	0	2-F-4-AcC ₅ H ₃ N	26
4-MeOCC ₅ H ₄ N	0	2-F-4-MeOCC ₅ H ₃ N	61

Earlier studies of Meinert and Cech^{110,111} showed that the fluorination of pyridine with a F_2/N_2 mixture in $CFCl_3$ at $-80^\circ C$ results in a pyridine-fluorine complex, *viz.*, *N*-fluoropyridinium fluoride. This compound manifests fluorinating activity at low temperatures (particularly, with respect to uracil and some chloro alkenes). It is very unstable and is decomposed explosively at temperatures above $-2^\circ C$. In practice, fluorination with *N*-fluoropyridinium fluoride can be carried out only at temperatures below $-20^\circ C$, which restricts the applicability of the method.

Attempts to replace the fluoride ion by other, less nucleophilic anions were undertaken aimed at obtaining stable *N*-fluoropyridinium salts. These studies are well documented.

Fluorination of pyridine and its derivatives in the presence of trifluoromethanesulfonic acid salts¹¹²⁻¹²² in aqueous acetonitrile¹²³ or in polyfluorinated alcohols¹²⁴ results in *N*-fluoropyridinium triflates **53a-h**.

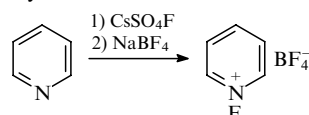


$R_n = H$ (**a**, 80%), 2-Me (**b**, 60%), 2,4,6-Me₃ (**c**, 49%), 3,5-Me₂ (**d**, 73%), 4-NO₂ (**e**, 86%), 3,5-(CF₃)₂ (**f**, 68%), 4-CN (**g**, 94%), 2,6-(COOMe)₂ (**h**, 72%).

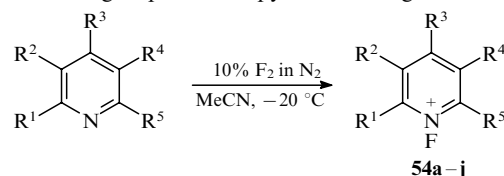
The salts **53** represent stable crystalline compounds which decompose without explosion only at, and above, melting points. They are soluble in organic solvents and do not react with glass. This class of fluorinating reagent has found wide application, particularly in fluorination of steroids, sugars and other natural compounds.

The range of stable fluorinating reagents on the basis of pyridine has been considerably extended¹²⁵⁻¹²⁸ owing to employment of salts (other than triflates) containing non-nucleophilic anions (BF₄⁻, PF₆⁻, SbF₆⁻) in their synthesis. This method was used for the preparation and characterisation (by ¹⁹F NMR) (see Refs 129-131) of numerous *N*-fluoropyridinium salts with different substituents in the pyridine ring and counterions. Thus the fluorination of pyridine with dilute fluorine ($F_2:N_2 = 1:4$) in the presence of trifluoromethanesulfonic acid in MeCN results in *N*-fluoropyridinium triflate (**53a**) in 97% yield.¹³¹

Other fluorinating reagents, *e.g.*, cesium fluoroxysulfate, can be used instead of fluorine.¹³³ Thus the reaction of pyridine with cesium fluoroxysulfate in acetonitrile ($0-5^\circ C$) in the presence of NaBF₄ results in stable *N*-fluoropyridinium tetrafluoroborate in 48% yield.



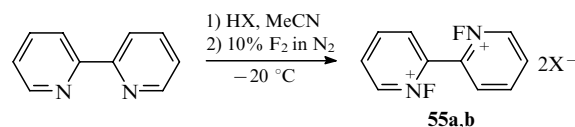
Internal pyridinium salts **54a-j** were synthesised by introduction of sulfo groups into the pyridinium ring.^{125, 134-136}



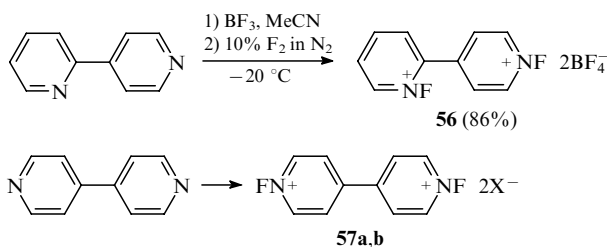
Compound 54	R ¹	R ²	R ³	R ⁴	R ⁵	Solvent	$T/^\circ C$	Yield (%)
a	Me	H	Me	H	SO ₃ ⁻	MeCN:H ₂ O (10:1)	-20	88
b	H	H	Me	H	SO ₃ ⁻	MeCN:H ₂ O (10:1)	-20	92
c	H	H	Et	H	SO ₃ ⁻	MeCN	-20	79
d	H	H	Bu ^t	H	SO ₃ ⁻	MeCN:H ₂ O (20:1)	-20	84
e	H	H	Me	H	SO ₃ ⁻	MeCN:H ₂ O (10:1)	-20	65
f	H	CF ₃	H	H	SO ₃ ⁻	MeCN	-20	90
g	H	CF ₃	H	Cl	SO ₃ ⁻	MeCN	-10	88
h	CF ₃	H	CF ₃	H	SO ₃ ⁻	MeCN	-40	95
i	H	H	H	SO ₃ ⁻	H	(CF ₃) ₂ CHOH	0	87
j	H	H	SO ₃ ⁻	H	H	(CF ₃) ₂ CHOH	0	74

The reaction is normally performed in MeCN; however, polyfluorinated alcohols $H(CF_2)_nCH_2OH$ ($n = 2, 3, 4$) can also be used as solvents. This approach was used to prepare *N*-fluoropyridinium-3-sulfonates (**54i,j**) (yields 87% and 74%, respectively).^{137, 138} Compounds **54** belong to the most potent fluorinating reagents. After completion of fluorination, the internal salts are converted into pyridinium sulfonates, which are readily soluble in water but poorly soluble in organic solvents, which facilitates the isolation of the target fluorination products and their separation from the products of degradation of the fluorinating reagent.

Umemoto *et al.*¹³⁹⁻¹⁴² synthesised *N,N'*-difluorobipyridinium salts by fluorination of bipyridine complexes with Lewis or Brønsted acids with nitrogen-diluted molecular fluorine (10% F_2 in N_2). The molecule of these salts has two mutually activating cationic centres.

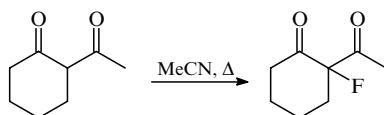


$X = BF_4$ (**a**, 90%), TfO (**b**, 89%).



Compound 57	Reaction conditions		Yield (%)
	1st step	2nd step	
a	TfOH, MeCN	10% F ₂ in N ₂ , 20 °C	89
b	BF ₃ , MeCN	10% F ₂ in N ₂ , 0 °C	96
a	LiOTf, MeCN	10% F ₂ in N ₂ , CFCl ₃ , CHCl ₃ , –35 °C	67

The reagents **53**, **55**–**57** differ in their fluorinating ability as can be exemplified in the reactions with 2-acetylcyclohexanone.¹³⁹



Fluorinating reagent	53a	55b	56	57a
<i>t</i> / h	19	0.1	2	5
Yield (%)	79	85	78	87

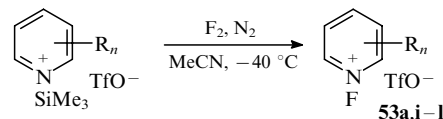
Compound **55b** turned out to be the most reactive among other compounds tested. 1,1'-Difluoro-2,2'-bipyridinium bis(tetrafluoroborate) (**55a**) can be regarded as one of the most efficient reagents for industrial manufacture of fluorine-containing compounds by virtue of its high reactivity, high (in comparison with other reagents) content of the active fluorine and ease of synthesis.¹³⁹ Bis(tetrafluoroborate) **55a** efficiently fluorinates compounds containing an active methylene group as well as aromatic and other compounds.¹⁴⁰

Some *N*-fluorinating reagents, *e.g.*, *N,N'*-difluoro-2,2'-bipyridinium (**55b**) and *N*-methyl-*N'*-fluoro-4,4'-bipyridinium (**58**) bistriflates and *N,N'*-difluoro-2,2'-bipyridinium (**57a**) bistetrafluoroborate, proved to be very convenient reagents for fluorination of various types of organic compounds (Tables 12 and 13).^{142, 143}

The introduction of readily polymerisable groups into the pyridine ring of the reagents **55**–**57** allows one to obtain polymers with molecular masses above 500 000 Daltons. The latter are used as electrolytes (*i.e.*, as an active cathode mass) in batteries and as solid fluorinating agents.¹³⁷

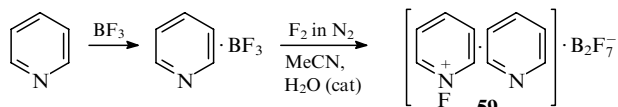
Among quaternary (charged) fluorinating reagents, pyridinium salts present the greatest interest for investigators; therefore, the methods for their synthesis are permanently improved and the areas of application are extended.

Thus yet another approach to the preparation of fluorinating reagents on the basis of pyridinium salts consists in fluorination of the corresponding *N*-trimethylsilyl derivatives with fluorine in MeCN.



R_n = H (**a**, 78%), 3-Cl (**i**, 79%), 3,5-Cl₂ (**j**, 55%), 2-CO₂Me (**k**, 69%), 2,3,4,5,6-Cl₅ (**l**, 67%).

The fluorination of the pyridine–BF₃ complex with nitrogen-diluted elemental fluorine (20% F₂ in N₂) in MeCN or CCl₄ at room temperature results in the heptafluorodiborate of a pyridine–*N*-fluoropyridinium complex (**59**) rather than *N*-fluoropyridinium tetrafluoroborate, which is also an efficient fluorinating reagent.^{115, 118–121}



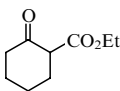
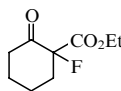
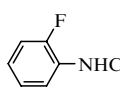
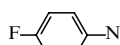
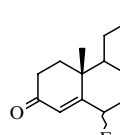
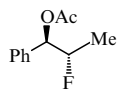
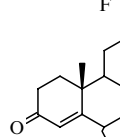
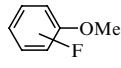
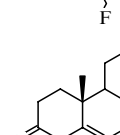
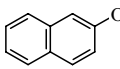
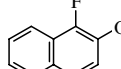
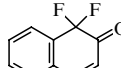
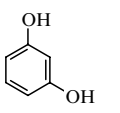
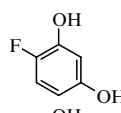
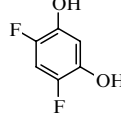
2,6-Dichloropyridine gives *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate upon fluorination with elemental fluorine in a BF₃–HF–H₂O–MeCN system at –15 °C (yield 76%). The effect of temperature on the fluorination of pyridine with elemental fluorine in a CF₃SO₃H–MeCN system was estimated by Nukui.¹⁴³ At –20 °C, the yield of *N*-fluoropyridinium triflate was 92% after 30 days and at 40 °C it was 99%. Polyfluorinated secondary alcohols (RR'CHOH, where R,R' are C₁–C₄ fluoroalkyl) are used as solvents in the synthesis of the salts.¹³⁴

The fluorinating ability of *N*-fluoropyridinium salts depends not only on the nature of the substituent in the pyridine ring, but also on the nature of the counterion. The effect of the latter on the efficiency of fluorination of 1-trimethylsilyloxycyclohexene with *N*-fluoropyridinium salts has been studied by Umemoto *et al.*¹³⁴

Table 12. Fluorination of aromatic compounds with *N,N'*-difluorobipyridinium derivatives **57b** and **58** (in MeCN).¹⁴²

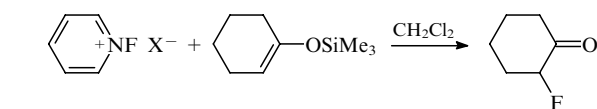
Fluorinating reagent	Substrate	<i>T</i> / °C	<i>t</i> / h	Reaction products	Yield (%)
 57b		20	20		52
		20	18		61
 58		80	15		60
	PhOMe	80	15	2- and 4-FC ₆ H ₄ OMe	55
		20	15		40
		60	20		40

Table 13. Fluorination of organic compounds with the reagent **55b** (in MeCN).¹⁴³

Substrate	<i>T</i> / °C	<i>t</i> / h	Reaction product	Yield (%)	Substrate	<i>T</i> / °C	<i>t</i> / h	Reaction product	Yield (%)
	boiling	8		76	PhNHCO ₂ Et	boiling	48		48
AcCH(Me)CO ₂ Et	"	8	AcCF(Me)CO ₂ Et	73					32
PhCOCH ₂ COPh ^a	"	48	PhCOCHF(COPh) ₂	10, 76					82 ^f
Ph-CH=CH-Me (see ^b)	"	0.25		51					46 ^g
PhOMe	"	9		73 ^c					19
	(see ^d)	20		61					
				18					
	boiling	< 0.1		72					
				10					

^a In the presence of 20 mol. % of TfOH. ^b The reaction was carried out in AcOH. ^c The 2-F : 4-F : 2,4-F₂ ratio is 6.5 : 4.6 : 1. ^d The reaction was carried out in HCO₂H. ^e 50 mol. % of NaHCO₃. ^f The α : β ratio is 1 : 1.7. ^g The α : β ratio is 1 : 1.4.

The best results were obtained with *N*-fluoropyridinium triflates. They manifest high regio- and stereoselectivity in fluorination of aromatic compounds, compounds containing activated methylene groups, the Grignard reagents, sodium salts of CH-acids, vinyl acetates, enolates, alkyl and silyl enol ethers, organic sulfides, enamides, alkenes, *etc.*

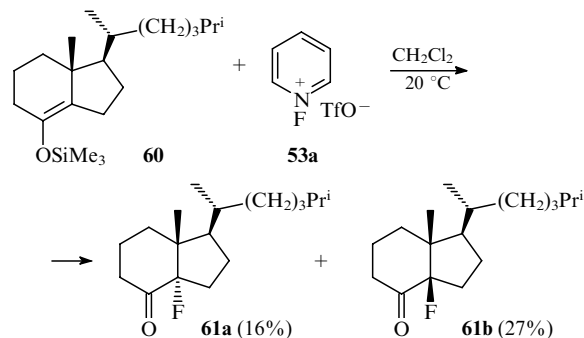


X	<i>T</i> / °C	Time/h	Yield (%)
CF ₃ SO ₃	20	7	87
BF ₄	20	72	traces
BF ₄	36	64	1
SbF ₆	36	8	23
ClO ₄	36	19	0

Some examples of fluorination of organic compounds with *N*-fluoropyridinium triflates are given in Table 14.¹⁴⁴

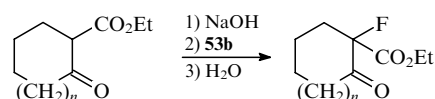
The regioselective fluorination of enol esters and ethers with *N*-fluoropyridinium salts leads to α-fluorocarbonyl compounds.¹¹⁴ A modified general fluorination procedure has been proposed which consists in the conversion of a carbonyl compound into enol trimethylsilyl ether or enol acetate which is subject to fluorination.

α-Fluorinated carbonyl compounds are convenient as starting compounds in fine organic syntheses.^{130, 144–147} Thus the fluorination of the silyl ether **60** with the reagent **53a** yields a mixture of α- and β-fluoro ketones **61a,b**.^{116, 148}



N-Fluoropyridinium salts containing the BF₄[−], SbF₆[−] or PF₆[−] counterions give 2-fluoropyridines in good yields upon treatment with bases (Et₃N, Pr₂NH, Py, MeONa, Bu^tOK, MeCOONa, Bu₄NF) at room temperature.^{141, 149, 150}

On heating with *N*-fluoro-2,4,6-trimethylpyridinium triflate (**53b**) in the presence of NaOH, ethyl 2-oxocyclohexanecarboxylate is converted into ethyl 1-fluoro-2-oxocyclohexanecarboxylate (yield 84%). Five- and seven-membered cyclic fluorinated β-oxo esters are obtained in a similar way.^{123, 151}



n = 0–2.

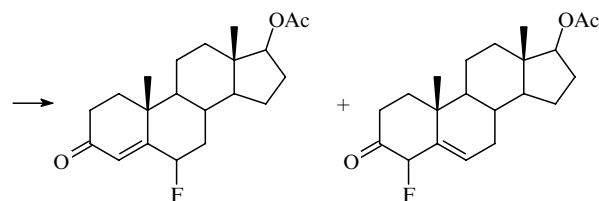
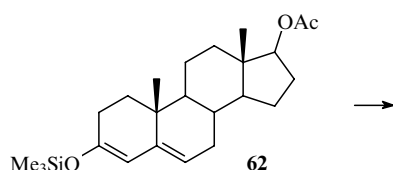
Fluoro derivatives with a predetermined position of the fluorine atom can be synthesised using reagents of the type **53** or **54** for fluorination of steroids under various reaction condi-

Table 14. Fluorination of organic compounds with *N*-fluoropyridinium triflates **53a,b,j,l**.¹⁴⁴

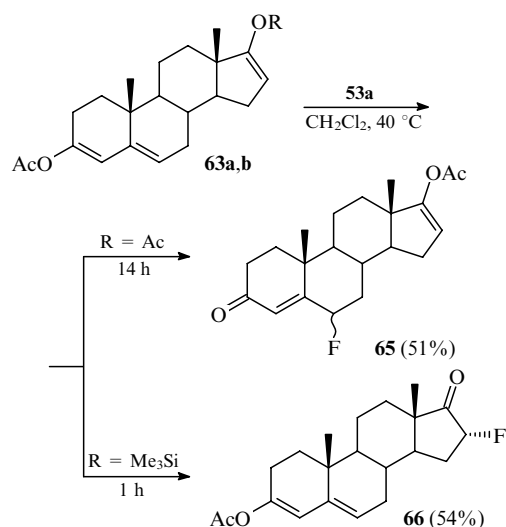
Fluorinating reagent	Substrate	Solvent	<i>T</i> / °C	<i>t</i> / h	Reaction product	Yield (%)
53a	PhOH	CH ₂ Cl ₂	100	24		75 ^a
	1-naphthol	CH ₂ Cl ₂	36	22	2-fluoro-1-naphthol (A) 4-fluoro-1-naphthol (B) 2,2-difluoro-1-(2 <i>H</i>)naphthalenone (C)	56 ^b
	4-NO ₂ C ₆ H ₄ OH	CH ₂ Cl ₂	20	17	2-F-4-NO ₂ C ₆ H ₃ OH	65
	PhCH = C(OEt)(OSiMe ₃)	CH ₂ Cl ₂	20	2	PhCHFCO ₂ Et	65
	<i>n</i> -C ₇ H ₁₅ CH = C(OSiMe ₃)Me	CH ₂ Cl ₂	20	2	<i>n</i> -C ₇ H ₁₅ CHFCOMe	72
	PhCH = C(OSiMe ₃) ₂	CH ₂ Cl ₂	20	2	PhCHFCO ₂ H	68
	53b					
	<i>n</i> -C ₁₂ H ₂₅ MgCl	Et ₂ O	0	0.5	<i>n</i> -C ₁₂ H ₂₅ F	75
	PhMgCl	THF	0	0.5	PhF	58
	Na ⁺ [CH(CO ₂ Et) ₂] [−]	THF	0	0.1	FCH(CO ₂ Et) ₂	73
	Na ⁺ [MeC(CO ₂ Et) ₂] [−]	THF	0	0.2	MeCF(CO ₂ Et) ₂	78
	Na ⁺ [PhC(CN) ₂] [−]	THF	0	0.2	PhCF(CN) ₂	71
	Na ⁺ [PhSO ₂ CHCO ₂ Et] [−]	THF	0	0.2	PhSO ₂ CF ₂ CO ₂ Et (D) PhSO ₂ CHFCO ₂ Et (E)	53 ^c
53b	Na ⁺ [ClC(CO ₂ Et) ₂] [−]	THF	0	0.2	ClCF(CO ₂ Et) ₂	86
	CH ₂ (COPh) ₂ (see ^d)	CH ₂ ClCH ₂ Cl	60	18	CF ₂ (COPh) ₂	88
	MeCOCH ₂ CO ₂ Et (see ^d)	CH ₂ ClCH ₂ Cl	60	24	MeCOCHF(CO ₂ Et) (F) MeCOCF ₂ CO ₂ Et (G)	81 ^e
	CH ₂ (CO ₂ Et) ₂ (see ^d)	CH ₂ ClCH ₂ Cl	60	48	CHF(CO ₂ Et) ₂	80
	53j					
	4-ClC ₆ H ₄ OH	CH ₂ ClCH ₂ Cl	20	23	2-F-4-ClC ₆ H ₃ OH	54
	2-naphthol	CH ₂ Cl ₂	20	26	1-fluoro-2-naphthol (J) 1,1-difluoro-2-(1 <i>H</i>)-naphthalenone (K)	95 ^f
	4-HOC ₆ H ₄ CO ₂ Me	CH ₂ ClCHCl ₂	20	40	3-F-4-HOC ₆ H ₃ CO ₂ Me	53
	53l					
	PhNHCOMe	CH ₂ Cl ₂	20	48	2-FC ₆ H ₄ NHCOMe (H) 4-FC ₆ H ₄ NHCOMe (I)	51 ^g
53l	PhCH = CH ₂	AcOH	20	1	PhCH(OAc)CH ₂ F	72
		AcOSiMe ₃	20	72	PhCH(OAc)CH ₂ F	56
		MeOSiMe ₃	20	120	PhCH(OMe)CH ₂ F	54
		EtOSiMe ₃	20	432	PhCH(OEt)CH ₂ F	29
	<i>trans</i> -PhCH = CHMe	AcOH	20	0.3	PhCH(OAc)CHFMe	80 ^h
	PhCH = CHMe (see ⁱ)	AcOH	20	1	PhCH(OAc)CHFMe	80 ^h
	Ph(Me)C = CH ₂	AcOH	20	0.08	Ph(CH ₂ F)C = CH ₂	25
		Pr ⁱ OH	20	0.16	PhC(Me)(OPr ⁱ)CH ₂ F	70
		CH ₂ Cl ₂	20	0.08	Ph(CH ₂ F)C = CH ₂	73
	Me(CH ₂) ₆ C(OSiMe ₃) = CH ₂	CH ₂ Cl ₂	20	3	Me(CH ₂) ₅ CHFCOMe	42
	Me(CH ₂) ₅ CH = C(OSiMe ₃)Me	CH ₂ Cl ₂	20	3	Me(CH ₂) ₅ CHFCOMe	58
	cyclo-C ₆ H ₁₁ (OSiMe ₃)C = CHMe	CH ₂ Cl ₂	20	10	cyclo-C ₆ H ₁₁ COCHFMe	61

^a The *ortho:para:meta* ratio is 9 : 3 : 1. ^b The **A** : **B** : **C** ratio is ~ 8 : 2 : 1. ^c The **D** : **E** ratio is ~ 1 : 12. ^d The fluorination was performed in the presence of 0.4 equiv. of ZnCl₂. ^e The **F** : **G** ratio is ~ 6 : 1. ^f The **J** : **K** ratio is ~ 8 : 1. ^g The **H** : **I** ratio is ~ 1 : 1. ^h The *threo* : *erythro* ratio is 1 : 1. ⁱ The *trans* : *cis* ratio is 1 : 1.

tions.^{130, 144, 146, 147} Oxo steroids are preliminarily converted into *O*-silyl enol ethers.^{146, 147} In the case of α,β -unsaturated oxo steroids, these are to be first converted into trimethylsilyl enol ethers. The choice of a fluorinating reagent makes it possible to selectively synthesise a required isomer. Thus the reagent **54a** predominantly fluorinates the trimethylsilyl ether **62** at position 6, whereas the reagent **53a** leads to 6- and 4-fluoro derivatives in comparable yields.

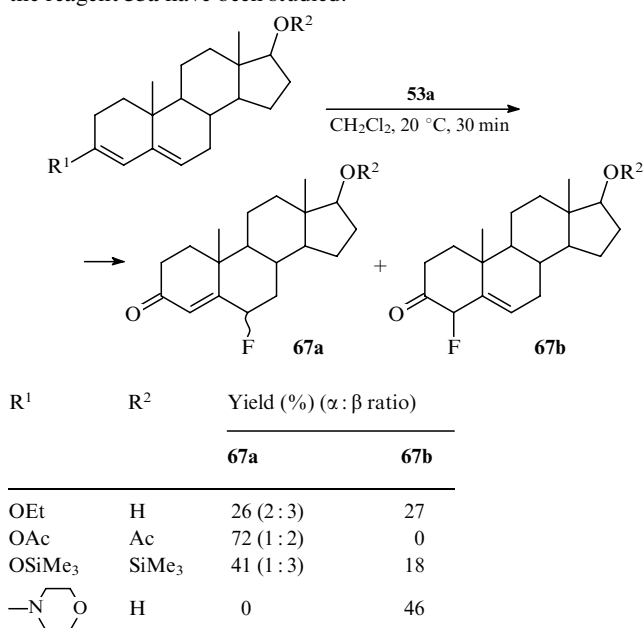


Fluorination of 3,17-diacetoxyandrosta-3,5,16-triene (**63a**) with *N*-fluoropyridinium triflate (**53a**) occurs selectively and yields compound **65** with the fluorine atom in position 6. The corresponding silyl ether **63b** is selectively fluorinated into ring *D* to yield compound **66**.^{100, 117, 152–154}

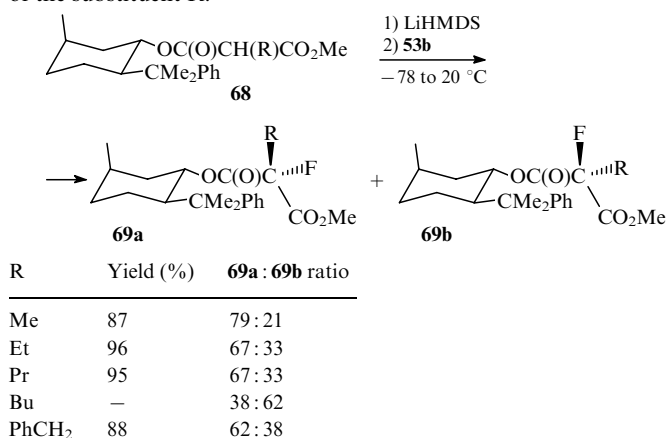


3,17β-Diacetoxyandrosta-3,5-diene is converted into a mixture of 6α- and 6β-fluoro-17-acetoxystosterones (total yield ~ 81%) upon treatment with the reagent **53a** in acetic acid (3 h, 77 °C).¹⁵⁵

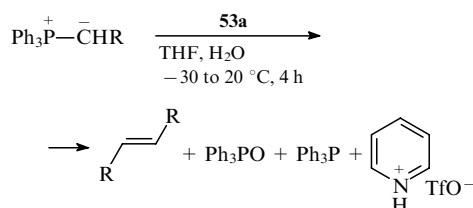
The stereo- and regioselectivity of fluorination of steroids with the reagent **53a** have been studied.^{115, 116, 143}



The reagent **53b** was used for stereoselective introduction of fluorine into the α-position relative to the carbonyl group of compound **68**. The ratio of enantiomers **69a,b** depends on the size of the substituent R.^{154, 155}

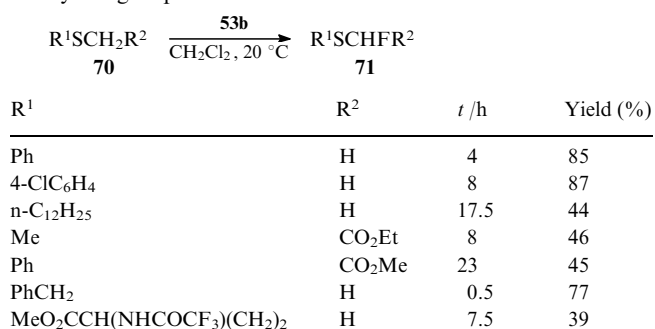


The use of reagents **53a,b** is not confined to fluorination reactions; they can also be used in the synthesis of *trans*-alkenes. Thus treatment of the Wittig reagents with *N*-fluoropyridinium triflate **53a** makes it possible to obtain the corresponding *trans*-alkenes under mild conditions and in acceptable yields.¹⁵⁶

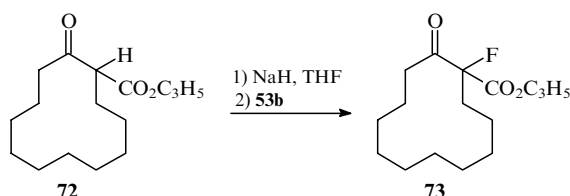


R = COOEt (51%), CPh (50%), COMe (44%), 2-NO₂C₆H₄ (47%), 4-NO₂C₆H₄ (55%), 4-MeOC₆H₄CO (81%), 4-NO₂C₆H₄CO (71%).

The reaction of sulfides **70** with *N*-fluoro-2,4,6-trimethylpyridinium triflate (**53b**) yields sulfides **71** fluorinated at the methylene group.¹⁵⁷

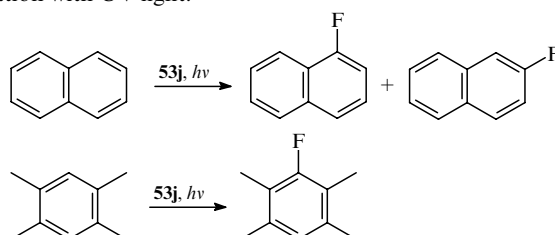


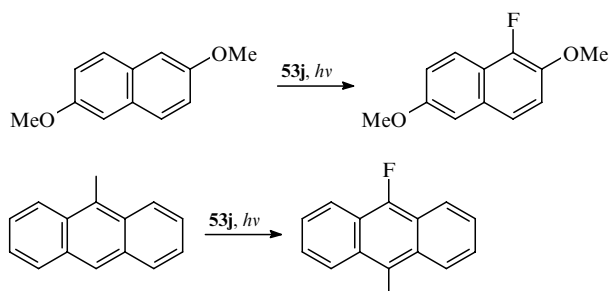
Fluorination of β-oxo acid allyl ester **72** with *N*-fluoro-2,4,6-trimethylpyridinium triflate (**53b**) affords the α-fluoro derivative **73** in 84% yield.¹⁵⁸



N-Fluoro-3,5-dimethylpyridinium triflate (**53c**) and other salts with a substituted pyridine ring fluorinate aromatic compounds. Thus benzene is fluorinated with *N*-fluoro-2,6-dimethoxycarbonylpyridinium triflate to fluorobenzene (yield 56%); *N*-(ethoxycarbonyl)aniline gives a mixture of the corresponding 2- and 4-fluoro derivatives (yields 60% and 27%, respectively). Phenylurethane also yields fluorination products in positions 2 (47%) and 4 (32%) of the aromatic ring. The fluorination of anisole results in a mixture of *o*- and *p*-fluoroanisoles which points to the electrophilic nature of the fluorination reaction.^{129, 132, 158–161} The value of the electrochemical reducing potential ($E_p^c = -0.66$ V) of the *N*-fluoropyridinium cation also indicates that this cation is a strong electrophile.¹⁶²

Bockman *et al.*¹⁶⁰ studied fluorination of aromatic compounds with 3,5-dichloro-*N*-fluoropyridinium triflate **53j** on irradiation with UV light.



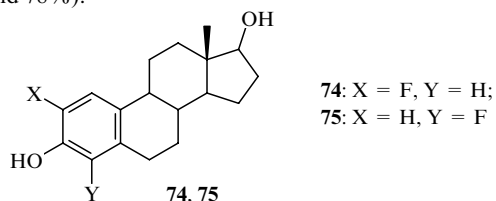


N-Fluoropyridinium sulfonates manifest high selectivity in fluorination of activated aromatic compounds. Thus fluorination of phenol, naphthol, *O*-trimethylsilylphenol and phenylurethane with the reagent **54j** results in the predominant formation of the corresponding *ortho*-isomers: for phenol, the conversion is 88% and the *ortho:para* ratio is 40:1; the *ortho:para* ratio for *O*-trimethylsilylphenol is 34:1; and 1-naphthol gives 63% of 2-fluoro-1-naphthol.^{114, 129}

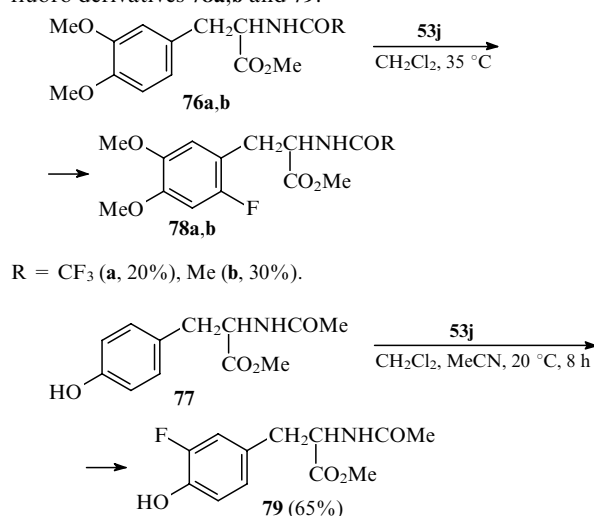
Chloro- and bromophenols as well as *N*-acylhalogenoaniline are fluorinated with *N*-fluoropyridinium salts with high selectivity to give high yields of *ortho*-fluorination products. Thus the reaction of 4-chlorophenol with 2-chloro-6-trichloromethyl-*N*-fluoropyridinium tetrafluoroborate in $\text{ClCH}_2\text{CHCl}_2$ (3 h, 45 °C) gives 4-chloro-2-fluorophenol in 68% yield.¹⁶²

N-Fluoropyridinium triflates^{155, 163, 164} along with acetylhydropyruvate¹⁶⁵ are used for fluorination of biologically active compounds. Thus a mixture of 2-fluoro-17 β -estradiol (**74**) and 4-fluoro-17 β -estradiol (**75**) (total yield 60%) was obtained by fluorination of 17 β -estradiol in CH_2Cl_2 –MeCN (9:1) (12 h, 20 °C) with the reagent **53j**.

Estrol upon fluorination with *N*-fluoropyridinium triflate also yields a mixture of 2- and 4-fluoro derivatives (ratio 2.5:1, total yield 78%).^{155, 164}

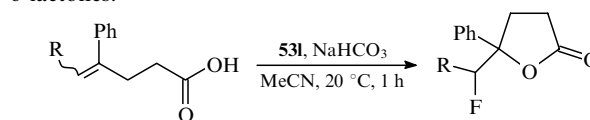


Fluorination of dopamine derivatives **76a,b** and the dopamine analogue **77** with 3,5-dichloro-*N*-fluoropyridinium triflate (**53j**) proceeds under mild conditions and results in the corresponding fluoro derivatives **78a,b** and **79**.¹⁶³



Pentachloro-*N*-fluoropyridinium triflate (**53l**) proved to be efficient in fluorination of unsaturated acids containing a phenyl

substituent in positions 4 or 5 leading to fluorinated γ - and δ -lactones.¹⁶⁶



R	Yield (%)	Diastereomer ratio
H	69	
(<i>Z</i>)-Et	72	2.1:1
(<i>E</i>)-Et	51	1:2.4

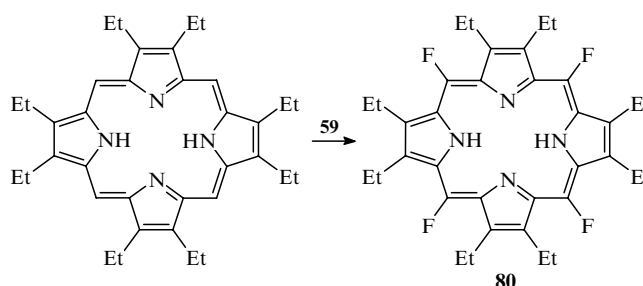
N,N'-Difluoro-2,2'-bipyridinium- (**55b**) and *N,N'*-difluoro-4,4'-bipyridinium triflates (**57a**) react with 2-acetylcyclohexanone in boiling acetonitrile to give 2-acetyl-2-fluorocyclohexanone (yields 85% and 87%, respectively).¹⁶⁷ The reagent **57a** is more efficient in this case.

Treatment with *N*-fluoropyridinium salts was used for electrophilic fluorination of azulene and its derivatives.¹⁶⁸ Relatively low yields of fluorination products (14%–40%) are due to side reactions. In addition, a prominent role is played by the solvent. For example, the reaction of azulene with *N*-fluoro-4-methylpyridinium triflate **53b** in acetonitrile or CH_2Cl_2 gives a mixture of mono- (yields 12% and 3%, respectively) and difluoro derivatives (yields 17% and 5%, respectively). In dichloroethane, the yield of the monofluoro derivative is increased to 24%.¹⁶⁸

The heptafluoroborate of the *N*-fluoropyridinium pyridine complex (**59**) proved to be an excellent fluorinating reagent in the synthesis of monofluoro derivatives of various classes (Table 15).¹¹⁵ The reagent **59** is highly selective; the reactions occur under mild conditions.^{129, 136–140, 145}

More complex compounds can also be subject to selective fluorination without oxidation and decomposition. Highly selective *meso*-fluorination of porphyrins is effected with 2,6-dichloro-*N*-fluoro-pyridinium, 3,5-dichloro-*N*-fluoropyridinium and pentachloro-*N*-fluoropyridinium triflates.¹⁵³ This reaction is carried out in acetonitrile or hexafluorobenzene as solvents and K_2CO_3 or SrCO_3 as bases. The yield of the fluorinated product is low. For example, the tetrafluoro derivative **80** is obtained in 20% yield on boiling of octaethylporphyrin for 2 days in hexafluorobenzene.¹⁵³

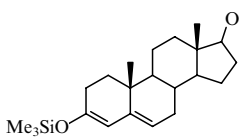
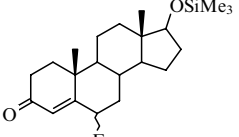
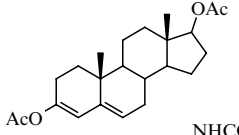
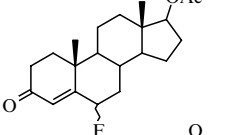
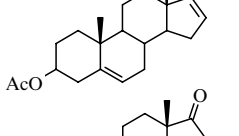
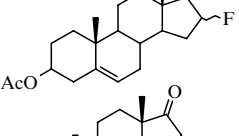
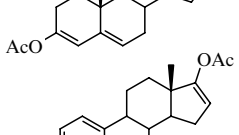
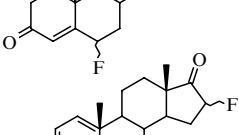
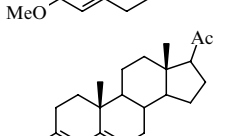
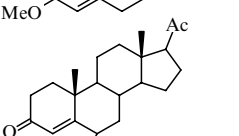
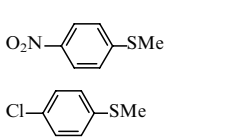
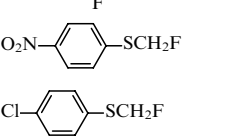
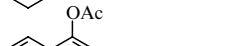
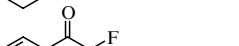
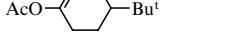
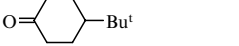
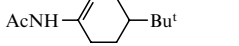
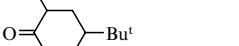
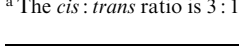
Salts of *N*-fluoropyridinium and its derivatives have obvious advantages over other fluorinating reagents. They are stable, transportable and fit for long-term storage without any deterioration of their properties; besides, they are explosion-proof and non-toxic. The fluorination is performed under mild conditions and is not accompanied by side reactions, which is especially important for steroids, sugars and other biologically active compounds.



2. *N*-Fluoroquinuclidinium and 4-alkyl-1-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts

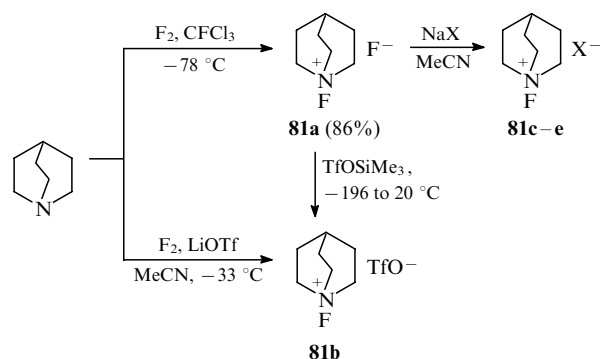
Like *N*-fluoropyridinium salts, *N*-fluoroquinuclidinium salts belong to the most efficient fluorinating reagents of the *N*-fluoroamine series. The main method for their synthesis is direct fluorination of the corresponding NH-precursors.^{132, 169–176} *N*-

Table 15. Fluorination with the complex *N*-fluoropyridinium–pyridine (**59**) heptafluorodiborate in MeCN.¹¹⁵

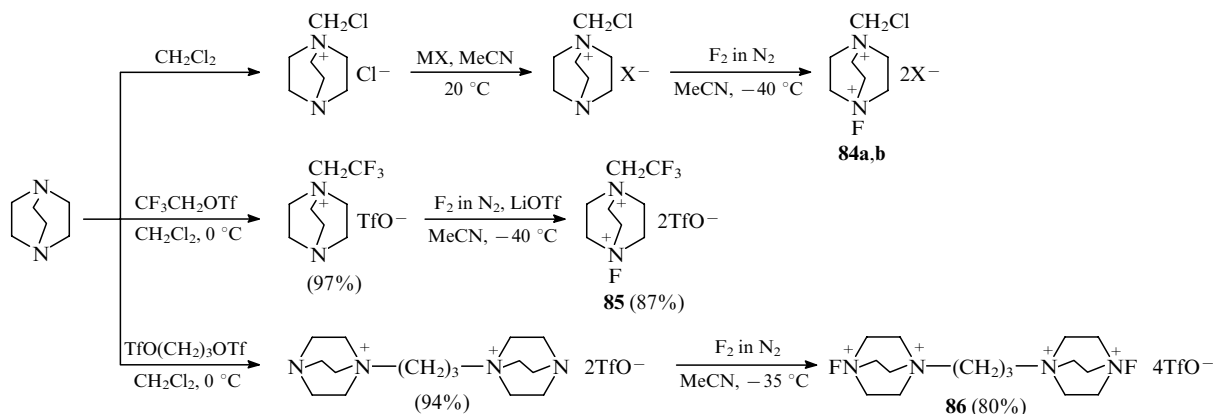
Substrate	<i>T</i> /°C	<i>t</i> /h	Reaction product	Yield (%)
	25	18		88
	80	5		57
	40	48		96
	25	120		82
	25	72		69
	80	18		38
	25	120		82
	40	72		68
	80	10		23
	40	96		60
	80	5		39
	40	72		99
	80	6		87
	40	72		46
	80	36		36
	25	18		45
	25	18		26
	0	1		37
	80	18		61
	80	18		62 ^a
	25	48		93 ^b

^a The *cis*:*trans* ratio is 3:1. ^b The *cis*:*trans* ratio is 4:1.

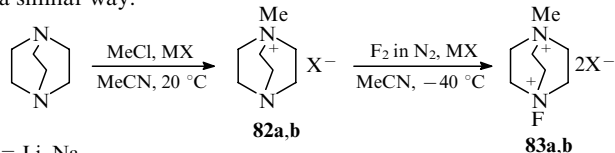
Fluoroquinuclidinium fluoride (**81a**) was obtained in 83%–89% yield by direct fluorination of quinuclidine with 10% F₂ in CFCl₃ at –78 °C.^{169, 171, 175, 176} Later, preparation of *N*-fluoroquinuclidinium salts with other counterions was performed by fluorination of quinuclidine in the presence of the corresponding salts (the Umemoto method). With LiOTf, *N*-fluoroquinuclidinium triflate (**81b**) was obtained in 88% yield (fluorination in MeCN at –33 °C). The salts **81a,b** are non-hygroscopic compounds soluble in water and polar organic solvents;¹⁷ they are non-explosive and convenient for experimenting in glassware. The synthetic procedure is simple and gives high yields of target products.

X = BF₄ (**c**, 63%), CF₃CO₂ (**d**, 72%), n-C₃F₇CO₂ (**e**, 47%).

Scheme 1



The fluorination of 1-alkyl-1-azonia-4-azabicyclo[2.2.2]octane salts with elemental fluorine in the presence of alkali metal salts gives 4-alkyl-1-fluoro-1,4-diazabicyclo[2.2.2]octanes. Thus treatment of a mixture of 1-methyl-1-azonia-4-azabicyclo[2.2.2]octane (**82a**) and lithium triflate with elemental fluorine in acetonitrile (3 h, -35 °C) leads to 1-fluoro-4-methyl-1,4-diazabicyclo[2.2.2]octane triflate (**83a**) in 88%–94% yield.^{167, 176–182} The tetrafluoroborate **83b** is prepared in a similar way.

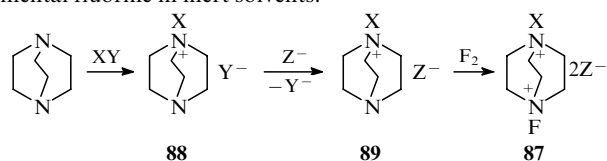


X	Compounds 82 , 83	Yield of 82 (%)	Yield of 83 (%)
TfO	a	86	84
BF ₄	b	98	94

1,4-Diazabicyclo[2.2.2]octane *N*-oxide can also be used as a starting compound. Its reaction with elemental fluorine in acetonitrile in the presence of BF₃·Et₂O or HBF₄ at 0 °C results in 75% of *N*-hydroxy-1-azonia-4-azabicyclo[2.2.2]octane tetrafluoroborate.¹⁸³

The *N*-fluoro derivatives **84a,b** and **85** containing one fluorine atom and the bisfluoro derivative **86** have been synthesised in which two bicyclic fragments are linked through a trimethylene bridge (Scheme 1).^{182–187} The structure of some of these salts has been confirmed by X-ray diffraction analysis. Thus the length of the N–F bond in compounds **84a** and **84b** is 1.406 and 1.37(2) Å, respectively.¹⁸⁵

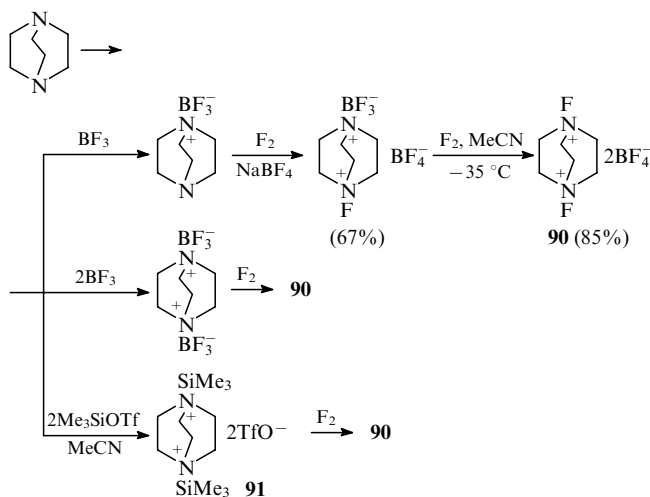
Preparation of 1-fluoro-1,4-diazabicyclo[2.2.2]octanes **87** containing various functional groups at the second nitrogen atom involved treatment of 1,4-diazabicyclo[2.2.2]octane with reagents XY containing the corresponding functional group X and a good leaving group Y. In intermediates **88**, the anion Z is substituted for the leaving group Y. Then the salts **89** are fluorinated with elemental fluorine in inert solvents.^{183, 188}



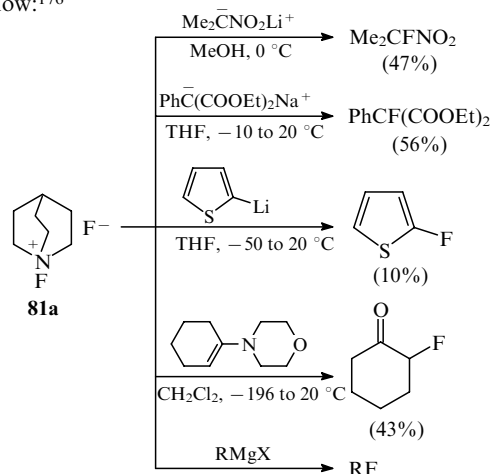
X = OH, OR, OCOR, SO₃, SO₂R, NO₂, NO, P(O)(OR)₂;
Z = FSO₃, BF₄, PF₆, ClO₄, R₃SO₃.

The attempts to synthesise 1,4-difluoro-1,4-diazabicyclo[2.2.2]octane salts have long been unsuccessful. The synthesis of the reagent **90** could be carried out by fluorination of 1,4-diazabicyclo[2.2.2]octane with elemental fluorine in acetonitrile in

the presence of BF₃ and PF₅ or in acetone in the presence of BF₃.¹⁶⁹ Later, polyfluorinated alcohols [e.g., (CF₃)₂CHOH] and sulfuric acid were used as fluorination media (yield > 80%). Yet another convenient approach to the synthesis of the reagent **90** is the fluorination of the trimethylsilyl derivative **91**.^{179, 180, 182, 187}

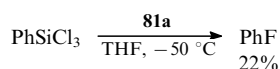


Reagents of the type **81** efficiently fluorinate carbanions, the Grignard reagents and aromatic compounds.^{17, 166, 169, 175, 181, 182, 188–191} Some examples of fluorination of organic compounds with the reagent **81a** are given below:¹⁷⁶

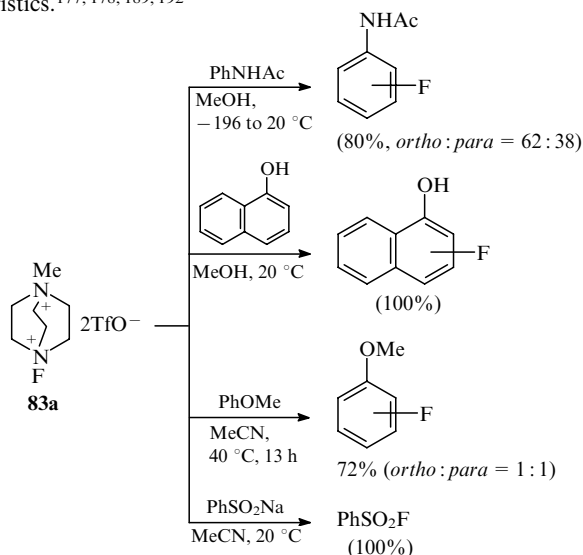


R = Ph, X = Br (26%); R = cyclo-C₆H₁₁, X = Cl (20%).

Fluorobenzene is formed in 22% yield upon reaction of the reagent **81a** with phenyltrichlorosilane.¹⁶⁹



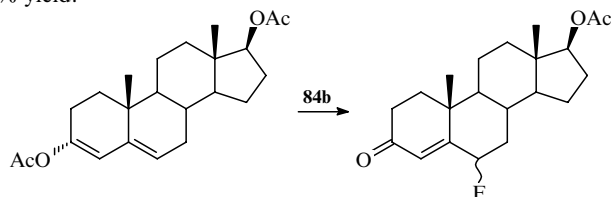
Such popular reagents as 1-fluoro-4-methyl-1,4-diazoniabicyclo[2.2.2]octane bistriflate (**83a**) and 4-chloro-1-fluoro-methyl-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate (**84b**) (commercial names, F-TedaBF₄ or SelectfluorTM) possess excellent fluorinating properties and physicochemical characteristics.^{177, 178, 189, 192}



The reagents **83a,b** and **84b** are highly efficient reagents for introducing fluorine into steroids, aromatic compounds, CH-acids and sulfides containing α -hydrogen atoms. These reactions occur under mild conditions and give high yields of fluorination products.^{132, 177, 178}

As a rule, fluorination of oxo steroids is performed using acetates or trimethylsilyl derivatives of the corresponding enols as substrates.^{192, 193} The yields and regioselectivity can be rather high. Fluorination of hydrocortisone, prednisolone and other oxo steroids with the reagent **84b** gives 6- or 16-monofluoro derivatives under extremely mild conditions.¹³²

Reaction of 3,17 β -diacetoxyandrost-3,5-diene with the reagent **84b** in a mixture of acetic acid and 1,2-dichloroethane (3 h, 77 °C) yields a mixture of 6 α - and 6 β -fluoro derivatives in 81% yield.



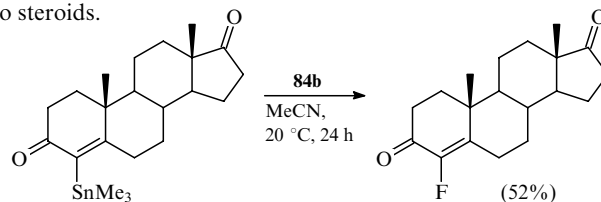
The advantages of the reagents **84b** over other fluorinating reagents are illustrated in Table 16.

Fluorination of Δ^4 - and $\Delta^{1,4}$ -3-oxo steroids with the reagent **84b** normally gives a mixture of 4- and 6-fluoro derivatives. The presence of a trimethylstannyl group at the multiple bond of the

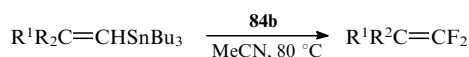
Table 16. Fluorination of 3,17 β -diacetoxyandrost-3,5-diene.

Reagent	<i>T</i> / °C	<i>t</i> / h	Yield (%)	The α : β ratio
FCIO ₃	20	1	58	1 : 3
CF ₃ OF	−70		38	1 : 3
CF ₃ C(O)ONa, F ₂	−78	0.25	70	3 : 5
MeC(O)OF	−78	0.25	61	1 : 2
53a	40	10	71	1 : 2
84b	20	0.15	95	2 : 3

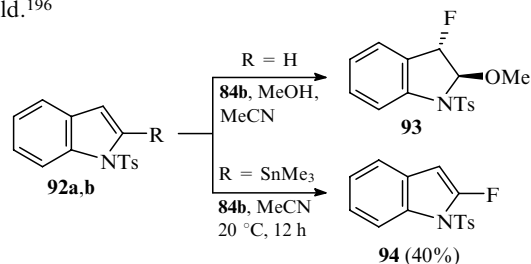
steroid allows the introduction of fluorine atoms under mild conditions and in a more selective manner. The yields of 4-fluoroandrost-4-ene-3,17-dione and 17-*O*-benzoyl-4-fluorotestosterone prepared by this method are about 50% and the results obtained are not much lower than those obtained with cesium fluoroxysulfate¹⁹⁴ which is potentially explosive.¹⁹⁵ Fluorination with the reagent **84b** can be used for introducing the isotope ¹⁸F into steroids.



Fluorodestannylation with reagent **84b** is rather widely used in stereospecific syntheses of complex fluoroalkenes.¹⁸⁴



Fluorination of 1-tosylindole **92a** with the reagent **84b** in MeCN–MeOH leads to 3-fluoro-2-methoxy-1-tosyl-2,3-dihydroindole **93** in 48% yield.¹⁹⁶ The *trans*-arrangement of the substituents in the reaction product has been confirmed by X-ray diffraction analysis. In this case, the reaction occurs as conjugated vicinal fluoromethoxylation. The substitution of fluorine for the trimethylstannyl group in the derivative **92b** occurs under the action of reagent **84b** in acetonitrile to give compound **94** in 21% yield.¹⁹⁶

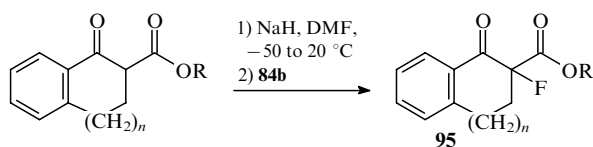


R = H (a), Me₃Sn (b).

Some other reactions of this kind are documented.^{41, 177, 178, 197, 198}

The fluorination of ethyl 1-indanone-2-carboxylate and methyl 5,7-difluoro-1-indanone-2-carboxylate with the reagent **84b** leads to ethyl 2-fluoro-1-indanone-2-carboxylate (yield 80%) and methyl 2,5,7-trifluoro-1-indanone-2-carboxylate (yield 83%).¹⁹²

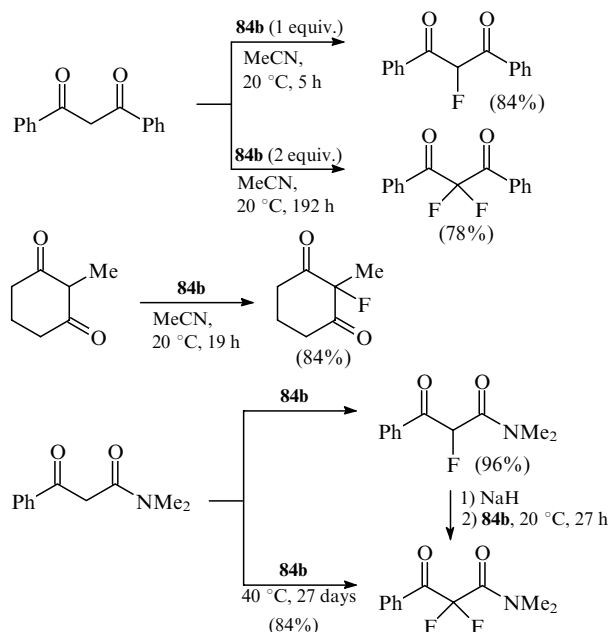
The fluorination of methyl and menthyl 1-tetralone-2-carboxylates and 1-indanone-2-carboxylates with the reagent **84b** affords the corresponding α -fluoro esters **95** in high yields.¹⁹⁹



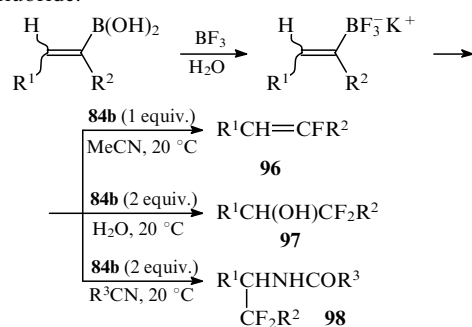
n = 0, 1; R = Me, menthyl.

The oxidation of hydroxy compounds was studied in order to determine the activity of fluorine in the fluorinating reagents **17**, **59** and **84b**. It was found²⁰⁰ that the reagent **84b** quantitatively oxidises hydroquinone to *p*-benzoquinone (2 h, 25 °C). The yield of *p*-benzoquinone upon treatment with the reagent **17** is low (30%), whereas the reagent **59** does not react with hydroquinone under these conditions.

Treatment of acyclic and cyclic 1,3-diketones, β -oxo esters and β -oxo amides with the reagent **84b** results in the corresponding mono- and difluoro compounds.^{189, 190} Selective fluorination of β -dicarbonyl compounds with the reagent **84b** is used to obtain biologically active compounds.¹⁸⁸

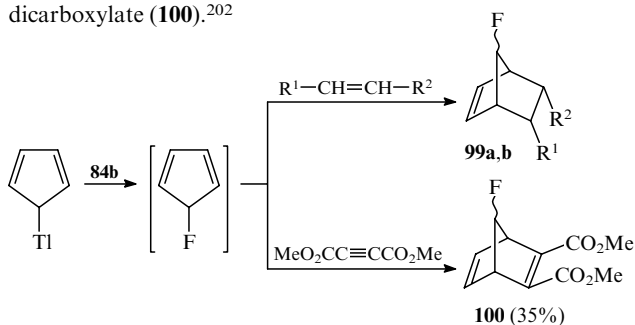


Petasis *et al.*²⁰¹ have developed a new procedure for the synthesis of alkenyl fluorides **96**, substituted alcohols **97** and difluoroalkylamides **98**, which is based on fluorination of alkenylboric acids with the reagent **84b** in the presence of boron trifluoride.



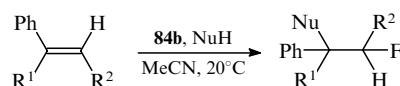
R^1	R^2	Yield of 96 (%)	<i>E</i> : <i>Z</i> ratio	Yield of 97 (%)	R^3	Yield of 98 (%)
Ph	H	89	1:1	69	Me	82
					Et	62
4-MeC ₆ H ₄	H	87	1:1	71	Me	68
Ph	Ph	71	5.8:1	58	Me	77
Bu	H	58	1:1			
4-ClC ₆ H ₄	H			67	Me	81
Ph	Me			75		

The reaction of the tetrafluoroborate **84b** with cyclopentadienylthallium affords 5-fluorocyclopentadiene, which was not isolated but its formation was confirmed by identification of cycloaddition products to acrylates **99a,b** and dimethyl acetylenedicarboxylate (**100**).²⁰²



$\text{R}^1 = \text{Cl}$, $\text{R}^2 = \text{CN}$ (**a**, 18%); $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{CO}_2\text{Me}$ (**b**, 17%).

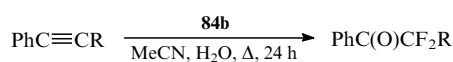
Fluorination of unsaturated compounds with the reagent **84b** occurs in accordance with the Markownikoff rule. The reaction begins with the addition of the pseudo-positive fluorine to the multiple bond and generation of an intermediate carbocation. Its outcome depends on the presence of other nucleophiles in the system. Thus the tetrafluoroborate **84b** reacts with styrene, α -methylstyrene and stilbene in MeCN in the presence of H_2O , AcOH and MeOH, which are involved into the reaction.^{7, 203, 204}



R^1	R^2	Nu	Yield (%) (<i>erythro</i> : <i>threo</i> ratio)
H	H	OH	48
Me	H	OMe	98
Me	H	OH	89
Me	H	OAc	65
Me	H	F	66
H	Ph	OMe	75 (72:28)
H	Ph	OH	86 (69:31)
H	Ph	OAc	77 (60:40)
H	Ph	F	65 (66:34)

As can be seen from the data of Table 17, the rate of methoxyfluorination of substituted alkenes increases with a decrease in their ionisation potential which is in favour of the ionic mechanism of the reaction.

In the fluorination of phenylacetylenes with the tetrafluoroborate **84b** in aqueous acetonitrile, the addition of fluorine to the triple bond is accompanied by the addition of water. This reaction occurs with high regioselectivity and yields α,α -difluoroketones. It was shown that the nature of the alkyl substituent in phenylacetylenes influences only the fluorination rate without any effect on the yield of the final products.^{197, 198, 205}



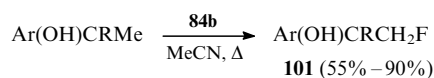
R	k_{rel}	Yield (%)
H	< 0.01	36
Me	1	51
Bu ^t	0.63	48
Ph	0.56	51

The reagent **84b** was also used for fluorination of tertiary alcohols. In this case, substitution of fluorine for the hydrogen atom of the methyl group occurs to give β -fluoroalkanols **101**.

Table 17. Relative rates of methoxyfluorination of some alkenes with the reagent **84b** in MeCN.²⁰³

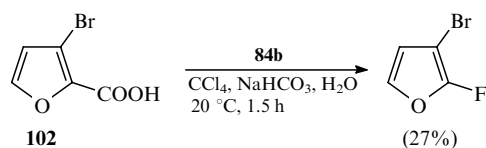
Alkene	k^a	<i>IP</i> /eV
2-Phenylprop-1-ene	0.64	8.40
<i>trans</i> -1-Phenylprop-1-ene	0.54	8.36
1,1-Diphenylethylene	1.00	8.24
1,1-Diphenylpropene	8.60	8.14
Indene	0.47	8.40
1,2-Dihydronaphthalene	0.63	8.26
1-Phenylcycloheptene	29.0	7.92
3-Phenyl-1 <i>H</i> -indene	27.8	7.73
1,2-Dihydro-4-phenylnaphthalene	32.2	7.67
1-Phenyl-6,7-benzocyclohept-1-ene	11.3	7.91

^a Hereinafter k is the relative reaction rate constant with respect to that of 1,1-diphenylethylene.

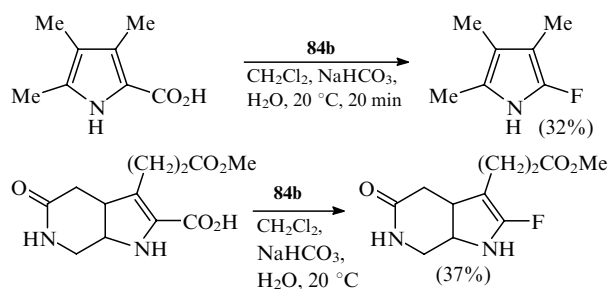


R = Me, Ar'.

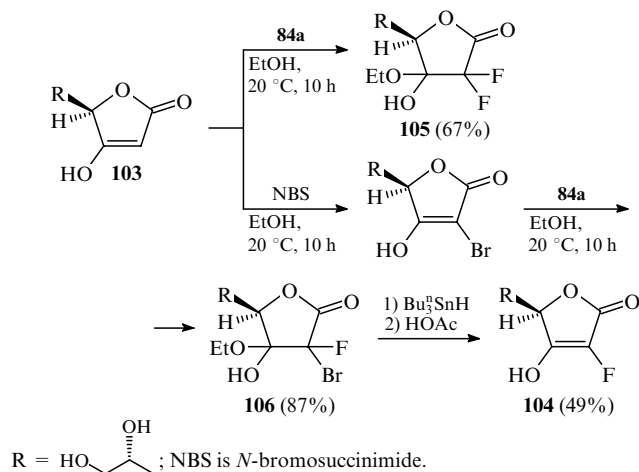
Reaction of the reagent **84b** with some carboxylic acids can occur as fluorodecarboxylation. The possibility of synthesis of fluoro derivatives from the corresponding carboxylic acids is especially important in the furan and pyrrole series. Until very recently, fluorinated furans and pyrroles were not considered to be readily accessible compounds, although they have always attracted attention as starting compounds for the synthesis of fluorinated analogues of natural bactericides. In this particular case, fluorinated reagents with the N–F bond proved to be more efficient than other reagents, in the first place, the elemental fluorine. For example, the reaction of 3-bromofuran-2-carboxylic acid (**102**) with the reagent **84a** in a biphasic system aqueous CCl_4 – NaHCO_3 yields 3-bromo-2-fluorofuran.²⁰⁶



Pyrrole-2-carboxylic acids containing electron-donor substituents give the corresponding 2-fluoropyrroles upon treatment with the reagent **84b** (yields 32%–47%).

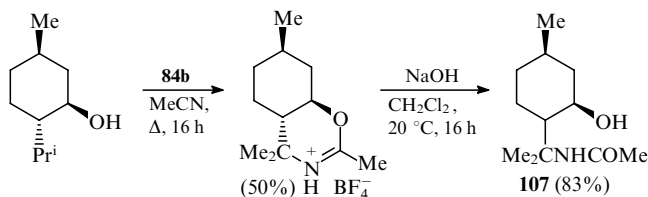


Tetronic acid derivatives attract attention in connection with the presence of its fragment in some natural biologically active compounds. Direct fluorination of 2-deoxy-L-ascorbic acid (**103**) with the reagent **84b** afforded only traces of the 2-fluoro derivative **104**.^{207, 208} When the reaction is performed in ethanol, a product of fluorine and the ethoxy group addition to the double bond (compound **105**) is formed. Compound **104** could only be obtained by treatment of the bromofluoro derivative **106** with tributyl-tin hydride (yield 49%).

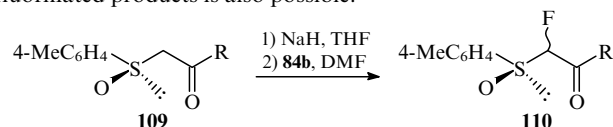


In the reaction of (–)-menthol with the reagent **84b** in acetonitrile, the hydrogen atom at the tertiary exocyclic carbon atom is selectively substituted by fluorine. Presumably, the further

course of this reaction involves the substitution of the fluorine atom with participation of the solvent. Subsequent saponification leads to the reaction product **107**.²⁰⁹

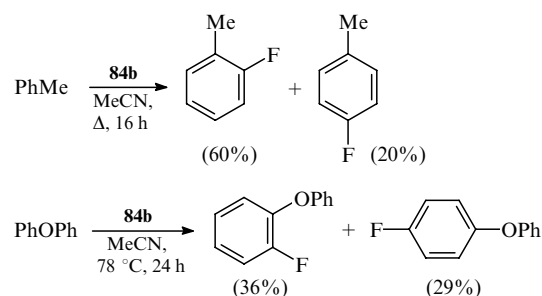


Fluorination of chiral β-oxo sulfoxides **109** with the compound **84b** resulted in a mixture of diastereoisomeric α-mono-fluoro chiral compounds **110**.²¹⁰ The formation of α,α-difluorinated products is also possible.



R	Me	Ph	2-pyridyl	4-pyridyl	CH ₂ F	CHF ₂	CF=CHPh
Conversion (%)	60	48	84	73	90	70	87
Yield (%)	80	23	82	52	23	19	70

Benzene derivatives containing electron-donor substituents are fluorinated with the reagent **84b**.^{7, 147, 188, 198, 199} The fact that fluorine occupies the *ortho*- or *para*-position testifies to the electrophilic nature of the reagent.

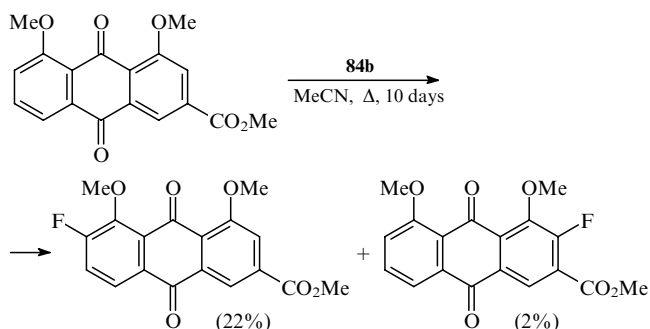


Fluorination with the reagent **84b** can be accompanied by oxidation of functional groups. For example, substituted benzyl alcohols and aromatic aldehydes give the corresponding benzaldehydes or benzoic acids.²¹¹

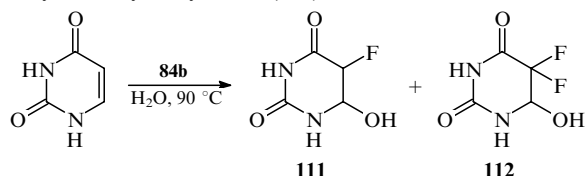
Polycyclic aromatic compounds (biphenyl, naphthalene, anthracene, phenanthrene) and their derivatives give monofluoro derivatives.^{174, 198} The fluorination of azulene and its derivatives with the reagent **84b** affords a mixture of mono- and difluoro derivatives.²¹²

R	Yield of the monofluoro derivative (%)	Yield of the difluoro derivative (%)
H	34	3
6-Pr ⁱ	27	8
4,6,8-Me ₃	12	2

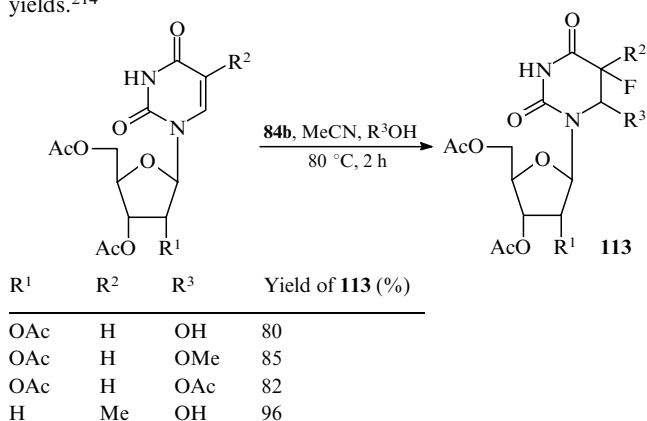
Regioselective fluorination of anthraquinone derivatives with the reagent **84b** presents interest for the synthesis of biologically active compounds.²¹³



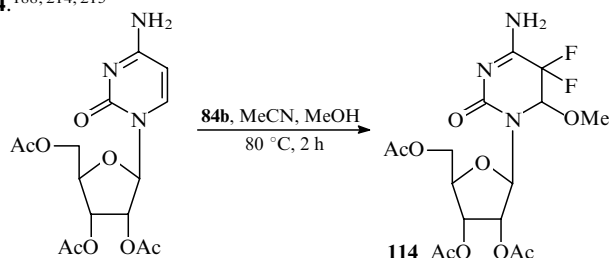
Reactions of the reagent **84b** with uracil, thymidine and nucleosides in the presence of an external nucleophile occur as conjugated addition. Thus 5-fluoro- (**111**) and 5,5-difluoro-6-hydroxy-5,6-dihydroxyuracils (**112**) were obtained from uracil.²¹⁴



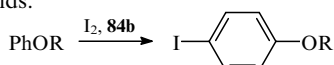
Uracil and thymidine derivatives give compounds **113** in high yields.²¹⁴



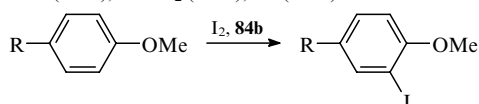
2',3',5'-Tri-*O*-acetylcytidine is fluorinated in MeCN in the presence of methanol to give the difluoromethoxy derivative **114**.^{188, 214, 215}



The reagent **84b** is used in iodination of aromatic compounds.²¹⁶ Thus treatment of alkylphenyl ethers and *para*-substituted anisoles with iodine in the presence of an equimolar amount of the reagent **84b** affords monoiodo derivatives in high yields.

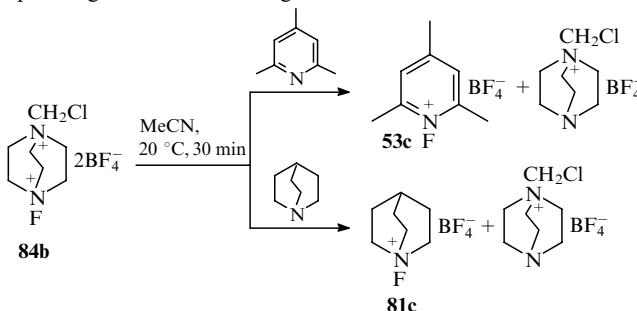


R = Me (89%), PhCH₂ (90%), Ph (80%).



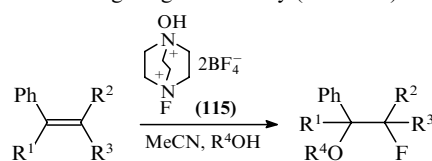
R = F (87%), Cl (89%), Br (91%), I (88%), Ac (90%), CHO (85%), Bu^t (92%).

N-Fluoroquinuclidinium (**81c**), *N*-fluoropyridinium (**53a**) and *N*-fluoro-2,4,6-trimethylpyridinium (**53c**) tetrafluoroborates were obtained in sufficiently high yields by fluorination of the corresponding bases with the reagent **84b**.²¹⁷



Properties of 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate (**115**) (commercial names, NFTh and AccufluorTM) are similar to those of the reagent **84b**. This compound fluorinates the same substrates in high yields and with high stereoselectivity. The reagent **115** can be obtained by fluorination of 1,4-diazabicyclo[2.2.2]octane *N*-oxide with elemental fluorine in acetonitrile at 8 °C in the presence of BF₃·Et₂O and HBF₄ (yield 75%).^{183, 218} This fluorinates naphthalene to 1-fluoronaphthalene, phenanthrene to 9-fluorophenanthrene and pyrene to 1-fluoropyrene²¹⁹ but is less stable. It was shown^{206, 220} that the stability of fluorinating reagents in water, acetonitrile, alcohols and aqueous alkali decreases in the following order: **17** > **84b** > **115**.

Fluorination of unsaturated compounds with the reagent **115** in the presence of alcohols occurs as the conjugated vicinal fluoroalkoxylation; the formation of monofluoro derivatives occurs with high regioselectivity (Table 18).²²¹



Treatment of alkenes with the reagent **115** in acetonitrile results in the corresponding fluorinated amides.²²²

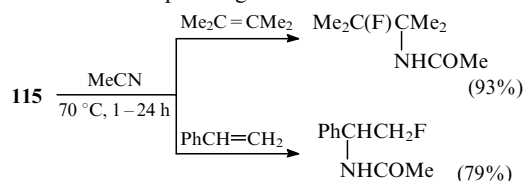


Table 18. Fluorination of substituted styrenes with the reagent **115**.²²¹

R ¹	R ²	R ³	R ⁴	T / °C	t / min	Yield (%)	k
H	H	H	H	80	60	90	< 0.001
			Me	80	60	92	
Me	H	H	H	35	60	93	0.89
			Me	35	60	93	
			Ac	35	60	90	
Ph	H	H	H	35	30	95	1.00
			Me	35	30	95	
			Ac	35	30	93	
Ph	Ph	H	H	35	30	98	2.5
			Me	35	30	97	
			Ac	35	30	95	
Ph	Ph	Ph	H	80	60	96	0.24
			Me	80	60	96	

Table 19. The stereochemistry of methoxyfluorination of cyclic alkenes with the reagent **115**.²²¹

Alkene	<i>T</i> / °C	<i>t</i> / min	Yield (%)	The <i>syn</i> : <i>anti</i> ratio
	35	60	92	60 : 40
	35	10	89	53 : 47
	22	5	96	73 : 27
	35	5	96	59 : 41
	35	30	95	25 : 75
	80	45	95	25 : 75
	22	5	97	40 : 60
	35	10	96	1 : 100

The stereochemical features of fluoroalkoxylation were studied with cyclic compounds containing a multiple bond as examples (Table 19).²²¹

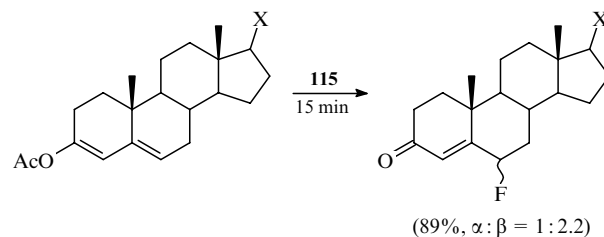
The bistetrafluoroborate **115** is a highly efficient regioselective reagent for the fluorination of ketones (Table 20).²²³

Treatment of *N*-acetylaniline with the reagent **115** leads to a mixture of *o*- and *p*-fluoro-*N*-acetylanilines (67 : 33); 4-*tert*-butyl-1-trimethylsilyloxycyclohexene gives a mixture of *cis*- and *trans*-4-*tert*-butyl-2-fluorocyclohexanones (10 : 1), while anisole in acetonitrile at 20 °C gives a mixture of *o*- and *p*-fluoroanisoles (1 : 2.4) (total yield 83%). Some steroids give monofluoro derivatives under extremely mild conditions.^{224–226}

Table 20. Direct fluorination of ketones with the reagent **115**.²²³

Substrate	<i>t</i> / h ^a	Product	Yield (%) ^b
	<i>n</i> = 1		80 (70)
	<i>n</i> = 2		92 (84)
	<i>n</i> = 3		85 (78)
	<i>n</i> = 4		85 (78)
	<i>n</i> = 1		88 (80)
	<i>n</i> = 2		81 (75)
	8		82 (72)
	<i>n</i> = 1		95 (88)
	<i>n</i> = 2		95 (88)
	<i>n</i> = 3		90 (82)
	2		85
Bu ⁿ CO	12	Bu ⁿ COCHFPr ⁿ	91 (81)
C ₆ H ₁₃ COMe	10	C ₅ H ₁₁ CHFCOMe	86 (78)
PhCOMe	48	PhCOCH ₂ F	33 (23)
PhCOCH ₂ Me	30	PhCOCHFMe	88 (80)
PhCOCHMe ₂	12	PhCOCFMe ₂	83 (74)

^a Reaction conditions: 2 mmol of ketone, 2.2 mmol of the reagent **115** in MeCN (30 ml), 80 °C. ^b The yield was calculated from the ¹⁹F NMR spectroscopy data for a mixture of reaction products prior to workup. The isolated yields are given in parentheses.



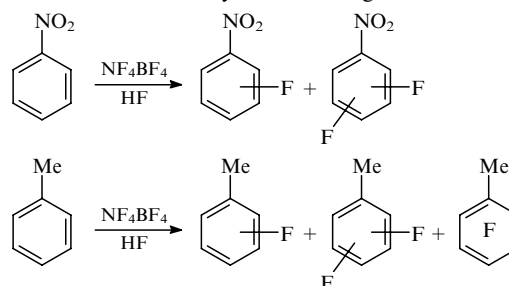
X = COCH₂OAc.

The reactivities of the fluorinating reagents **84b**, **115** and *N*-fluoro-2,6-difluoropyridinium tetrafluoroborate in the fluorination of dibenzofuran, diphenyl ether and biphenyl were found to be similar. *ortho*-Isomers are predominant in the reaction products.¹⁷⁴

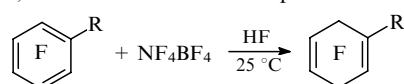
IV. Some examples of fluorination with inorganic tetrafluoroammonium salts

Inorganic tetrafluoroammonium salts (*e.g.*, NF₄BF₄, NF₄SbF₆) are formal analogues of organic *N*-fluoro derivatives.

Christe *et al.*^{227,228} showed that NF₄BF₄ fluorinates benzene and its derivatives in anhydrous HF to give fluorinated products.

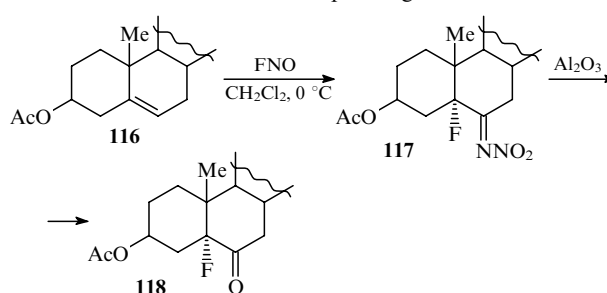


The fluorination of nitrobenzene results in substitution of both the hydrogen atoms of the benzene ring (the predominant formation of the *meta*-isomer testifies to electrophilic substitution) and the nitro group, resulting in fluorobenzene. The reaction of tetrafluorobenzene, pentafluorobenzene and hexafluorobenzene with NF₄BF₄ gives perfluorocyclohexadienes, *i.e.*, in this case, fluorine adds to the multiple bonds.^{227–229}

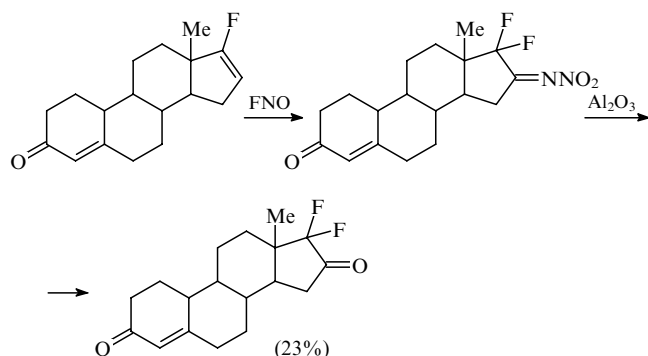


R = H, F.

Among inorganic fluorinating reagents, nitrosyl fluoride is worthy of note. This compound is a low-boiling highly toxic gas, and its application as a fluorinating reagent is very limited. Nitrosyl fluoride was used for fluorination of cholesteryl acetate **116** to give 5 α -fluoro-6-nitroimine **117** in high yield. The latter was further converted into the corresponding ketone **118**.²³⁰



Fluorination of steroidal vinyl fluorides with nitrosyl fluoride leads to α,α -difluoro ketones *via* the intermediate nitroimines.^{231,232}

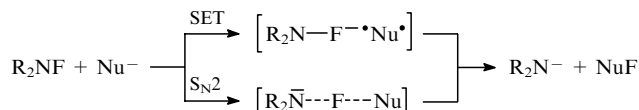


Prakash *et al.*^{233, 234} proposed to use the Olah reagent (hydrogen fluoride in pyridine) for the activation of nitrosyl fluoride. This results in a highly active fluorinating reagent which fluorinates many organic compounds. Thus the fluorination of ketoximes and thioacetals affords the corresponding *gem*-difluoro derivatives, while alkynes and alkenes are fluorinated to tetrafluoro- and trifluoroalkanes in sufficiently high yields. Interestingly, fullerene C₆₀ is polyfluorinated with nitrosyl fluoride. Treatment of alkyl phenyl sulfides with this reagent affords products of substitution of the hydrogen atoms of the alkyl group by fluorine atoms.^{233, 234}

V. On the mechanism of fluorination with *N*-fluoroamines and their analogues

The experimental data concerning the use of *N*-fluoroamines and their analogues in organic synthesis altogether suggest that these compounds are electrophilic fluorinating agents. Inasmuch as the formation of F⁺ is a thermodynamically very unfavourable process and this species is very unstable and can be detected only by spectral methods in the gas phase, the formation of F⁺ in fluorination is hardly probable.^{132, 184} This contradiction has led to an idea of specific polarisation of the N–F bond with the appearance of a partial positive charge on the fluorine atom, *i.e.*, the concept of ‘pseudo-positive’ fluorine. However, the idea that *N*-fluorinating reagents are the sources of ‘pseudo-positive’ or ‘electrophilic’ fluorine does not contribute any rationale to the real mechanism of fluorination. However, *N*-fluoro reagents can also be regarded as sources of the fluorine radical the existence of which is established (see Ref. 175). The oxidising properties of *N*-fluorinating reagents, particularly their ability to displace iodine from inorganic iodides (this reaction is of analytical importance) is attributed to the electrophilic nature of the fluorine radical.

As a matter of fact, the mechanistic studies of fluorination available are aimed at establishing whether this occurs as single-electron transfer (SET), nucleophilic substitution at the fluorine atom (S_N2) or both.



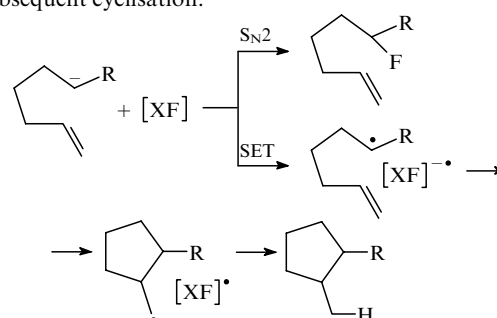
In considering the mechanism of fluorination, one should take into account that *N*-fluorinating reagents comprise two groups of compounds, which differ basically in their structures, *viz.*, R₂NF and [R₃NF]⁺A[−]. In addition, the role of nucleophiles can be played by compounds of various classes (*e.g.*, aromatic, unsaturated, organometallic, *etc.*), whereas the term ‘fluorination’ embraces various types of reactions (substitution, addition, *etc.*).

Hence, all the plausible mechanisms of fluorination can in general be realised. The mechanism established in a specific study may be true only for the particular group of *N*-fluorinating reagents and substrates and for the particular reaction types that had been studied.

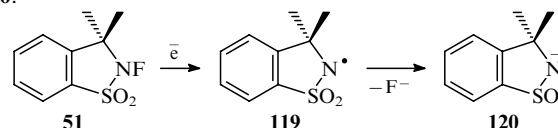
Differding *et al.*^{106, 108, 235, 236} who studied the fluorination of various substrates with *N*-fluoro sultam **51** attempted to distinguish between S_N2 and SET mechanisms. To this end, they compared experimental rate constants with those calculated theoretically within the single-electron transfer theory. These calculations were based on the known standard redox potentials, *E*^o, and Marcus rearrangement energies for both reactants.

As can be seen from Table 10, the values of experimental constants are by many orders of magnitude higher than might be expected based on the electron transfer concept, *i.e.*, the reaction does not occur as a single-electron transfer. Correspondingly, the S_N2 mechanism is realised in this case.

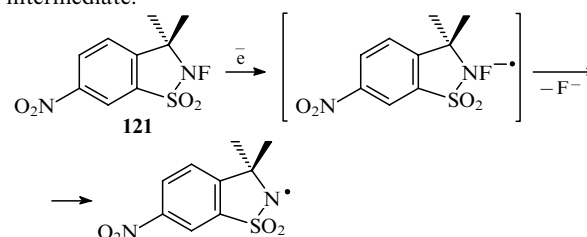
The reaction of an ester enolate (derived from citronellate) with *N*-fluoro reagents leads exclusively to the products of electrophilic fluorination at the carbon atom of the carbanion centre. This finding provides additional support in favour of the S_N2 mechanism.^{108, 235} If the reaction proceeded as a single-electron transfer, the substrate would undergo oxidation with subsequent cyclisation.



However, there are literature data in favour of the SET mechanism. This process is partly realised in fluorination with XeF₂, which is known to react by a radical mechanism. The electrochemical reduction of *N*-fluoro sultam **51** results in electron transfer, which is accompanied by simultaneous cleavage of the N–F bond with elimination of the fluoride anion and reduction of the reagent **51** to the radical **119** and further to the amide anion **120**.^{106, 108, 235}



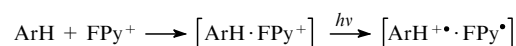
The electrochemical reduction of *N*-fluoro sultam **121** containing a nitro group in the benzene ring yields a radical anion as an intermediate.



According to Differding *et al.*,²³⁵ this step is characteristic of compounds showing high electron affinity.

It should be noted that reactions of *N*-fluoro sultam **51** with nucleophiles (see Table 10) follow the S_N2 mechanism.

In studies of photochemical electrophilic fluorination of aromatic compounds^{160, 161} it was concluded that the reaction occurs through the initial formation of a donor-acceptor complex, since the UV spectra contain absorption bands characteristic of a charge transfer complex (CTC).



The excitation energy, $h\nu_{CTC}$, is correlated with the ionisation potential of the aromatic donor. With a decrease in IP , $h\nu_{CTC}$ decreases favouring the electron transfer, as a result of which the substrate becomes potentially more reactive in electrophilic fluorination where the complex is converted into the final reaction products.

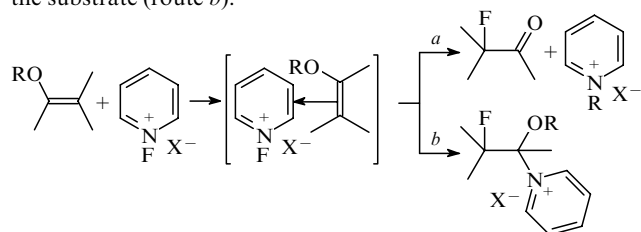
A mechanism involving the formation of CTC was also proposed by Des Marteaux *et al.*⁸⁰ who studied fluorination with $(CF_3SO_2)_2NF$ (**14a**).

The study into the single-electron transfer mechanism carried out by Umemoto *et al.* (see Ref. 144) was based primarily on the analysis of the composition of fluorination products. The concept of the single-electron transfer, which implies the formation of the fluorine radical, was used for rationalisation of various fluorination processes, *viz.*, reactions of *N*-fluoropyridinium salts with anions, neutral substrates, the Grignard reagents, alkenes, aromatic compounds, *etc.*

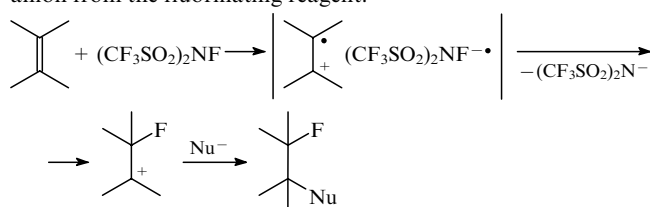
According to Umemoto, three different mechanisms can be realised in the fluorination of unsaturated compounds, *viz.*, a single-electron transfer, classical electrophilic addition and a purely radical mechanism.

In accordance with one of these schemes, the first step of this reaction envisages the formation of a π -complex between the fluorinating reagent and the enol ester/ether.

Further reactions can follow two different routes, *viz.*, transfer of fluorine to the substrate and transfer of the radical R to the pyridinium salt (route *a*) and the addition of the pyridinium salt to the substrate (route *b*).



Fluorination can also occur through the intermediate formation of a radical cation from the unsaturated system and radical anion from the fluorinating reagent.

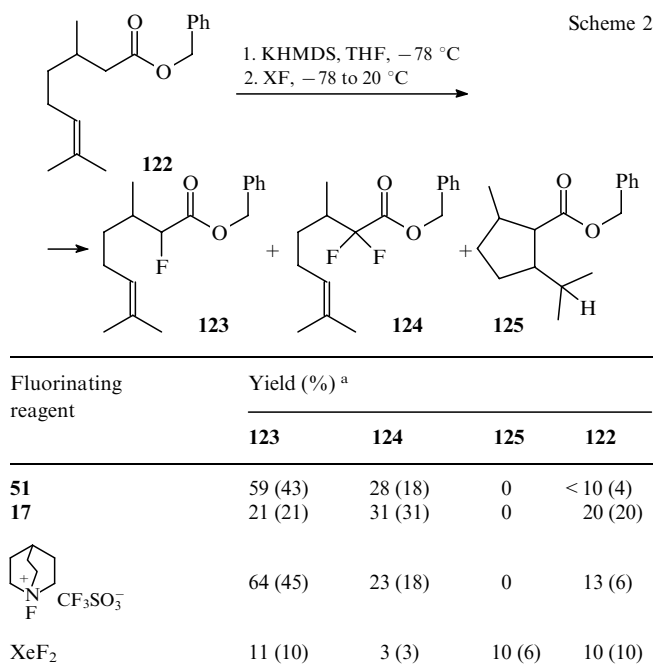


It should be noted that the experimental data currently available do not contradict these schemes. Thus the regio- and stereoselectivity of alkene fluorination fits well into the mechanism of formation of a fluoro carbocation as an intermediate species.^{7, 79, 175} Alkenes in which the intermediate carbocation cannot be stabilised by substituents (*e.g.*, oct-1-ene or cyclohexene) do not react with the fluorinating reagent **84b**. As expected, polar solvents that favour the formation of a complex between the substrate and the fluorinating reagent facilitate fluorination.

The generation of intermediate radical species from fluorinating reagents is confirmed by the formation of products of their reaction with the radicals present in the system. The formation of radical anions is confirmed by their capture with 1,4-benzoquinone.

The introduction of electron traps suppresses the conversion of alkenes. Thus the conversion of *trans*- β -methylstilbene in the reaction with $(CF_3SO_2)_2NF$ decreases from 100% to 80% in the presence of 1,4-dinitrobenzene

The fluorination of benzyl citronellate (**122**) with *N*-fluorinating reagents gives a mixture of α -mono- (**123**) and α,α -difluoro derivatives (**124**), which points to the electrophilic nature of the reagent, whereas the reaction with XeF_2 affords the cyclic product **125** typical of radical fluorination (Scheme 2).²³⁵



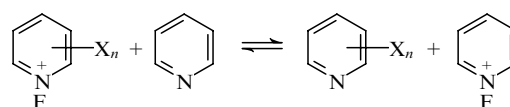
^a The figures in parentheses refer to the yields of the isolated compound.

VI. The effect of the solvent in fluorination reactions with *N*-fluoro amines and their analogues. Comparative reactivities of fluorinating reagents containing the N–F bonds

Despite the evident role of the medium in fluorination reactions, the data accumulated in this area have not yet been adequately generalised and analysed in the literature. Systematic studies in this field have been undertaken comparatively recently by Solkan and Fainzilberg.^{237–239}

A programme for quantum-chemical calculations aimed at quantitation of various effects of the solvent (the effect of solvation, in particular) on the thermodynamic parameters of the fluorination reaction was elaborated. This programme utilises both the point dipole model and the polarising continuum model in the framework of semi-empirical quantum-chemical methods (MNDO, AM-1, MNDO-PM3).

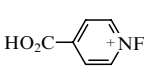
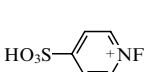
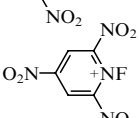
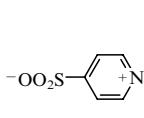
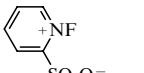
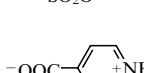
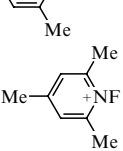
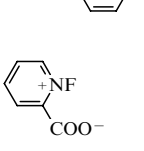
The studies^{237, 239} were carried out with *N*-fluoropyridinium salts, which are readily available compounds. Their fluorinating ability varies over a wide range depending on the electronic and steric characteristics of substituents (NO_2 , SO_2F , CF_3 , CO_2Me , F, Cl, Br, Me, CO_2H , SO_2OH , CO_2^- , SO_3^-) whose position and number can be varied. Unsubstituted pyridine was selected as a substrate.



The reaction of *N*-fluoropyridinium salts with non-substituted pyridine is convenient because it allows comparison of the reactivities of fluorine carriers both with each other and with that of a classical fluorinating reagent such as the *N*-fluoropyridinium cation. If the enthalpy of the reaction is negative, a given fluorine carrier surpasses *N*-fluoropyridinium in the fluorinating ability; in the case of positive enthalpy, it is inferior to the latter.

In order to establish the criterion of fluorinating activity (the thermal effect, ΔH) of an exchange reaction in the gas phase, $\Delta H(g)$, and in polar solvents, $\Delta H(s)$, the authors calculated the corresponding enthalpies of formation of the reactants with account of the solvent effect within the framework of the point

Table 21. Thermodynamic parameters of the fluorination of pyridine with *N*-fluoropyridinium salts.²³⁷

Fluorinating reagent	$\Delta H(g)$ /kcal mol ⁻¹	$\Delta H(s)$ /kcal mol ⁻¹	Fluorinating reagent	$\Delta H(g)$ /kcal mol ⁻¹	$\Delta H(s)$ /kcal mol ⁻¹
	16.0	10.6		7.9	5.8
	31.9	26.9		8.1	7.6
	43.1	36.8		-76.4	35.8
	-2.6	0.4		-91.6	24.7
	-4.9	0.9		-79.0	38.9
	-7.6	0.9		-101.1	22.0

dipole model [$\Delta H_f(g)$ and $\Delta H_f(s)$]. The results of this study are summarised in Table 21.^{237, 239}

An analysis of experimental data^{237, 239} and some results presented in Table 21 allow the following conclusions about the role of solvation in fluorination with *N*-fluoropyridinium salts.

1. In strongly polar solvents, the $\Delta H(s)$ values are higher (CO₂Me, Cl, Br, Me) or lower (NO₂, F, CF₃, SO₂F) than those in the gas phase.

2. The additivity of the substituent effects holds to considerable extent.

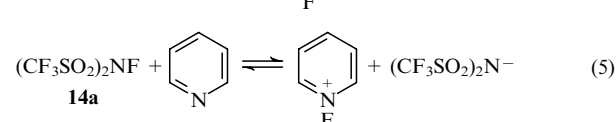
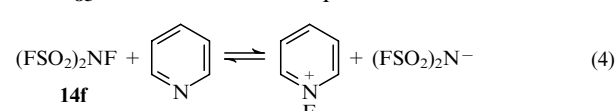
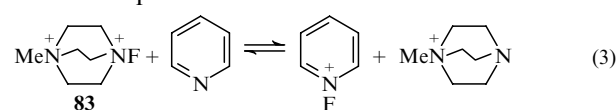
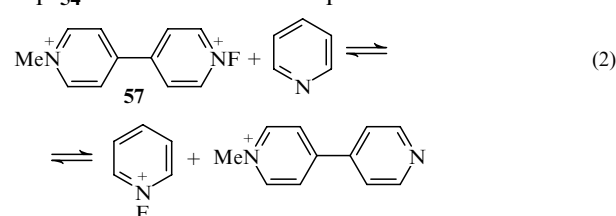
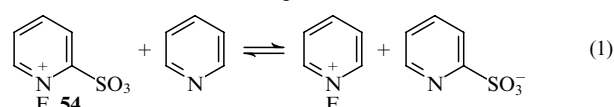
3. The largest increase in ΔH in the transition from the gas to the liquid phase is observed for internal *N*-fluoropyridinium salts containing the CO₂⁻ and SO₃⁻ groups as substituents. In the latter case, the effect is so strong that it can be attributed to the crucial role of solvation in the fluorination reaction.

However, the fluorinating ability of *N*-fluoropyridinium salts containing uncharged substituents in the ring depends on the number of substituents and their electronic effects rather than on the solvation effect. In order to increase the fluorinating activity of a compound containing uncharged substituents up to the level of internal *N*-fluoropyridinium salts, it is necessary to introduce not less than three electron-accepting nitro groups into the molecule (see Table 21). Hence, the introduction of a substituent able to form an internal salt into *N*-fluoropyridinium salt and the use of polar solvating solvents is a simpler procedure, which enhances the fluorinating activity of the reagent.

Solkan and Fainzilberg²⁴⁰ have established the activation barriers for the reaction of *N*-fluoropyridinium salts with pyridine. These calculations made it possible to select the most plausible transition states and to calculate the activation energies (E_a) in a highly polar solvent. Comparison of E_a values and enthalpies of fluorination in solutions $\Delta H(s)$ has revealed their nearly linear dependence, *e.g.*, an increase in the heat of reaction by 3 kcal mol⁻¹ was accompanied by the decrease in the activation barrier by ~ 1 kcal mol⁻¹. Thus, the heats of fluorination reactions can be used in estimation of the corresponding activation energies without determination of the structure of the transition state.

Other types of *N*-fluoro derivatives extensively employed in recent synthetic studies have also been studied.²³⁹ The calculations were performed by a semi-empirical quantum-chemical method

(MNDO-PM3) using a polarising continuum model.²⁴¹ The thermal effects of analogous reactions were calculated for comparative assessment of fluorinating activities of various fluorine carriers in solvents of different polarities.



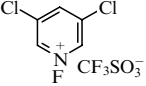
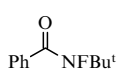
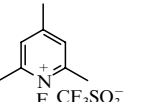
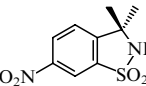
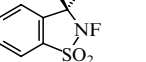
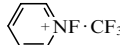
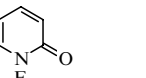
The calculation of enthalpies of formation of the reagents and the reaction products in the gas phase [$\Delta H_f(g)$] and in solution [$\Delta H_f(s)$] is an indispensable step in the calculation of ΔH . In the latter case, the calculations of the Gibbs energy of solvation were carried out for charged molecules. The results of these studies are summarised in Table 22.

As can be seen from these data, the fluorination reactions (1)–(5) are exothermic even if solvents of medium polarity ($\epsilon = 10$) are used. This implies that the reagents **14a**, **f**, **54**, **57** and **83** surpass *N*-fluoropyridinium in fluorinating activity. An increase in the solvent polarity results in manifestation of difference in the behaviour of compounds **14a**, **f**, **54** and **57a**, **83**. For the

Reaction	$-\Delta H(s)/\text{kcal mol}^{-1}$			
	$\varepsilon = 10$	$\varepsilon = 20$	$\varepsilon = 30$	$\varepsilon = 78$
(1)	-14.7	-21.9	-24.7	-27.8
(2)	-17.6	-13.6	-12.2	-10.4
(3)	-45.7	-40.4	-38.6	-36.4
(4)	-14.5	-21.3	-23.6	-26.6
(5)	-29.7	-36.1	-38.4	-41.2

On the whole, the approach to the study of the solvent effects in fluorination reactions²³⁷⁻²⁴⁰ holds great promise, for the information it provides is comprehensive. This approach makes it possible: (i) to obtain the main thermodynamic characteristics of the fluorination reaction, viz., its thermal effect, which serves as a basis for quantitative evaluation of the fluorinating activity of fluorine carriers in various solvents; (ii) to determine the values of heats of solvation for all reactants (the starting compounds and reaction products); (iii) to perform comparative analysis of heats of reaction in order to evaluate the differences in fluorination rates for various reagents and in different solvents. The use of this

It is of note that $E_{1/2}$ seems to be a more reliable criterion than E_{redox} . According to recent data,²⁴⁴ in some cases it is difficult to

Reagent	E_{redox}	$E_{1/2}$	Ref.	Reagent	E_{redox}	$E_{1/2}$	Ref.
	-0.10	+0.38	243		-1.53	-1.48	243
$(\text{PhSO}_2)_2\text{NF}$	-0.78	—	242		-1.58	-0.53	243
	-0.54	+0.16	243				
	-0.37	—	242				
	-0.63	+0.085	243	$\text{O}_2\text{S}-\text{NF}$			
	-0.65	-0.21	243	$(\text{CF}_3\text{SO}_2)_2\text{NF}$	+0.18	—	242
	-0.75	-0.23	243	$\text{FN}^+\text{N}^+\text{CH}_2\text{Cl} \cdot 2\text{BF}_4^-$	-0.04	—	242
				$\text{FN}^+\text{N}^+\text{Me} \cdot 2\text{CF}_3\text{SO}_3^-$	-0.04	—	242
	-1.21	-0.31	243	$\left[\text{Py} \cdot \text{N}^+\text{F} \right] \cdot \text{B}_2\text{F}_7^-$	-0.34	—	242
$4\text{-MeC}_6\text{H}_4\text{SO}_2\text{NFMe}$	-2.10	—	242		-0.47	—	242
	-1.44	-0.50	243				
	-1.52	-1.30	243	$4\text{-MeC}_6\text{H}_4\text{SO}_2\text{NFPr}^n$	-2.10	—	242

^a In MeCN relative to the standard calomel electrode.

Table 24. Some commercially available *N*-fluoro reagents.

Reagent	Properties			Manufacturer
	state of aggregation	B.p. /°C	M.p. /°C	
	liquid	49	—	FLCHEM ^a
	white crystalline substance	—	266–268	FLCHEM ^a
	the same	—	185–187	ALD, ^b FLCHEM, ^a PCR ^c
	"	—	234 (dec.)	ALO, ^b APCI, ^d FLCHEM, ^a JANCHIM ^e
	50% of reagent on Al ₂ O ₃	—	—	ALD-SGL ^f
	white crystals	(see ^g)	42–44	ALD, ^b PCR ^c
(PhSO ₂) ₂ NF	the same	—	114–116	ALD, ^b PCR, ^c FLCHEM, ^a ALD-SGL ^f
	dark crystals	—	196–197	ALD, ^b PCR, ^c FLCHEM, ^a ALD-SGL ^f
	white crystals	—	166–168	AP-SC ^h

^a FLCHEM — Fluorochem Ltd, Wesley St., Old Glossop, Derbyshire, SK 13 9RY UK; ^b ALD — Aldrich Chemical Company, Milwaukee, WI 53201 USA; ^c PCR — PCR Inc., Gainesville, FL 32602 USA; ^d APCI — Air Products and Chemicals Inc., Allentown, PA 18195-1501 USA; ^e JANCHIM — Janssen Pharmaceuticaaan, 3, 2440 Geel, Belgium; ^f ALD-SGL — Allied-Signal Inc., Buffalo, NY 14210 USA; ^g B.p. 90 °C (0.01 Torr); ^h AP-SC — Apollo Scientific Ltd, SK4 1RS, Cheshire, UK.

determine E_{redox} with a sufficiently high degree of reliability because of broad maxima on the electrochemical wave curves. Differding and Bersier²⁴³ also hold this viewpoint and offer an original approach to the estimation of the fluorinating ability of *N*-fluoro reagents. This approach is based on a semi-empirical quantum-chemical calculation of the 'reductant couple' (the original term introduced by the authors), $\Delta H_f^\circ(\text{R}_3\text{N}) - \Delta H_f^\circ(\text{R}_3\text{N}^+ \text{F}^-)$; however, a consistent scale of relative reactivities could be obtained only for structurally related compounds, *e.g.*, of the pyridinium series.²⁴⁵

On the whole, all presently known attempts to create scientific grounds for comparative quantitative assessment of the fluorinating activity of various *N*-fluoro reagents are represented by the examples described in this section. A wealth of quantitative estimates is scattered over numerous synthetic papers which mainly emphasise the crucial role of the *N*-fluorinating reagent structure on fluorination.

VII. Conclusion

The data surveyed in this review demonstrate the intensive development of the chemistry of fluorine carriers in the past

decades. Fluorination with *N*-fluoro reagents has stimulated the research in the field of fluorine chemistry as a whole and provided a basis for fine organic synthesis, the synthesis for organofluorine compounds of medicinal purposes, in particular. A technology for the production of a series of fluorine carriers has been developed by leading chemical companies of the USA, Great Britain and Japan. The main characteristics of some commercially available *N*-fluoro reagents are given in Table 24.

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New condensation polymers having low dielectric constants

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Abstract. The review considers factors that determine the dielectric properties of the medium as well as the basic approaches to the preparation of film materials with low dielectric constants based on condensation polymers that contain fluorinated and/or alicyclic units and of polymeric nanofoams. The bibliography includes 147 references.

I. Introduction

Nowadays, the problem of creating film materials with reduced dielectric constants which can be used as interlayer dielectrics (ILD) in packages of multiintegrated circuits is becoming ever more topical.^{1,2} It is known that the velocity of electrical pulses is inversely proportional to $\varepsilon^{1/2}$, where ε is the dielectric constant (DC) of the medium.^{3,4} In addition, the minimum distance between the lines in integrated circuits is limited by 'noises' arising because of the 'cross effect' dependent on the DC of the insulating material, *i.e.*, currents elicited in conductors near the active signal lines. For this reason, a decrease in ε results in the reduction of the machine cycle, and it becomes possible to increase the density of integrated circuits. One of the materials most widely used for ILD is silicon dioxide for which ε ranges from 4 to 10 depending on moisture content. Materials with ε values lower than that of SiO₂ are divided into four basic groups:⁴

- SiO₂ modified by fluorine treatment ($\varepsilon = 3.0$ – 4.0);
- organic polymers ($\varepsilon = 2.0$ – 3.0);
- nanofoms of organic polymers ($\varepsilon = 1.1$ – 3.0);
- SiO₂ aerogels ($\varepsilon = 1.1$ – 4.0).

Additionally, the materials for ILD should meet the requirements for manufacture technologies and operation of circuit elements. These include high thermal stability and mechanical strength in combination with low thermal expansion and residual stress in the thermal cycle. Organic condensation polymers meet these requirements the best, and this review is devoted to the analysis of major achievements in these directions.

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II. Factors influencing the dielectric constants of polymers

The dielectric constant of polymers is mainly influenced by their free volume,⁵ polarisability⁶ and hydrophobicity.⁷

An increase in the free volume may be regarded as replacement of a portion of a polymer ($\varepsilon \simeq 3$) by air ($\varepsilon = 1$) resulting in a decrease in DC of the material.

The ε value of any material is proportional to the total polarisability (α_{tot}), and ε increases with the increase in α_{tot} . The total polarisability includes components of three types of polarisation: electronic (α_e), atomic (α_a) and resulting from dipole orientation (α_0):^{5–8}

$$\alpha = \alpha_e + \alpha_a + \alpha_0.$$

The total dielectric constant ε is also the sum of increments related to each type of polarisation

$$\varepsilon = \varepsilon_e + \varepsilon_a + \varepsilon_0.$$

Electronic polarisation is determined by a slight deviation from the equilibrium distribution of electrons relative to the positively charged nuclei with which they are associated.^{5–8} As this process includes only the motion of electrons, it can occur very fast, and usually the time constant is $\sim 10^{-13}$ s. At optical frequencies, where only optical polarisation can take place, the Maxwell equation operates:

$$\varepsilon = n^2,$$

where n is the refractive index.

Atomic polarisation results from changes in the disposition of atomic nuclei under the action of an electric field. This type of polarisation is characterised by a typical time constant of $\sim 10^{-13}$ s. For solid organic compounds, the contribution of α_0 to the total polarisation accounts for $\sim 10\%$ of α_e .^{5–8}

The polarisation resulting from dipole orientation is the consequence of redistribution of charges, *i.e.*, reorientation of a group of atoms with a constant dipole moment in space under the action of an electric field. Since reorientation involves large-mass particles, the process proceeds more slowly than the electronic or atomic polarisation and is characterised by a time constant of $\sim 10^{-9}$ s even in the gas phase. In this case, it is necessary to overcome high inertia for changing the direction of motion in each cycle of the electrical field oscillation. In the liquid phase and to a larger extent in the solid phase, intermolecular friction forces operate, which also decelerate the process and decrease the α_0 values characteristic of the static conditions.

The polarisation resulting from dipole reorientation often makes the major contribution to the formation of ϵ values of fluids and gases; however, in solids the contribution from α_e is often more substantial. Naturally, in solids the mobility of dipoles, which depends on the frequency and temperature of measurements, is increased at temperatures above the glass transition temperature T_g , though appreciable motion of dipoles may also occur below T_g due to β -transitions.⁸

The dielectric properties of polymers are also dependent on their hydrophobicity,^{7,9,10} since orientation of water dipoles occurs readily and is retained up to high frequencies of the electrical field (10^{13} Hz for free water). In addition, a water-containing polymer may be regarded as a composite material in which one component (water) has DC equal to 80,⁷ which makes an appreciable contribution to the additive value of ϵ_{tot} of this material.

Thus, hydrophobicity of polymers can play an important role in the formation of electrophysical properties of materials.

The contributions from the above-listed factors to DC values of polymers can differ substantially on going from one structure to another. Thus the contribution of free volume to the DC of polyimides can vary from 25% to 94% depending on the polymer structure.⁵

III. Condensation polymers with low dielectric constants

Aromatic hetero- and especially carbon-chain polymers (CP) are the most promising materials for the creation of ILD. The greatest attention of researchers was attracted to hydrophobic and non-polarisable fluorinated CP and to polymers with cycloaliphatic fragments. The dependence of ϵ on the frequency of measurements, temperature and moisture creates certain difficulties in the establishment of a clear-cut dependence of DC on the structure of polymers. Nonetheless, the available experimental data make it possible to reveal basic regularities and dependences in the structure–DC relationships for a broad range of CP. As most of the studies analysed in this review are concerned with the film-forming (*i.e.*, high-molecular-weight) systems, the influence of the degree of polymerisation on the properties of the materials was not considered.

1. Fluorine-containing condensation polymers

Introduction of fluorine into macromolecules of carbochain polymers results in an increase in their hydrophobicity and free volume with a concomitant decrease in their polarisability.⁷ Of different approaches to the introduction of fluorine into macromolecules, those based on the use of monomers with the hexafluoropropane-2,2-diyl groups (HFPG) are the most popular.^{11–16}

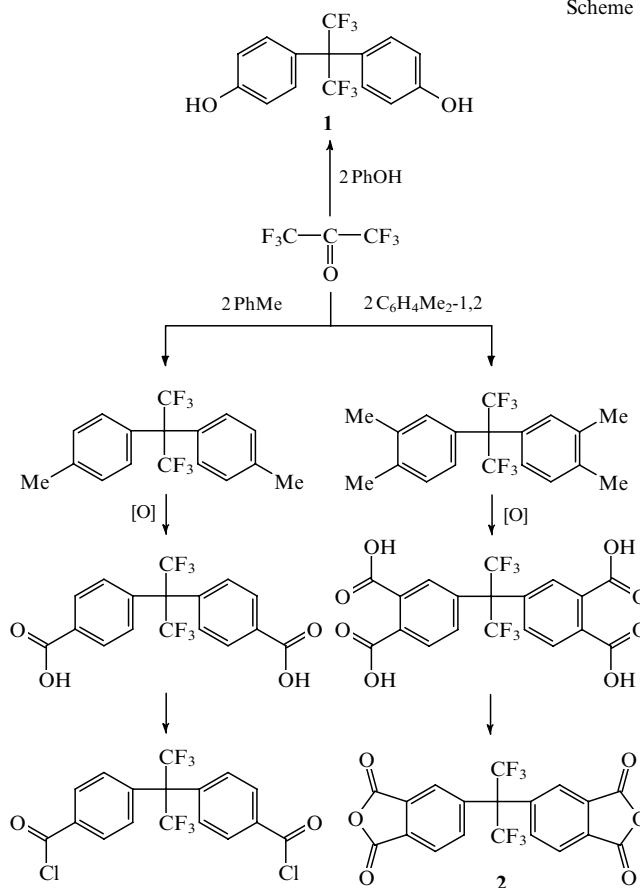
The first representatives of HFPG-containing monomers, *viz.*, 1,1,1,3,3,3-hexafluoro-2,2-bis(4-hydroxyphenyl)propane (**1**), 1,1,1,3,3,3-hexafluoro-2,2-bis(4-carboxyphenyl)propane and its dichloro and 1,1,1,3,3,3-hexafluoro-2,2-bis(3,4-dicarboxyphenyl)propane dianhydride (**2**), were synthesised starting from hexafluoroacetone according to Scheme 1.

These monomers are either used directly for the preparation of aromatic CP or are applied for the synthesis of more complex HFPG-containing monomers.¹⁴ In addition to HFPG, trifluoromethyl^{17–20} and other perfluoroalkyl^{17,21} substituents and perfluoroaromatic fragments^{17,22–24} were incorporated into macromolecules.

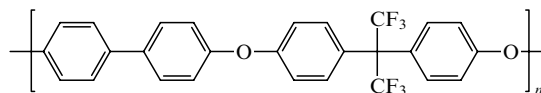
Among fluorinated aromatic condensation polymers with reduced DC, aromatic polyethers (APE) and polyimides are the most interesting.

The most popular method for the synthesis of APE is nucleophilic aromatic polysubstitution^{25–27} with bisphenoxides and activated dihalogenoaromatic or dinitroaromatic compounds as the starting reagents.

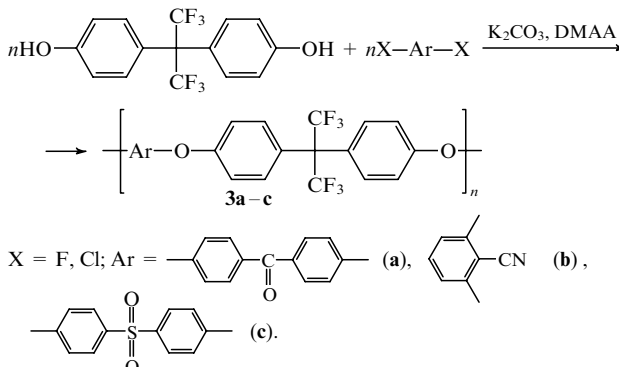
Scheme 1



The first fluorine-containing APE



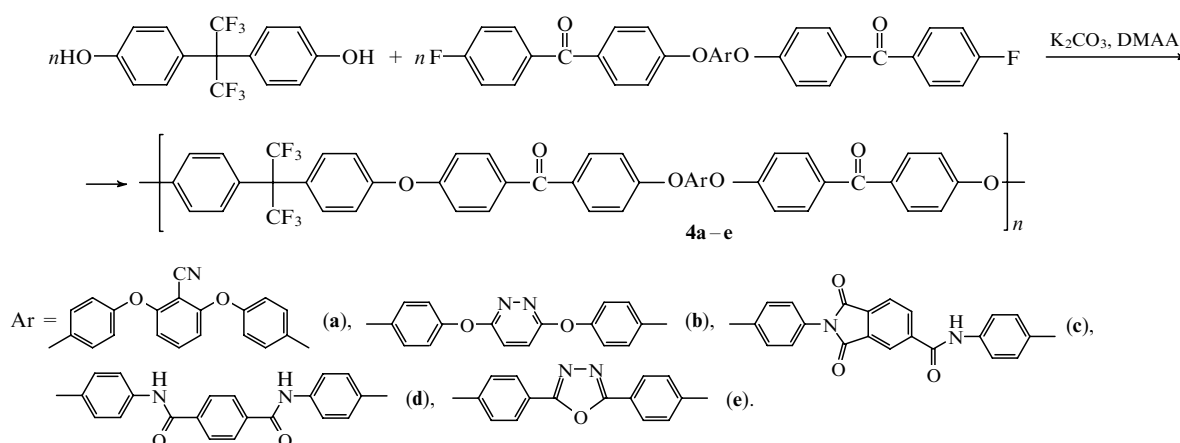
was the polycondensation product of disodium bisphenoxide **1** with 4,4'-dibromobiphenyl.²⁸ Fluorine-containing APE of the general formula **3** were obtained by the reaction of dipotassium bisphenoxide **1** with 4,4'-difluorobenzophenone, 2,6-difluorobenzonitrile and bis(4-chlorophenyl) sulfone.^{22,29,30}



The dielectric constant of APE **3a–c** characterised by a moisture absorption of $\sim 0.9\%$ varies from 2.94 to 3.03 at a relative humidity (r) equal to zero (Table 1). Comparatively high values of ϵ for APE **3a–c** are determined by the presence of such polarisable groups as carbonyl, sulfonyl and nitrile groups in their molecules.

The reaction of dipotassium bisphenoxide **1** with bis(4-fluorobenzophenone)-based monomers containing the amide,

Scheme 2

**Table 1.** Moisture absorptivity and DC of fluorine-containing APE.²²

Polymer	Moisture absorption (%)	ε	
		$r = 0$	humid medium
3a	0.91	2.94	3.25 ($r = 57.5\%$)
3b	0.78	2.99	3.39 ($r = 67.3\%$)
3c	1.21	3.03	3.63 ($r = 69.0\%$)

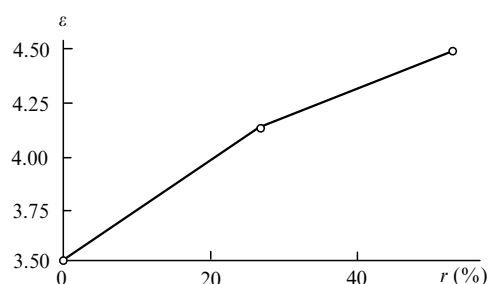
amido-imide, nitrile, 1,3,4-oxadiazole and pyridazine fragments (Scheme 2, see Ref. 31) yielded APE **4a–c** belonging to the class of polyetherketones (PEK), which are being intensively studied in the last decades.³²

Films based on these polymers are elastic and thermostable. At $r = 0$, the dielectric constant of PEK **4a–e** varies from 3.02 to 3.54 (measurements at 10 kHz) (Table 2). The dependence of ε on r for PEK **4a** is presented in Fig. 1.

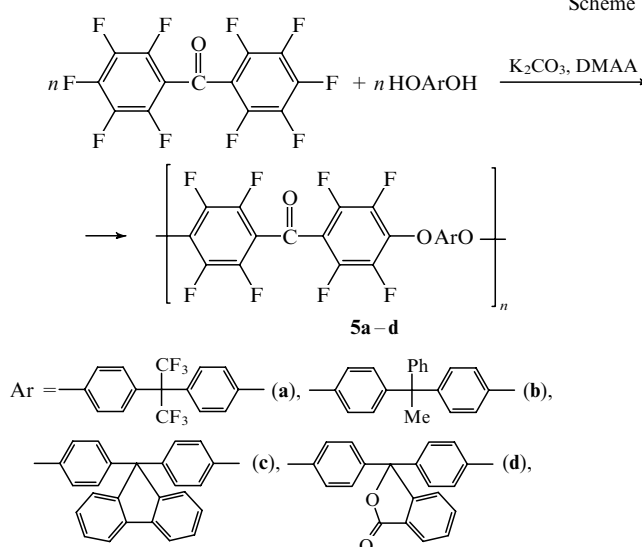
Table 2. Glass transition (T_g) and destruction temperatures (T_d) and DC of fluorine-containing polyetherketones **4**.³¹

Polymer	$T_g / ^\circ\text{C}$	$T_d / ^\circ\text{C}$	ε	
			$r = 0$	humid medium
4a	162	497	3.02	3.51 ($r = 70\%$)
4b	176	498	3.09	3.53 ($r = 70\%$)
4c	146	409	3.11	4.73 ($r = 54\%$)
4d	185	458	3.51	4.54 ($r = 54\%$)
4e	164	366	3.54	4.15 ($r = 52\%$)

Polymers obtained using decafluorobenzophenone as the electrophilic monomer have considerably better characteristics. Thus PEK containing the perfluoroaromatic fragments and

**Figure 1.** Dependence of dielectric constant on relative humidity for polyetherketone **4a**.

Scheme 3



obtained according to Scheme 3³³ possess rather high thermal stability, while the values of ε vary from 2.68 to 2.98 at $r = 0$ and from 2.79 to 3.10 at $r = 68\%$ (Table 3). The dependences of ε on r for PEK **5a–d** are presented in Fig. 2. Comparison of Figs 1 and 2 shows that an increase in r results in an increase in the values of ε for fluorinated APE and PEK, this being particularly pronounced for polymers with high moisture absorptivity.

Table 3. Glass transition and destruction temperatures and DC of fluorinated polyetherketones **5**.³³

Polymer	$T_g / ^\circ\text{C}$	$T_d(\text{air}) / ^\circ\text{C}$	ε	
			$r = 0$	$r = 68\%$
5a	155	425	2.68	2.79
5b	175	442	2.75	2.95
5c	223	436	2.80	3.00
5d	215	359	2.98	3.10

To make the dielectric constant of polymers still lower, it is necessary to remove the polar carbonyl groups from their macromolecules. For this purpose, perfluorinated aromatic hydrocarbons such as hexafluorobenzene^{34–37} and especially decafluorobiphenyl (**6**)^{22–24, 38–45} were used instead of decafluorobenzophenone for the synthesis of APE.

Synthesis of APE based on **6** was carried out according to Scheme 4.^{22, 24}

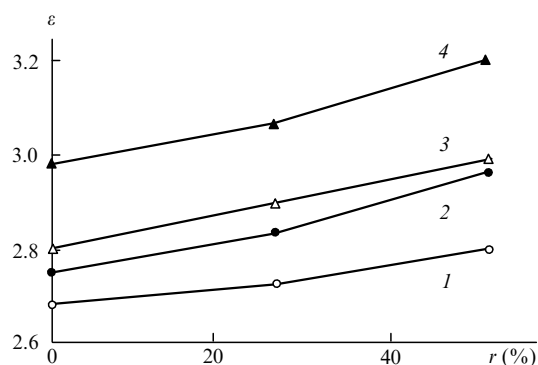
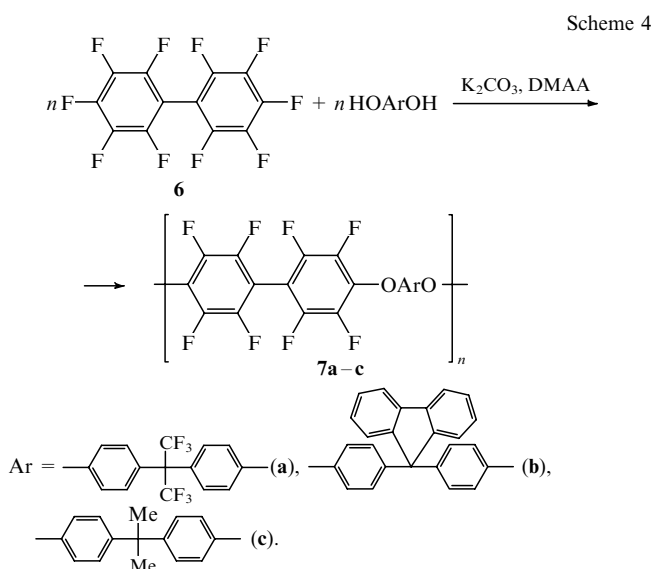


Figure 2. Dependence of dielectric constant of fluorine-containing polyetherketones **5a** (1) **5b** (2) **5c** (3) **5d** (4) on relative humidity.³³



A slight excess of **6** was used to prepare polymers with the terminal nonafluorobiphenyl groups. Some characteristics of fluorinated APE **7a**, **b** are presented in Table 4.

Table 4. Electrical and mechanical properties of APE based on decafluorobiphenyl.⁴⁰

Property	Polymer	
	7a	7b
T_g /°C	189	260
Moisture absorptivity (%)	0.1	0.15
ϵ ($\nu = 10$ kHz)		
$r = 0$	2.50	2.62
$r = 60\%$	2.62	2.66
Thermal expansion coefficient	76	65
α /ppm (°C) ⁻¹		
T_d (DTGA) /°C		
in air	500	500
in a nitrogen atmosphere	510	540
Loss of mass at 1000 °C in air (%)	60	37.5
Isothermal loss of mass in air (%)		
3 h at 400 °C	2.5	2.7
3 h at 450 °C	19.8	3.6
Tensile elongation Δl (%)	85.0	36.0

Aromatic polyethers of general formula **7** are linear or slightly branched (due to the reaction of more than two fluorine atoms with bisphenoxides) polymers soluble in DMAA, THF, bis-2-

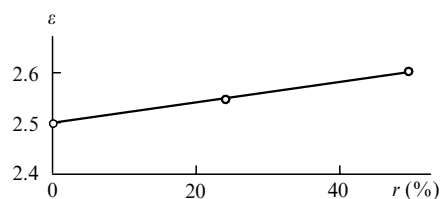


Figure 3. Dependence of dielectric constant on relative humidity for APE **7a**.⁴⁰

ethoxyethanol and isobutyl methyl ketone. Strong transparent films were prepared by casting from solutions or compression of these APE devoid of carbonyl, sulfonyl, nitrile and other polar groups. Such films have low DC ($\epsilon \leq 2.8$) and moisture absorptivity ($\leq 0.1\%$) and are distinguished by high thermal stability and mechanical strength. Figure 3 gives the dependence of ϵ on r for APE **7a** as an example.

Fluorinated APE were used to prepare the family of FLARE polymers with low values of ϵ and moisture absorptivity. For example, the values of ϵ for FLARETM 1.0 and FLARETM 1.51 are 2.43 and 2.52 and the coefficients of thermal expansion are 73 and 33 ppm (°C)⁻¹, respectively.⁴⁵

Fluorine-containing polyimides have also attracted the attention of researchers. A drawback of the systems based on polyimides as regards manufacture of materials with low DC is the presence of four carbonyl groups in each repeating unit. However, the possibility to modify their structures (including fluorination) over wide limits in combination with high thermal stability and mechanical strength make polyimides rather attractive materials for this purpose. Polyimides used in electronics have $\epsilon = 2.9-3.4$. The decrease in DC is achieved by the introduction of fluorine atoms^{5-8, 22, 46-84} into the macromolecules, most often in the form of HFPG^{5-8, 11-16, 61, 63, 80, 81, 83} and trifluoromethyl substituents.^{74-79, 82, 83}

Synthesis of fluorinated polyimides is performed mainly with the use of dianhydride **2**. This is determined by a relative accessibility of this monomer and by low DC of polymers based on it compared to analogous polymers based on other dianhydrides (see below).

The reaction of **2** with various fluorinated diamines was carried out according to Scheme 5.^{21, 22, 63}

Moisture absorptivity and DC values of the polyimides obtained are listed in Table 5. For comparison, the table also contains the corresponding characteristics of poly(diphenylene oxide pyromellitimide) **9**, which is most widely used in microelectronics as an insulator.⁸⁵

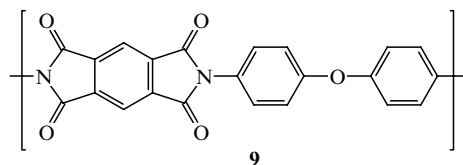
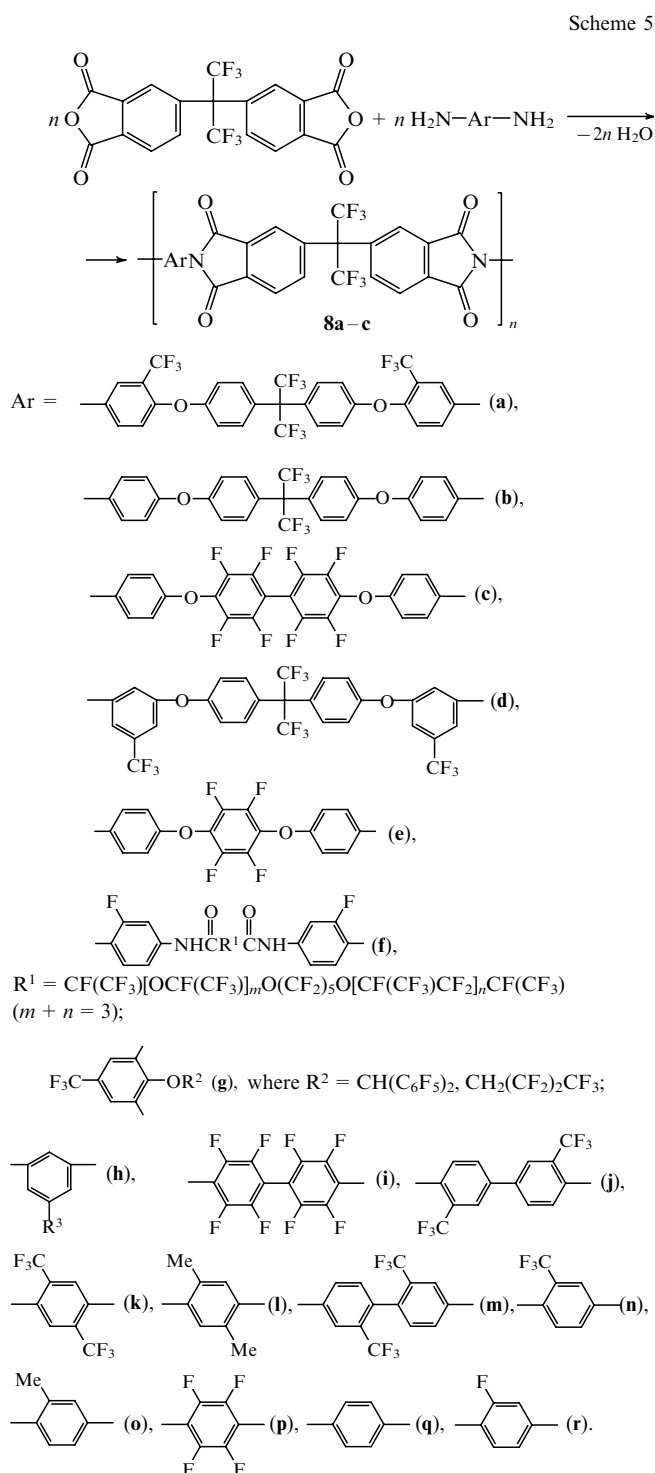


Table 5. Fluorine content, moisture absorptivity and DC of polyimides **8** and **9**.

Polymer	[F] (%)	Moisture absorp-tion (%)	ϵ		Ref.
			$r = 0$	humid medium	
8a	32.0	0.79	2.71	3.04 ($r = 56.8\%$)	22, 30
8b	24.6	0.85	2.72	3.02 ($r = 56.8\%$)	22, 30
				2.96 ($r = 50.0\%$)	63
8c	28.9	0.71	2.74	2.99 ($r = 54.5\%$)	22, 30
				2.78 ($r = 50.0\%$)	63
9	0	2.77	3.10	3.71 ($r = 58.2\%$)	22, 30



It is seen that the parameters of polyimides based on **2** are superior to those of fluorine-free polyimide **9**. For polyimides **8**, the structure of diamines affects little the moisture absorptivity, DC and changes in DC depending on the relative humidity; however, at $r = 0$ the most attractive seems to be the polymer **8a** for which $\epsilon = 2.71$. The isomeric polyimide **8d** possesses identical properties.⁸³

Fluorinated diamines were used in polycondensation with **2**⁶³ to yield polyimides with high content of fluorine. Dielectric properties of the polyimides **8e–g** are presented in Table 6.

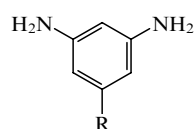
For all the polyimides, the largest ϵ values in the temperature range studied were found to be at 300 °C, which is due to the increased mobility of polyimide molecules at this temperature exceeding the T_g of the polymers under consideration.

Table 6. Fluorine content and DC of fluorine-containing polyimides **8e–g**.⁶³

Polyimide	[F] (%)	ϵ ($\nu = 100$ kHz, $r = 50\%$)			
		25 °C	100 °C	250 °C	300 °C
8e	24.61	2.83	2.81	2.89	2.95
8f	48.06	2.93	2.91	2.82	3.00
8g	38.87	2.93	2.98	2.90	3.08

An analogous phenomenon was observed⁵⁵ in studies of polyimides based on **2** and octafluorobenzidine. Analysis of the data presented in Table 6 made it possible to conclude that the reduction of ϵ is more efficient if fluorine atoms are introduced into the aromatic rings of macromolecules rather than into the aliphatic fragments.⁶³

The reaction of **2** with fluorine-containing substituted *m*-phenylenediamines



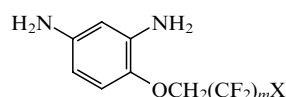
R = SF₅ (**a**), CF₃ (**b**), OCH₂CF₃ (**c**), CH₂C(CF₃)₂C₃F₇ (**d**), H (**e**),

yielded polyimides **8h** which are characterised by low values of ϵ (Table 7) decreasing in the following order R:H > CH₂C(CF₃)₂C₃F₇ > OCH₂CF₃ > CF₃ > SF₅.

Table 7. Dielectric constants of polyimides **8h**.

R	ϵ	ν ($r = 50\%$) /kHz	Ref.
SF ₅	2.51	10 ⁶	66
CF ₃	2.58	10 ⁶	74
OCH ₂ CF ₃	2.60	1	59
CH ₂ C(CF ₃) ₂ C ₃ F ₇	2.70	3 × 10 ³	68
H	3.00	1	59

For polyimides based on **2** and *m*-phenylenediamines containing fluorinated alkoxy substituents,^{59, 84}



$m = 3, 6, 7, 10$; X = H, F,

the values of ϵ are lower than for polyimides based on **2** and nonsubstituted *m*-phenylenediamine (Fig. 4); with an increase in the fluorine content in these polymers, the value of ϵ decreases to 2.6.

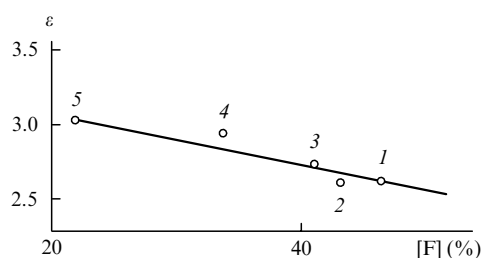


Figure 4. Dependence of dielectric constant (at a frequency of 1 kHz) on the fluorine content in polyimides of general formula **8b**. R: (1) OCH₂(CF₂)₁₀H; (2) OCH₂(CF₂)₇F; (3) OCH₂(CF₂)₆F; (4) OCH₂(CF₂)₃F; (5) H.

These results may be explained by a decrease in the interchain interactions in polyimides;⁵⁰ an increase in the length of the fluorinated alkoxy group leads to a steric hindering of the interchain interaction, which, in turn, decreases ϵ .

Introduction of fluorinated alkoxy groups is related to two opposite aspects of the influence of fluorine atoms on DC. On the one hand, fluorine has low electronic polarisability,⁸⁶ due to which DC of a polyimide is reduced. On the other hand, considerable electron affinity determined by the high electronegativity of fluorine atoms⁸⁷ favours the appearance of additional permanent dipoles on the methylene fragments of the fluorinated alkoxy groups and/or the benzene rings linked with the fluorinated alkoxy groups. These dipoles increase the orientational polarisation and DC. In polyimides, the contribution of these additional permanent dipoles to DC is smaller compared to those of interchain interactions and electronic polarisation.⁸⁶

The reduced water and moisture absorptivity of fluorinated polyimides determines the stability of their dielectric characteristics. Thus after the films have been stored for 5 days at 25 °C and $r = 70\%$, the increase in ϵ was 0.1 (from 2.6 to 2.7) for the polymer **8h** [$R = \text{CH}_2\text{C}(\text{CF}_3)_2\text{C}_3\text{F}_7$] (see Table 7), which indicates that water absorptivity considerably influences the DC of the polymers.⁵⁹ It should be noted that the stability of the DC is one of the most important properties that should be inherent in ILD used in microelectronics.⁸⁷

A detailed investigation of the relationship between the structure of polyimides and their DC has been undertaken.^{7,8} Polyimides **8i–r** were obtained based on dianhydride **2** and different diamines with or without fluorine atoms in the benzene rings and side groups.

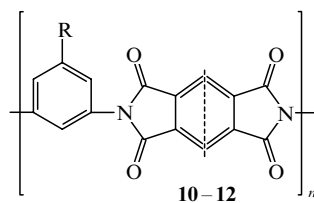
The values of ϵ for these polyimides are listed in Table 8. Under all measurement conditions the same trend was observed, *viz.*, a decrease in DC of polyimides with the increase in fluorine content in these polymers. Some deviations from this trend are determined, in particular, by the fact that the methyl-containing polymers with low fluorine content are partially aliphatic, which diminishes the DC.⁷ It should also be noted that an asymmetrical arrangement of fluorinated fragments in the amine residues leads to an increase in the DC of polyimides with the same number of fluorinated fragments arranged symmetrically.⁷ An analysis of the results presented in Table 8 shows that the DC of polyimides decreases in the following order: **8r** > **8q** > **8o** > **8p** > **8n** > **8l** > **8m** > **8k** > **8i**.

Table 8. Dielectric constants of polyimides **8i–r**.

Polyimide	ϵ (1 kHz)	
	$r = 0$	$r = 40\%$
8i	2.55	2.73
8j	2.56	—
8k	2.59	2.87
8l	2.68	2.90
8m	2.71	2.89
8n	2.72	3.05
8o	2.74	3.21
8p	2.75	3.16
8q	2.81	3.22
8r	2.85	3.19

The effect of the dianhydride structure on the properties of polyimides has been investigated^{59,66,68,74} in studies of physical properties (including DC) of polyimides of general formulae **10–12**. The results obtained are presented in Table 9. According to these data, the magnitude of ϵ decreases in the following order: **10e** > **10d** > **10c** > **10b** > **10a**.

Analysis of the properties of polyimides of general formula **11** revealed a different dependence.⁶⁶



$R = \text{CF}_3$ (**10**), SF_5 (**11**), $\text{CH}_2\text{C}(\text{CF}_3)_3$ (**12**).

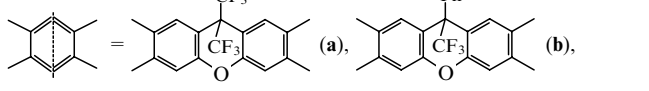
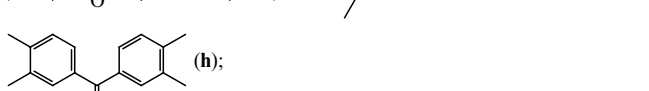
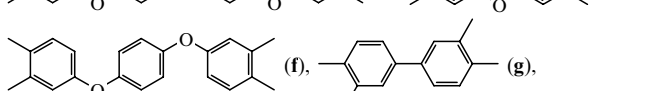
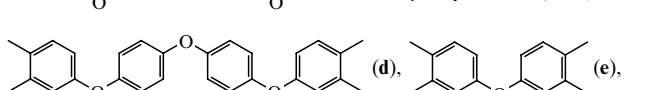
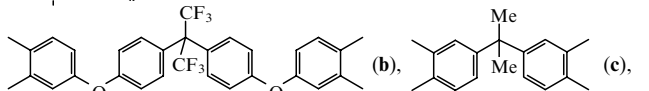
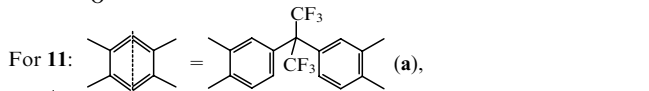
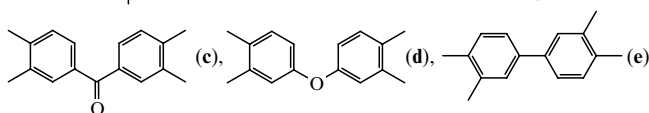
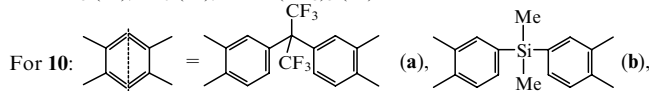


Table 9. Specific viscosity (η_{log}), glass transition temperature and DC of polyimides **10**.

Polyimide	$\eta_{\text{log}} / \text{dl g}^{-1}$	$T_g / ^\circ\text{C}$	ϵ (10 GHz)
10a	0.70	297	2.58
10b	0.64	263	2.75
10c	0.53	294	2.90
10d	0.34	274	2.91
10e	0.89	329	3.02

Note. Polyimides **10a–10d** are soluble in DMAA and *m*-cresol; films can be prepared from solutions of polyimides **10a**, **10c–10e** in *m*-cresol and DMAA.

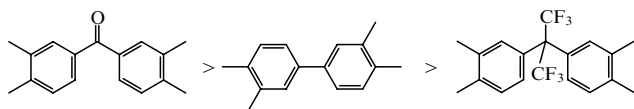
Some characteristics of these polymers are presented in Table 10. It is seen that values of ϵ decrease in the order: **11h** > **11g** > **11f** > **11e** > **11d** > **11c** > **11b** > **11a**. The values of ϵ for SF_5 -containing polyimides presented in Table 10 are rather low: at a frequency of 10 GHz they vary from 2.51 to 3.00, *i.e.*, they are about 0.2 unit lower than those for the corresponding polymers based on *m*-phenylenediamine.

Table 10. Specific viscosity, glass transition temperature, temperature of 10%-mass loss (DTGA) and DC of SF₅-containing polyimides **11**.

Polyimide	$\eta_{\text{log}}/\text{dl g}^{-1}$	$T_g/^\circ\text{C}$	$T_{10\%}/^\circ\text{C}$	ε ($\nu = 10\text{ GHz}$)
11a	0.35	305	476	2.51
11b	0.44	243	480	2.61
11c	0.38	300	426	2.68
11d	0.45	235	457	2.80
11e	0.48	287	470	2.82
11f	0.40	263	471	2.83
11g	0.44	344	471	3.00
11h	0.40	308	461	3.00

Similar polyimides with pentafluorosulfanyl (Table 10) and trifluoromethyl (Table 9) substituents, have close ε values; sometimes the former are characterised by lower ε values, which is related to a higher fluorine content in these systems.

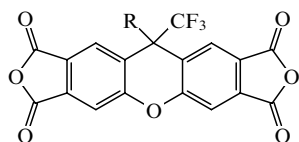
For the polyimides based on *m*-phenylenediamines with fluorinated alkoxy groups, the ε values decrease in the series of dianhydrides:⁵⁹



Of all of the analysed polyimides, those based on dianhydride **2** and containing the bulky hexafluoropropane-2,2-diyl have the lowest ε values compared to polyimides derived from other tetracarboxylic acid dianhydrides. It is the dianhydride **2** that served as the basis for manufacture of polyimide films with $\varepsilon < 3.0$ (for the Hoechst Sixef film, $\varepsilon = 2.6$) and low ($\sim 0.5\%$) water absorptivity.⁶¹

In later studies,^{67, 88–90} it was shown that a considerably better combination of mechanical and electrical properties can be reached by introducing fluorine-containing groups into rigid ‘rod-like’ monomers; films of such polymers have low thermal expansions typical of metals and ceramics.^{91–93}

Xanthene-2,3,6,7-tetracarboxylic acid dianhydrides were used for the preparation of rigid-chain fluorinated polyimides (see Refs 94, 95)



R = CF₃ (**a**), Ph (**b**).

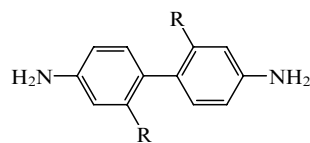
The reaction of these dianhydrides with a number of the above-mentioned fluorinated diimines yielded polyimides **12**, which are characterised by low ε values (lower than in polyimides based on **2**), low coefficients of thermal expansion and good solubility in organic solvents simultaneously. The properties of this type of polyimides are listed in Table 11.⁶⁸

Polyimides with even lower thermal expansion coefficients were obtained by the reaction of xanthene-2-3,5,6-tetracarboxylic

Table 11. Film thickness (d), tensile strength (σ), tensile elongation (Δl), elasticity modulus (η), thermal expansion coefficient (α), moisture absorptivity and DC for films based on fluorine-containing polyimides **12**.⁶⁸

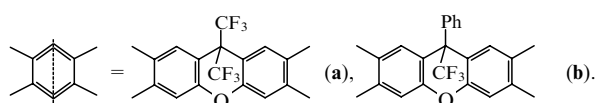
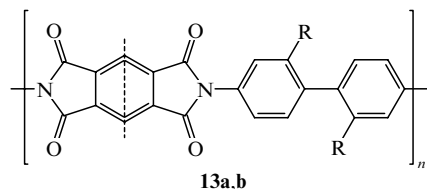
Polyimide	$d/\mu\text{m}$	σ/MPa	$\Delta l/\%$	η/GPa	$\alpha/\text{ppm } (^\circ\text{C})^{-1}$	Moisture absorption (%) ($r = 85\%$)	ε (1 MHz, $r = 0$)
12a	10.5	116	28	2.0	70	0.6	2.3
12b	13.6	115	25	1.9	67	1.1	2.5
12c	14.6	72	6	1.7	86	0.5	2.7

acid dianhydrides with ‘rigid’ fluorinated aromatic diamines, viz., bis(fluoroalkyl)- and bis(fluoroalkoxy)benzidines:



R = CF₃, OCF₃, OCF₂CF₂H.

The rigid-chain polyimides obtained had the following formula



Some characteristics of such fluorinated polyimides are listed in Table 12.^{69, 70}

Table 12. Fluorine content, tensile strength (σ), tensile elongation (Δl), elasticity modulus (η), thermal expansion coefficient (α), moisture absorptivity and DC for fluorine-containing polyimides **13**.⁶⁹

R	[F] (%)	σ/MPa	$\Delta l/\%$	η/GPa	$\alpha/\text{ppm } \times (^\circ\text{C})^{-1}$	Moisture absorption (%) ($r = 85\%$)	ε ($\nu = 1\text{ MHz}$, $r = 0$)
Polyimide 13a							
CF ₃	30.7	200	6	6.1	6	1.2	2.4
						1.4	2.7
OCF ₃	29.4	411	18	5.1	10	0.8	2.8
O(CF ₂) ₂ H	31.7	294	15	5.3	10	0.7	3.0
Polyimide 13b							
CF ₃	22.8	197	8	5.0	6.2	1.9	2.7
OCF ₃	21.8	143	7	3.4	36	—	2.6
O(CF ₂) ₂ H	24.77	249	19	4.0	40	0.8	3.1

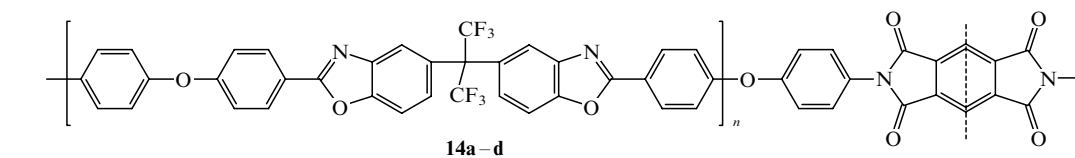
Polymers based on diamine with the OCF₃ substituents are characterised by small values of ε , low moisture absorptivities and low thermal expansion coefficients and, at the same time, possess high thermal stability. Such polymers are rather promising as the next-generation materials for microelectronics.

Along with fluorinated APE and polyimides, other types of fluorinated aromatic polymers were also used for the production of low-DC materials. Polybenzoxazoles (PBO) **14** are typical representatives of such polymers (Scheme 6).^{96–98}

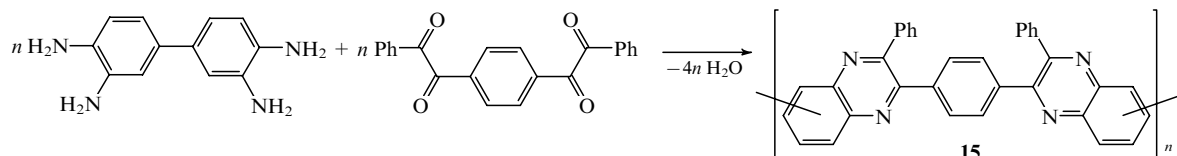
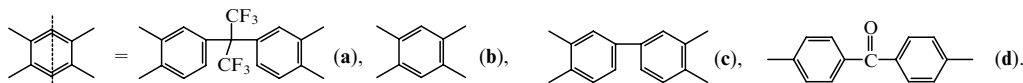
Despite the fact that introduction of benzoxazole units into macromolecules of polyimides did not result in a decrease in DC

Table 13. Dielectric constants of polyimides **14**.⁹⁹

Polyimide	ε	
	$r = 0$	$r = 70\%$
14a	2.88	3.70
14b	3.01	4.29
14c	3.21	4.80
14d	3.21	4.45



Scheme 6



Scheme 7

of the latter (Table 13),⁹⁹ highly fluorinated PBO^{100, 101} appear to be rather promising polymers for the creation of materials with low DC. In any case, for some fluorinated PBO in the humid state $\epsilon = 2.8$ (see Refs 102, 103), and a PBO with $\epsilon = 2.2-2.4$ has been reported.¹⁰⁴

Yet another promising class of heterocyclic polymers are polyphenylquinoxalines (PPQ).¹⁰⁵⁻¹⁰⁷ The information about dielectric properties of PPQ is rather limited,^{1, 108} but the fact that even a fluorine-free PPQ obtained by Scheme 7 has (depending on the temperature and measurement frequency) $\epsilon = 2.70-3.05$ (see Table 14) allows optimistic conclusions about DC of fluorinated PPQ. At present, there are real possibilities for the preparation of PPQ containing fluorine in both the phenyl groups¹⁰⁹ and the hexafluoropropane-2,2-diyl 'bridges'.¹¹⁰

Table 14. Temperature of measurement, frequency and DC of PPQ of general formula **15**.¹

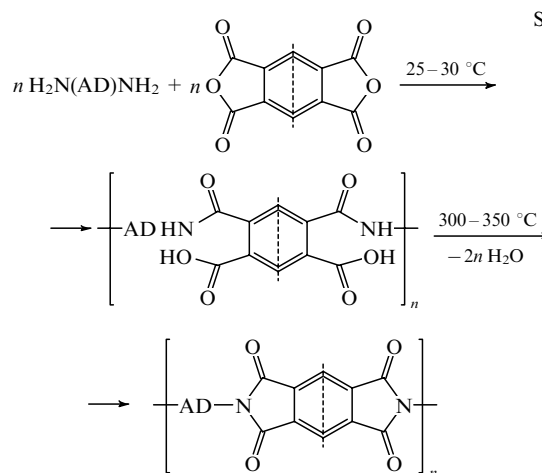
$T/^\circ\text{C}$	ν/kHz	ϵ
45	2×10^1	2.86
45	2×10^3	2.70
100	2×10^1	3.05
100	2×10^3	2.82

2. Polymers with alicyclic units

In the case of fluorinated polymers, a possibility exists of HF evolution in the course of their processing; therefore, in recent years ever-growing attention is paid to fluorine-free CP containing alicyclic fragments (ACF). The most popular ACF is adamantane and its derivatives.¹¹¹ In particular, adamantane-containing diamines used as starting compounds in the synthesis of polyimides have been described.¹¹²⁻¹¹⁶ Polyimides were synthesised by a two-step procedure consisting of low-temperature reaction of adamantane-containing diamines with tetracarboxylic acid dianhydrides and subsequent solid-phase thermal treatment of the resulting polyamido acids (Scheme 8).

Along with the two-step procedure for the synthesis of polyimides, a one-step high-temperature (200 °C) polycyclocondensation in *m*-cresol with isoquinoline as the catalyst can also be used to this end. As a rule, this yields higher-molecular-weight polyimides.

After incorporation of adamantane-containing fragments, the solubility of some polyimides in organic solvents is enhanced, they are less coloured than the aromatic polyimides and their DC values are diminished. The lowest ϵ values are characteristic of polyimides based on 4,9-bis[4-(4-aminophenoxy)phenyl]diada-



Scheme 8

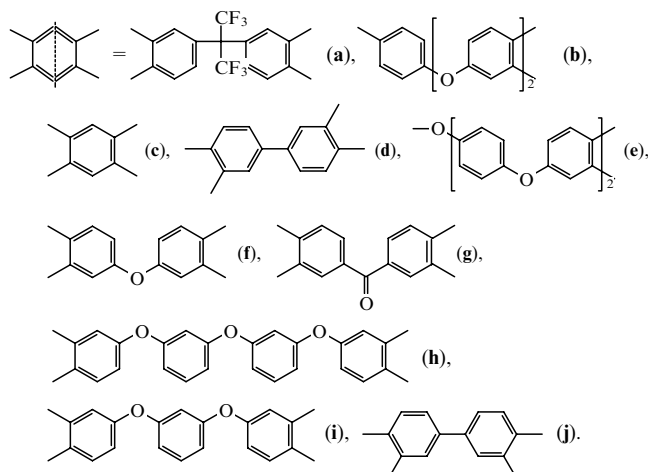
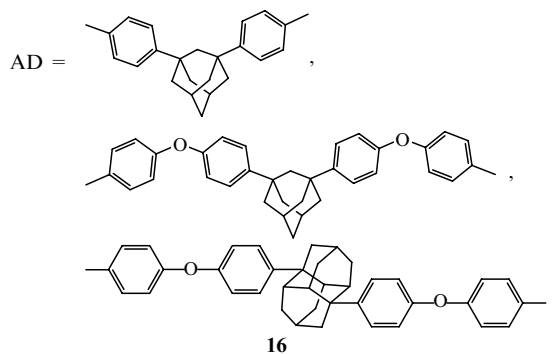


Table 15. Specific viscosity (30 °C, *N*-methylpyrrolidone), glass transition temperature, thermal expansion coefficient, moisture absorptivity and DC of polyimides **16**.¹¹⁴

Polyimide	$\eta_{\log}$ /dl g ⁻¹	T_g /°C (DSC)	α /ppm (°C) ⁻¹	Moisture absorption ($r = 85\%$)	ε ($\nu = 1$ kHz, $r = 0$)
16a	0.63	349	57.5	0.122	2.58
16b	0.43	292	67.1	0.149	2.65
16c	—	394	67.8	0.133	2.66
16d	—	—	72.4	0.149	2.66
16e	0.80	267	74.9	0.163	2.67
16f	0.52	319	56.5	0.137	2.69
16g	—	341	41.6	0.264	2.74

mantane of the general formula **6**.¹¹⁴ Some characteristics of these polyimides are listed in Table 15.

Along with the synthesis of polyimides, the diadamantane-containing monomers were also used for the synthesis of polybenzoazoles.¹¹⁷

IV. Thermostable polymeric foams

An alternative to the above approaches to the creation of polymeric materials with low DC is the use of thermostable polymeric foams.^{1,118–132} Polymeric foams were prepared from microphase-separated block- or graft-copolymers composed of thermostable and thermolabile blocks, the latter forming the dispersed phase.¹ The thermally degradable block should be a functional oligomer of a strictly determined structure; furthermore, it should undergo quantitative disintegration into non-reactive species that diffuse easily through a glassy polymeric matrix. The temperature of destruction of unstable blocks must be sufficiently high to allow preparation of standard films with the removal of a solvent; at the same time, it must be considerably lower than the glass transition temperature of the polyimide block in order to avoid foam degradation.¹²¹ Hence, the difference between the temperature of unstable block destruction and the glass transition temperature of the polymeric matrix determines the ‘processability window’ of the material. Upon heating, the thermally unstable blocks undergo degradation to produce pores, the size and shape of which are determined by the morphology of the initial copolymers.

This type of foams having pores of about 1 nm in size are called nanofoams.¹ A decrease in DC is achieved by replacing part of a polymer with $\varepsilon = 3.2$ by air with $\varepsilon = 1$ (see Ref. 1).

The choice of different polyimides,^{118–130} PPQ¹ or PBO,¹³¹ as thermostable polymeric matrices is determined by their high thermal stability together with solubility (at least, at the prepolymer stage) in organic solvents.

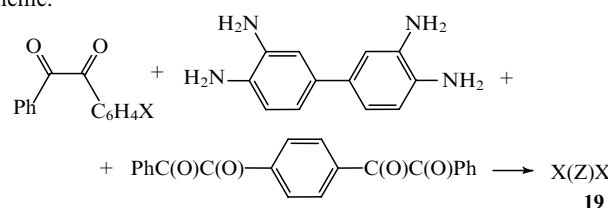
The following polymers are most often used as thermolabile blocks: poly(propylene oxide) (PPO),^{1,118–122,124,125,128,129,131} poly(methyl methacrylate) (PMMA),^{1,124} polystyrene,^{123,125} poly- α -methylstyrene^{123,125,127} and aliphatic polyethers.¹²⁶

Examples of such systems are amorphous polyimides based on a card diamine, 9,9-bis(4-aminophenyl)fluorene, with the terminal (**17**) or lateral (**18**) PPO blocks (Scheme 9).^{118,121}

In the synthesis of polyimides **17a,b** the second amine component was PPO *p*-aminobenzoate; in the case of **18a,b** part of the card diamine was replaced by PPO 3,5-diaminobenzoate. Films of soluble polymers **17a** and **18a** were obtained from solution, whereas films of insoluble polymers **17b** and **18b** were prepared in the stage of soluble polyamido acids with subsequent thermal cyclisation. Conditions of this stage (300 °C, 5–10 h) allowed formation of foams of both polyamide **17** and polyamide **18**.

The density of the polymers points clearly to the formation of intumescent structures: the density of matrix polyimides is 1.28 g cm⁻³, while those of nanofoams range from 1.09 to 1.27 g cm⁻³ (see Ref. 121). Thus, the volume fraction of pores makes up from 15% to 1%.

Nanofoams based on copolymers of PPQ (matrix) and PPO or PMMA (terminal blocks) were prepared using for their synthesis the monomer–oligomer approach according to the following scheme:



X = PPO (**a**), PMMA (**b**); Z = PPQ.

In order to induce destruction of terminal blocks, films of copolymers **19a, b** were heated in air for 9 h at 275 °C and for 5 h at 340 °C, respectively. The density of intumescent polymers reached 1.16–1.19 g cm⁻³, which is appreciably lower than the density of a PPQ homopolymer (1.32 g cm⁻³). Accordingly, 10%–12% of the film volume were voids. Some characteristics of intumescent polymers are listed in Table 16. It is seen that ε decreases from 2.7 for PPQ homopolymer to 2.31 for intumescent copolymers **19a**.

Scheme 9

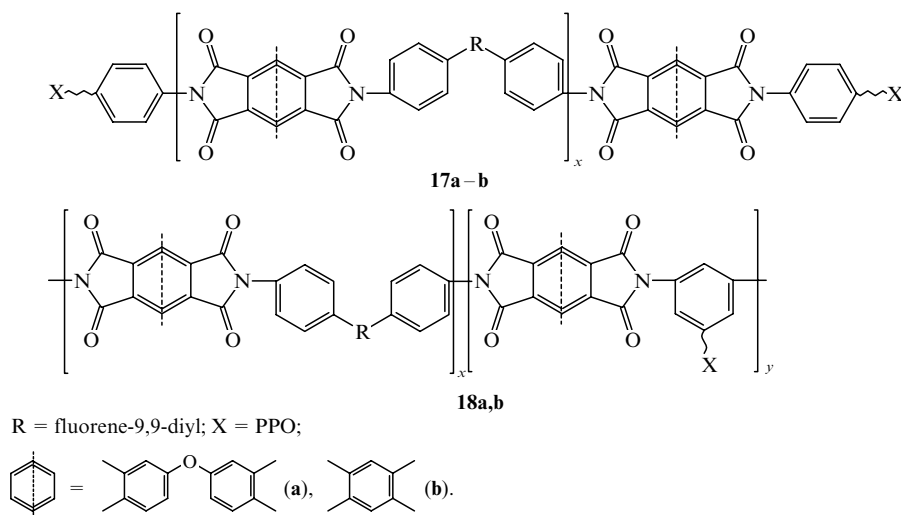


Table 16. Density, temperature of measurement, frequency and DC of a PPQ homopolymer and its intumescent copolymers.¹

ρ /g cm ⁻³	T /°C	ν /kHz	ϵ
PPQ–PPO copolymer			
1.16	45	20	2.38
	45	2×10^3	2.31
	100	20	2.36
	100	2×10^3	2.31
PPQ–PMMA copolymer			
1.19	45	20	2.55
	45	2×10^3	2.51
	100	20	2.54
	100	2×10^3	2.50
PPQ homopolymer			
1.32	45	20	2.86
	45	2×10^3	2.70
	100	20	3.05
	100	2×10^3	2.82

The results obtained confirm unequivocally the efficiency of this approach to the preparation of materials with low DC.

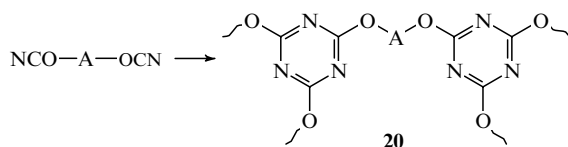
V. Conclusion

The data analysed in this review point to an appreciable progress in the preparation of polymers and polymeric materials with low DC. At present, polyimides meet best the requirements for the dielectric materials employed in microelectronics;¹³² however, these requirements are becoming more rigorous, which stimulates further search for new materials.

Computer-assisted analysis of different structures of polymers has shown¹³³ that considerable progress may be expected if heterochain and heterocyclic polymers are replaced by phenyl-substituted polyphenylenes devoid of polar groups such as C=O, C=N, etc. present in polyheteroarylenes.

Polymers of this type were obtained from phenyl-substituted bicyclopentadienones and diethynylarylenes by the Diels–Alder reaction.^{134–137} In this case, polyphenylenes with aliphatic^{135,136} and hexafluoropropane-1,2-diyl¹³⁷ groups were obtained along with the simplest systems containing only aromatic rings.¹³⁴ Apparently, polymeric materials with $\epsilon = 2.50$ – 2.60 will be prepared based on various modifications of these systems.

Yet another promising direction of studies aimed at the creation of low-DC materials appears to be synthesis of ‘cross-linked’ polycyclotrimers of fluorinated cyano esters **20**.^{138–142} These polymers, obtained according to the scheme,¹⁴⁰



A = CH₂(CF₂)_nCH₂; n = 3, 4, 6, 10,

are reported¹⁴⁰ to have the record DC values for homogeneous systems ($\epsilon \approx 2.27$). Taking into account the efficiency of the approach to the preparation of nanofoams, it may be expected that materials with uniquely low DC will be obtained based on **20**. The same object is pursued by studies in the field of maleimides, norbornenes, benzocyclobutenes and propargylic compounds.^{143–147}

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^a — *Polym. Sci. (Engl. Transl.)*

Novel insecticides and acaricides

A F Grapov

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Abstract. This review outlines the major achievements in design of novel chemical insecticides and acaricides, especially those with non-standard mechanisms of action, viz., neonicotinoids and oxidative phosphorylation decouplers. The bibliography includes 119 references.

I. Introduction

The assortment of modern commercially available insecticides and acaricides is rather wide and permits solution of virtually any problem associated with protection of plants against insects and mites. Nevertheless, studies aimed at improving the preparation forms and the methods of their application do not stop. The need in the search for new highly effective groups of compounds with unusual mechanisms of action and the development of novel insectoacaricides is dictated by both economical considerations and the more rigorous requirements of the health and ecological characteristics of chemicals from the aspect of pesticide industry controlling institutions. Novel, highly effective and selective pesticides with usage rates of about 10–100 g ha⁻¹ not only cut the finance, energy and labour expenditures per unit area treated but also decrease the impact of chemicals on the environment and enhance the safety of their application. Unfortunately, the high cost of the development and marketing of new pesticides (\$US 100–200 million per a product) has led to a decrease in the number of companies specialising in this problem.

Since the development of every novel pesticide represents a complex and multifactor problem, its successful solution can only be attained based on joint achievements in fundamental and applied sciences of different profiles. In the design of novel pesticides, one should pursue not only high efficacy of a novel product against pests but also its compatibility with other insectoacaricides in multicomponent systems used in integrated plant protection against insects and mites, especially against pesticide resistant populations. Thus, nowadays there are populations of more than 500 species of arthropod, which are resistant to organophosphorus, carbamate and halogen-containing insectoacaricides, including pyrethroids. In order to overcome this resistance or, in the other words, to develop systems of pesticide

alternation preventing the appearance of resistant populations in insects and mites, one should have at one's disposal pesticides with different mechanisms of action.

The nerve pulse, hormonal status of the insect and mite moulting process and metamorphosis, and oxidative phosphorylation may be distinguished as three vitally important functions disbalancing of which is currently used to suppress the mite and insect populations. Among these three, the nervous system is the most vulnerable and it is no surprise that the majority of insectoacaricides (more than 90%) block the conductivity of nerve fibres. Thus pyrethroids act on the neuronal sodium channels, carbamates and organophosphorus compounds (OPC) suppress the activity of acetylcholinesterase, whereas nereistoxin analogues block the acetylcholine receptors. A group of insectoacaricides that disturb the hormonal regulation of the moulting process and metamorphosis or block chitin biosynthesis is also used in the pest control programmes. So far, only the first steps have been made in the development of insecticides which decouple mitochondrial oxidative phosphorylation.

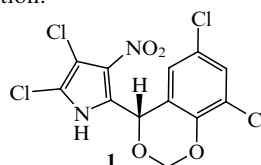
The present review is mostly devoted to novel insectoacaricides with unusual mechanisms of biological action.

II. Heterocyclic derivatives

The most impressive results and those interesting from the practical point of view, giving birth to new promising directions in the research and development of insectoacaricides, have been obtained for heterocyclic compounds belonging to derivatives of the pyrrole, pyridine, pyrazole and imidazole series.

1. Pyrrole derivatives

Pyrrole derivatives such as synthetic analogues of the antibiotic dioxapyrrolomycin (**1**) are of considerable interest as insecticides. This antibiotic has been isolated from *Streptomyces* and exhibited moderate toxicity against insects and mites. The mechanism of biological action of compound (**1**) consists in inhibition of electron transport during the mitochondrial oxidative phosphorylation.



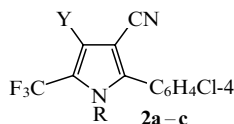
It was shown^{1–4} that certain derivatives of compound **1**, first of all, such as 2- and 3-arylpyrroles, bearing electron-withdrawing substituents in positions 3,4 or 2,4 of the benzene ring, possess

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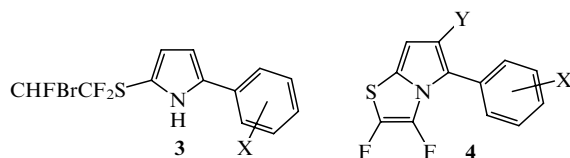
Uspekhi Khimii 68 (8) 773–784 (1999); translated by S V Chapyshev

enhanced insecticidal activity. The fairly high efficacy against various insect species has been found for 2-(4-chlorophenyl)-3-cyano-4-halogeno-5-trifluoromethylpyrroles **2a–c**, 3-aryl-4-halogeno-5-trifluoromethyl-2-trifluoromethylsulfenyl(sulfinyl, sulfonyl)pyrroles, 2-aryl-4-halogeno-5-trifluoromethyl-3-trifluoromethylsulfenylpyrroles and 2-(4-chlorophenyl)-3,4,5-tris(trifluoromethyl)pyrrole.^{5,6} Compound **2a** (AC-303630) is the most potent insecticide in this series. At doses of about 125–250 g ha⁻¹ this compound is effective against 35 insect species from 16 families and 5 orders;^{2,3,7} its LD₅₀ for rats is 223–459 mg kg⁻¹.



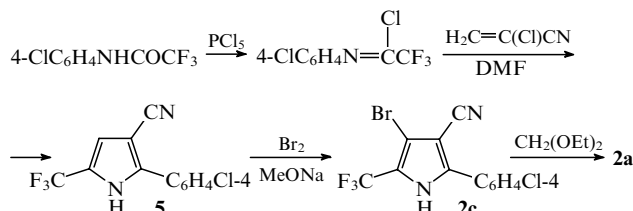
R = CH₂OEt, Y = Br (**a**), F (**b**); R = H, Y = Br (**c**).

The insectoacaricidal activity of compound **2b**, 5-aryl-2-(2-bromo-1,1,2-trifluoroethylthio)pyrroles **3** and the products of intramolecular cyclisation of the latter, *viz.*, pyrrolo[2,1-*b*]thiazoles **4**, is comparable with that of compound **2a**.⁸



X, Y are electron-withdrawing groups.

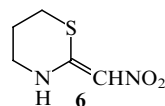
The most convenient method for the preparation of pyrrole **2a** consists in the treatment of *N*-(4-chlorophenyl)trifluoroacetamide with phosphorus pentachloride and subsequent cyclocondensation of the resulting imidoyl chloride with 2-chloroacrylonitrile in DMF. 5-(4-Chlorophenyl)-5-cyano-2-trifluoromethylpyrrole **5** thus obtained is brominated in the presence of sodium methoxide, and pyrrole **2c**, in turn, is alkylated with diethoxymethane.^{9,10}



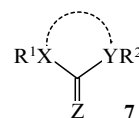
Studies on the mechanism of action of compound **2a** showed that in the insect organism this compound is activated through the oxidative dealkylation producing derivative **2c**, which acts as an inhibitor of oxidative phosphorylation blocking electron transport during ATP synthesis in the mitochondrial chain.^{11,12} As has already been mentioned, this mechanism of action is rather untypical for pesticides. Such a mechanism explains fairly well the absence of cross-resistance to compound **2a** among those insect populations which are resistant to the action of OPC, carbamates and pyrethroids.

2. Pyridine derivatives (neonicotinoids)

The group of compounds under consideration can be referred to as pyridine derivatives rather arbitrarily. The history of the development of these insecticides is quite interesting. In 1978, at the 4th International Congress on Pesticide Chemistry, Soloway *et al.*¹³ presented a report on the study of insecticidal activity of nitromethylidenepyridines, monocyclic and bicyclic nitromethylidenepiperidines and other five- and six-membered heterocycles and acyclic nitromethylidene derivatives. It was shown that 3-nitromethylidenetetrahydrothiazine (**6**) is several times more active against larvae of *Lepidoptera* than parathion.



This finding has stimulated studies on insecticidal properties of numerous acyclic, carbo- and heterocyclic compounds containing the nitromethylidene, cyanomethylidene, nitroimino and cyanoimino fragments of the general formula **7**.



R¹ = H, Alk, Ar, Bn, HetAr, HetArCH₂;

R² = Alk; X, Y = N, S, CH;

Z = CHNO₂, CHCN, YNO₂, NCN.

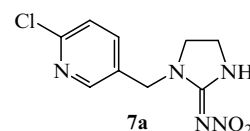
In the beginning, these investigations were unsuccessful and only when 6-chloro-3-pyridylmethyl substituents were introduced did the results obtained surpass all expectations! It is for this reason that this group of compounds is referred to as pyridine derivatives. Selected data on the activity of *N*-nitroimino- and nitroiminomethylideneimidazolidines and -thiazolidines are listed in Table 1. Overall, several thousand compounds of the general formula **7** have been synthesised and assayed.

Table 1. Insecticidal activity of some neonicotinoids of the general formula **7** (X = N) against rice green leaf hopper.^{14,15}

R ¹	Z	Y	R ²	LC ₉₀ /mg litre ⁻¹	Relative activity ^a
PhCH ₂	CHNO ₂	N	H	200	0.0016
4-ClC ₆ H ₄ CH ₂	CHNO ₂	N	H	40	0.008
Me-	CHNO ₂	N	H	200	0.0016
	CHNO ₂	N	H	8	0.04
Me-	CHNO ₂	N	H	1.6	0.2
Me-	CHNO ₂	N	H	0.32	1
	CHNO ₂	N	H	0.32	1
	NNO ₂	N	H	0.32	1
	NNO ₂	N	Me	1.6	0.2
	CHNO ₂	S		0.32	1
	NNO ₂	S		1.6	0.2
	CHNO ₂	N	H	0.32	1
	CHNO ₂	N	H	200	0.016

^a Relative activity was determined as a ratio of the LC₉₀ value for imidacloprid to that for the specified compound.

A new systemic insecticide 1-(6-chloro-3-pyridylmethyl)-2-nitroiminoimidazolidine (**7a**, imidacloprid), is widely used for seed dressing and treatment of soil and green plants.



Imidacloprid (**7a**) is employed against aphids, whiteflies, sawflies, flies, moths, leaf hoppers and noctuids at the usage rates of 30–100 g ha⁻¹ (see Refs 14–18). This is one of the most effective insecticides, which is not inferior to pyrethroids and surpasses OPC and carbamates in activity. The scale of its application is rapidly growing and presumably in the beginning of the XXIst century this will achieve the scale of application of pyrethroids. This is a very promising agent for preventing the appearance of resistant aphid populations. If pesticides are alternated in the series: compound **7a** → bifenthrin → chlorpyrifos → amitraz, a resistance of aphids to these preparations is not developed.

Imidacloprid (**7a**), being an agonist of nicotinic acetylcholine postsynaptic receptors, suppresses the activity of acetylcholinesterase and induces hyperpolarisation of a nerve fiber membrane in insects. The complex mechanism of its action is reduced to the prolonged opening of the sodium channels.^{19–21} The mode of action of compound **7a** and of its analogues resembles that of nicotine, and therefore this group of compounds has been named neonicotinoids. Imidacloprid (**7a**) is bound fairly well to the cerebral membrane of cockroaches, flies, bees and other insects, but very poorly to the cerebral membrane of vertebrates. This probably is the basic reason for its selective toxicity. In cockroaches, the main site of the action of compound **7a** is the synapse of the sixth ganglion.^{22, 23}

According to the X-ray data of the molecule of compound **7a**, the C=NNO₂ fragment and the imidazolidine ring are coplanar, the C–N bonds are shortened and the C=N bond is prolonged. Based on these data, two possible alternative schemes for the binding of compounds **7** to receptors have been suggested (*a* or *b*, Fig. 1).

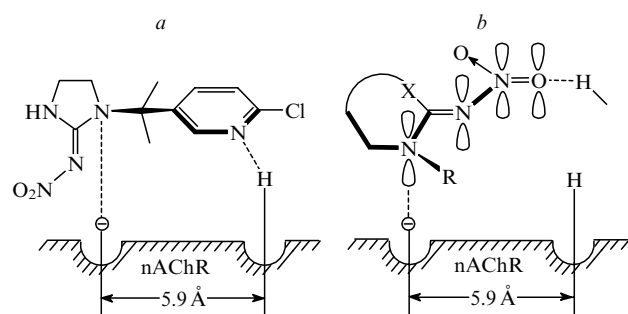
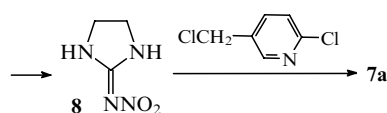
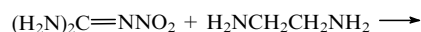


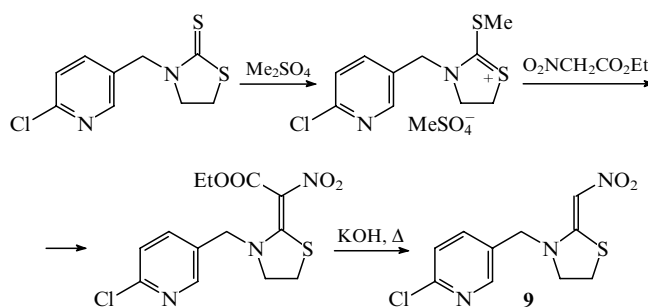
Figure 1. Schemes of interaction of imidacloprid (**7a**) with nicotinic acetylcholine receptors (nAChR).

The assumption of the existence of two distinct mechanisms for the binding permits one to rationalise both the high efficacy of compound **7a** and the lack of the cross-resistance to this agent.²⁴

Imidacloprid (**7a**) is obtained by the reaction of nitroguanidine with ethylenediamine followed by alkylation of 2-nitroiminoimidazolidine (**8**) with 2-chloro-5-chloromethylpyridine.²⁵

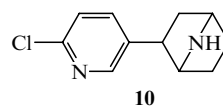


Compound **7a** is insufficiently effective against *Lepidoptera*. Its thiazolidine analogue **9**, obtained according to the scheme shown below,²³ can be successfully employed against insects which are relatively resistant to the action of imidacloprid (**7a**).

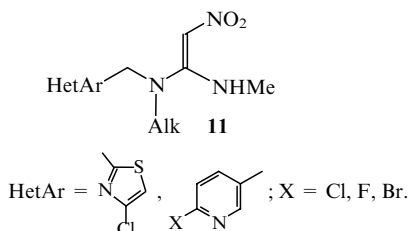


For example, the LC₉₀ values for compounds **7a** and **9** against rice green leaf hopper, cabbage looper *Trichoplusia ni*, cabbage moths and leaf roller *Cnaphalocrosis medinalis* are equal to 0.32 and 0.32, 40 and 1.6, 200 and 1.6, 200 and 8 mg litre⁻¹, respectively.²³

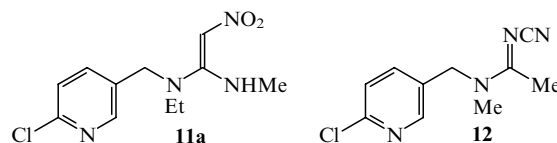
After discovery of the insecticidal properties of imidacloprid (**7a**) and its analogues, the antibiotic epibatidine (**10**), containing the 6-chloro-3-pyridyl fragment and possessing anti-cholinesterase and high analgesic activities, was isolated from the skin of the poisonous frog *Epipedobatis tricolor*. This antibiotic is highly toxic against aphids and spider mite *Tetranychus telarius* (LD₅₀ 0.5 and 6 mg litre⁻¹, respectively).^{26, 27}



1-(*N*-Alkyl-*N*-hetaryl)methylamino-1-methylamino-2-nitroethylenes **11** also possess high insecticidal activity. At a dose of 0.8 mg litre⁻¹ these compounds cause 100% death for cicada *Nilaparvata lugens*. Different modifications of the molecule **11** (replacement of the chlorine atom in the pyridine ring by the methyl or methoxy group, elimination of the methylene group or its replacement by the double or triple bond) do not lead to the enhancement of the biological activity.²⁵



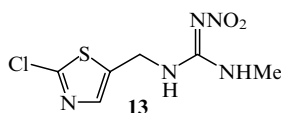
The most effective insecticide in this group of compounds is 1-[*N*-(6-chloro-3-pyridylmethyl)-*N*-ethylamino]-1-methylamino-2-nitroethylene (**11a**, nitenpyram), which is currently undergoing field testing as an aphicide.



The replacement of the nitromethylidene group by the cyanoimino group resulted in 1-(6-chloro-3-pyridylmethyl)-1,3-dimethyl-2-cyanoguanidine (**12**, acetamiprid). This compound, having the contact and systemic mode of action, is highly toxic against aphids, cabbage fly, army worms *Spodoptera litura* and *Mamestra brassicae*, whitefly and tobacco thrips in concentrations of 0.056–13.4 mg litre⁻¹.²⁸ In protecting the leaves against tobacco whitefly and cotton aphids, compound **12** considerably surpasses imidacloprid (**7a**).

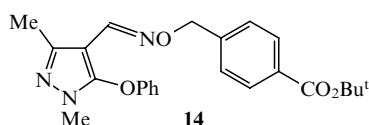
3. Derivatives of heterocycles with several heteroatoms in the ring

In some cases, the 2-chloro-5-thiazolyl moiety can successfully mimic the 6-chloro-3-pyridyl fragment in compounds of the nitromethylidene and nitroguanidine series, and the corresponding compounds manifest the neonicotinoid type of insecticidal activity. (*E*)-1-(2-Chlorothiazol-5-ylmethyl)-3-methyl-2-nitroguanidine (**13**, TI-435) in small doses kills sucking and chewing insects.²⁸



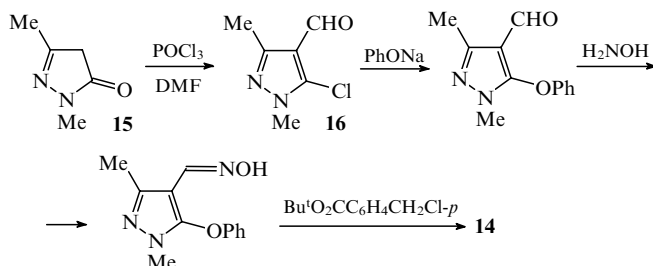
Pyrazole and pyrazoline derivatives constitute one of the basic groups of compounds which were employed in the search for novel insectoacaricides over the last 15 years. The activities of such compounds as substituted anilides of 1-alkyl- and 1-arylpyrazole-5-carboxylic acids, 1-arylpyrazole-3-carboxylic acids, 1,5-diphenylpyrazoline-3-carboxylic acids, 1-arylpyrazoline-3-carboxylic acids, 3,4-disubstituted 1-alkyl- and 1-aryl-5-aminopyrazoles, substituted oximes of pyrazole-4-carbaldehydes have been studied in detail.²⁹

One of the most original preparations of this group of compounds is *O*-4-*tert*-butoxycarbonylbenzyl-1,3-dimethyl-5-phenoxy pyrazole-4-carbaldoxime (**14**, fenpyroximate), which is a 10–100-fold more effective acaricide against mites *Tetranychidae*, *Tarsonemidae* and *Eryophyidae* than dicofol and cyhexatin. This compound not only gives rapid knockdown in mobile stages but also suppresses the moulting process in larval stages of mites.^{30, 31}

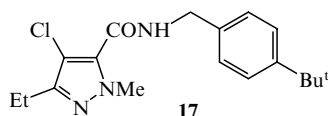


Fenpyroximate **14** acts as an inhibitor of the NADH-coenzyme Q-reductase, which is responsible for the electron transport in the process of mitochondrial oxidative phosphorylation.³²

The starting compound in the synthesis of fenpyroximate **14** is 1,3-dimethylpyrazolin-5-one (**15**), which is simultaneously formylated and chlorinated at the 5-position by the reaction with a mixture of POCl₃ and DMF. Successive treatment of the aldehyde **16** with sodium phenoxide, hydroxylamine and 4-(*tert*-butoxycarbonyl)benzyl chloride gives compound **14** in high yield.³³

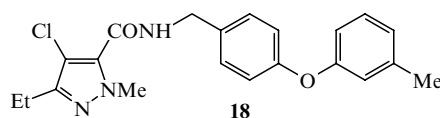


A novel acaricide, viz., *N*-(4-*tert*-butylbenzyl)-4-chloro-3-ethyl-1-methylpyrazole-5-carboxamide (**17**, tebufenpyrad), has been synthesised based on pyrazole-5-carboxylic acid derivatives.



At concentrations of 50–200 mg litre⁻¹ this agent is acute against mites *Tetranychus* sp., *Panonychus* sp., *Orygonychus* sp. and *Eotetranychus* sp. in all stages of their development, including even those populations, which are resistant to the action of dicofol, fenbutatin and hexythiazox.^{34–38} Compound **17** acts as

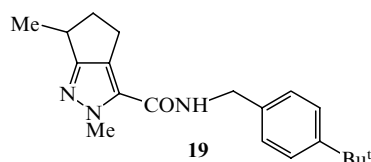
a systemic and translaminar acaricide. Its mechanism of action resembles that of compound **14** and involves the decoupling of the oxidative phosphorylation process.¹⁰ A detailed study of the chemical structure–biological activity relationships for analogues of **17**, using the QSAR programme, has led to the design of a novel insecticide, viz., *N*-[4-(3-methylphenoxy)benzyl]-4-chloro-3-ethyl-1-methylpyrazole-5-carboxamide (**18**, OMI-88), having a broad range of action.^{39, 40}



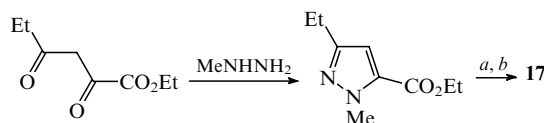
This agent is highly effective against cabbage moth, aphids, whitefly, leaf hoppers and thrips in concentrations of 75–150 mg litre⁻¹ without inducing cross-resistance to pyrethroids, OPC and phenylbenzoylureas in insects.⁴¹

Analogues of **17** and **18** containing 3-pyridylmethyl fragments instead of the benzyl one are less effective against spider mites.⁴²

Bicyclic pyrazole derivative **19** is not inferior in activity to compound **18**. According to the data of X-ray analysis, both compounds have similar crystal structures.⁴³

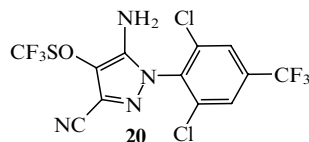


Compound **18** and its analogues were synthesised by cyclisation of alkyl α,γ -dioxocarboxylates with methylhydrazine followed by the chlorination and aminolysis.⁴⁴



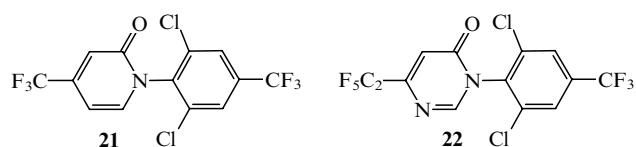
(a) Cl₂; (b) H₂NCH₂C₆H₄Bu^t-*p*.

Further variation of the structure by introduction of polar and non-polar substituents in the pyrazole ring has led to the design of a fine soil and seed treating insecticide, viz., 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulfinylpyrazole (**20**, fipronil). This agent is employed against soil insects at doses less than 100 g ha⁻¹. Compound **20** is effective not only against susceptible insect populations but also against those resistant to dieldrin, cypermethrin and carbaryl.^{45–48}

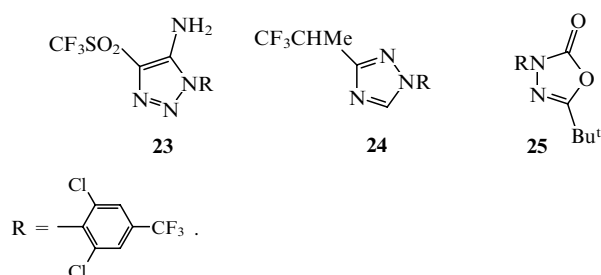


Insecticidal aminopyrazoles of the fipronil group (derivatives of compound **20**) are antagonists of the GABA-receptors. They block the GABA-regulated chloride channels in a membrane of the nerve fibres of insects. For the aminopyrazole **20**, the degree of blocking of the chloride channels in a membrane of the nerve cells of flies is much higher than that in a membrane of the nerve cells of rats.⁴⁸

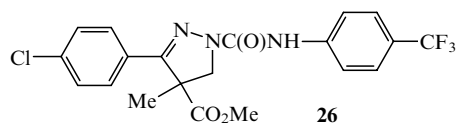
A study of the chemical structure–biological activity relationships for compounds of the type **20** has shown that introduction of a 2,6-dichloro-4-trifluoromethylphenyl substituent at the nitrogen atom of heterocycles enhances the insecticidal properties. According to the data of quantum-mechanical calculations, compound **20** and its pyridone (**21**) and pyrimidone (**22**) analogues have very similar electrostatic surfaces.^{47, 49} All of them are potent insecticides.



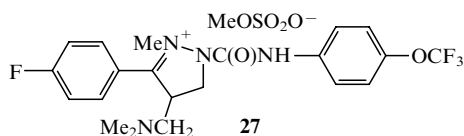
The insecticidal activities of 1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1,2,3- (**23**) and -1,2,4-triazoles **24** as well as of 5-*tert*-butyl-4-(2,6-dichloro-4-(trifluoromethyl)phenyl)-1,3,4-oxadiazolin-2-one (**25**) are substantially lower than that of compound **20**.^{50–52} Most likely, aminopyrazole **20** and compounds **23–25** have different electrostatic surfaces.



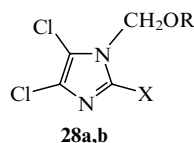
In comparison with the pyrazole derivatives, their pyrazoline analogues are less potent insectoacaricides. However, a novel insecticide, 4-methoxycarbonyl-3-(3-chlorophenyl)-4-methyl-1-[*N*-(4-trifluoromethylphenyl)carbamoyl]-4,5-dihydro-5*H*-pyrazole (**26**, RH-341), has also been found in this group of compounds. Compound **26** acts as an inhibitor of the conductivity of sodium channels, which are blocked, as a rule, by veratridin, batrachotoxin and pumylotoxin B. It is important to note that compound **26** is bound to the sodium channels at the sites different from those for alkylamides, pyrethroids and DDT analogues.^{53, 54}



Compound **27** of the similar structure is effective against various species of noctuids. Methods of optimisation of the biological properties using correlation analysis have been applied in the design of this agent, in which the primary attention has been focused on the increase in lipophilic characteristics of the molecule.⁵⁵



The trihalogenoimidazole derivatives represent another example of insecticides of non-standard mechanisms of biological action. They can be employed against insect populations resistant to other insecticides. The most active agent in this series of compounds is 2-bromo-1-methoxymethyl-4,5-dichloroimidazole (**28a**), which is highly effective against cockroaches.⁵⁶



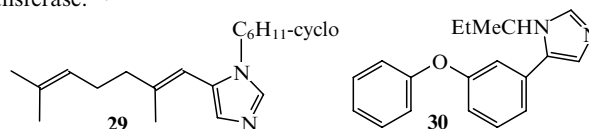
R = Me, X = Br (**a**); R = (CH₂)₄Cl, X = Cl (**b**).

The mode of action of trihaloimidazoles has been studied in detail using 1-(4-chlorobutoxymethyl)-2,4,5-trichloroimidazole (**28b**, S-377) as a model compound. Like pyrethroids, this agent inhibits the inactivation system of the sodium channels in a membrane of nerve cells thus inducing huge excitation poten-

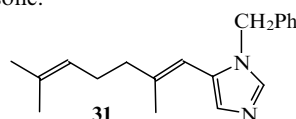
tials. However, the binding sites of trihaloimidazoles and pyrethroids to the sodium channels have been found to be different.⁵⁷

Insecticides of the class of 1,5-disubstituted imidazoles suppress the activity of insect juvenile hormones disturbing the growth, development and diapause of insects. The mechanisms of their activities are highly diverse and depend substantially on the substituents in the imidazole ring.

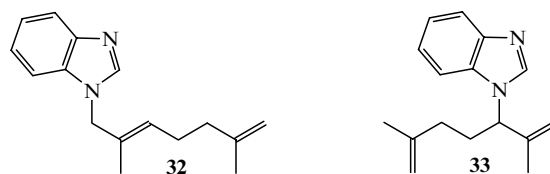
Thus 1-cyclohexyl-5-(2,6-dimethylhepta-1,5-dienyl)imidazole (**29**, KK-85) and particularly 1-*sec*-butyl-5-(3-phenoxyphenyl)imidazole (**30**, KK-98) at concentrations of 10^{−7}–10^{−8} mol litre^{−1} not only selectively inhibit the farnesoate epoxidases, but also suppress the activity of *O*-methyl farnesoate transferase.^{58, 59}



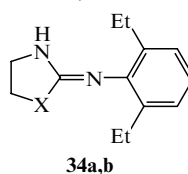
Compound **31**, 1-benzyl-5-(2,6-dimethylhepta-1,5-dienyl)imidazole (KK-42), which is structurally close to imidazole **29**, suppresses *in vitro* at low concentrations the biosynthesis of ecdisteroids in protoracal glands of silkworm and reduces the ecdisteroidal titre in hemolymph of silkworm larvae and pupae. This compound induces premature metamorphosis of silkworm larvae, which is eliminated by methoprene and 20-hydroxyecdysone.⁶⁰



Terpenoids having the 2,7-dimethyloctane skeleton and a benzimidazolyl substituent, (**32**, **33**) were obtained by catalytic alkylation of benzimidazole. They possess growth regulating properties toward mealworms *Tenebrio molitor*.⁶¹



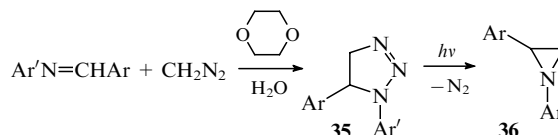
A rather unexpected mechanism of action has been found for such acaricides as *N*-substituted iminoimidazolidines and thiazolidines **34a,b**.



X = NH (**a**), S (**b**).

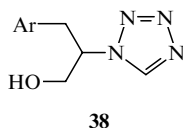
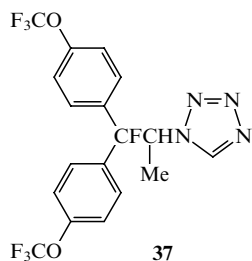
These compounds suppress the octopamine-sensitive adenylyltransferase.^{62, 63}

The products of 1,3-dipolar cycloaddition of diazomethane to Schiff bases, such as 1,5-diaryl-4,5-dihydro-1*H*-1,2,3-triazoles **35**, exhibit the aphicidal properties. The detailed study of the mode of their action has shown that compounds **35** are in fact proinsecticides. Upon UV irradiation, they are converted to 1,2-diarylaziridines **36**, which exhibit the aphicidal properties.



Model experiments have shown⁶⁴ that specially synthesised aziridines of the general formula **36** indeed manifest the same or higher activities against aphids.

1-Fluoro-1,1-bis(4-trifluoromethoxyphenyl)-2-(*N*-tetrazolyl)-propane **37** is comparable with pyrethroids in the level and the range of insecticidal activity. The mechanism of its action consists in the blockage of the axonal calcium-dependent potassium channels.⁶⁵



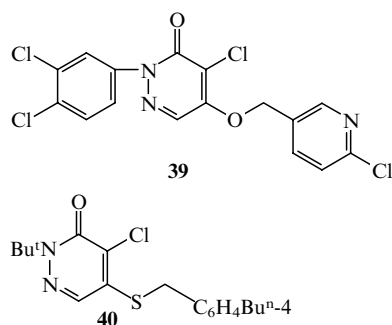
3-Aryl-2-(*N*-tetrazolyl)propanols **38** possess a good larvicidal activity against mosquito larvae and prevent the development of army worms *Spodoptera litura*.⁶⁶

Some groups of derivatives of six-membered heterocycles with two heteroatoms in the ring also exhibit high insectoacaricidal activity.

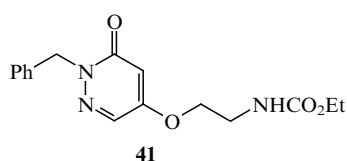
Each certain group has its own, specific mode of action. Thus 5-chloropyridazin-6-one derivatives are agonists of juvenile hormone and stimulate the biosynthesis of this hormone by activating the productivity of prothoracic glands *corpora allata*. This group of compounds not only suppresses the metamorphosis of insects, but also disturbs many other vitally important processes such as pigment biosynthesis, embryogenesis and diapause.

5-Chloro-4-(6-chloro-3-pyridylmethoxy)-1-(3,4-dichlorophenyl)pyridazin-6(2*H*)-one (**39**, NC-170) is employed as an experimental insecticide against leaf hoppers.^{67–69}

Another compound of this group, *viz.*, 1-*tert*-butyl-4-(4-*n*-butylbenzylthio)-5-chloropyridazin-6(2*H*)-one (**40**, pyridaben, NC-129), is effective against whitefly, aphids and thrips in all stages of their development. This is a tenfold more effective acaricide against mites of the orders *Tetranychus* and *Panonychus* than cyhexatin.^{70,71}

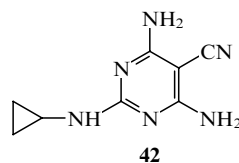


Being genetically associated with the group of juvenile hormone mimetics, 1-benzyl-4-(2-ethoxycarbonylamino)ethoxypyridazin-6(2*H*)-one (**41**) is of certain interest. This compound is more effective against rice green leaf hopper than fenoxycarb. It has systemic type of activity and can be applied in granulated form against soil pests at a usage rate of 200 g ha⁻¹.⁷²

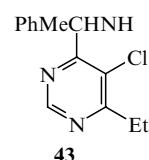


In the series of substituted pyrimidines, 4,6-diamino-5-cyano-2-cyclopropylaminopyrimidine (**42**, CGA-193893) is the most interesting experimental insecticide with the hormonal mode of

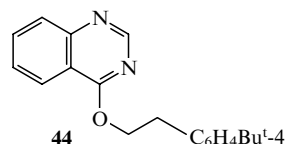
action. This compound is tenfold more effective against aphids, pupae and imago of flies, mosquitoes and lice than cyromazine.⁷³



N-Substituted 6-alkyl-4-amino-5-chloro- and 6-alkyl-4-amino-5-cyanopyrimidines, *e.g.*, compound **43**, are active against both phytophagous mites and noctuids.⁷⁴

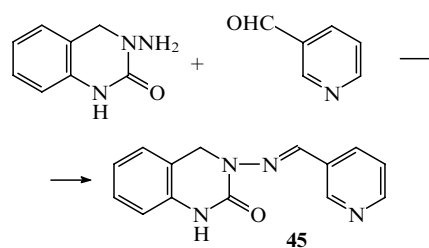


Among quinazoline derivatives, 4-[2-(4-*tert*-butylphenyl)-ethoxy]quinazoline (**44**, fenazaquin) can be distinguished as an interesting acaricide with ovicidal and larvicidal types of activity and with good ecological characteristics. Its usage rates are only 1–15 g ha⁻¹, and 85% of the preparation is decomposed after 7 days. As regards the mechanism of its action, fenazaquin is assigned to a new group of insecticides, *viz.*, the mitochondrial oxidative phosphorylation decouplers.^{75–78}

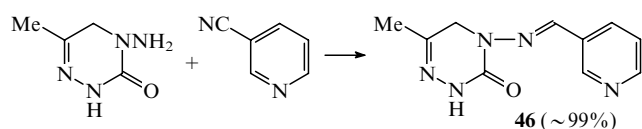


Analogues of compound **44** containing the pyridopyrimidine, thienopyrimidine, pteridine, pyrazolopyrimidine, purine, isoxazolopyrimidine and isothiazolopyrimidine fragments instead of the quinazoline moiety also possess acaricidal activity.⁷⁸

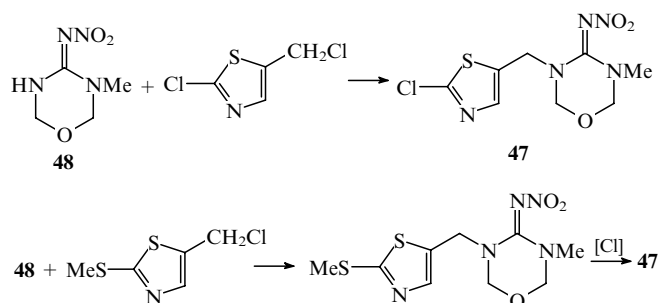
3-(3-Pyridylmethylideneamino)-3,4-dihydroquinazolin-2-one (**45**) was obtained from 1-aminoquinazolin-2-one and nicotinaldehyde.⁷⁹ At usage rates of 75–150 g ha⁻¹ this compound is effective against aphids resistant to pyrethroids, OPC and carbamates but does not affect useful insects.



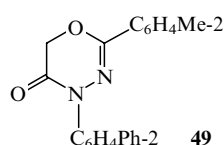
An analogous derivative of an asymmetrical triazine, *viz.*, 2,5-dihydro-6-methyl-4-(3-pyridylmethylideneamino)-1,2,4-triazin-3-one (**46**, pymetrozine, CGA-215944), is also considered as a promising insectoacaricide. This agent with contact and ingested modes of action is effective against both susceptible and resistant populations of aphids, noctuids and whiteflies at low usage rates and can be applied for protection of vegetables in field and greenhouse plantations. This compound exhibits the antifeedant activity thus violating the insect behavioural instincts. The convenient method of its industrial preparation is based on the reduction of a mixture of commercially available 4-amino-6-methyl-1,2,4-triazin-3-one and nicotinonitrile with hydrogen over Raney Ni.^{80–82}



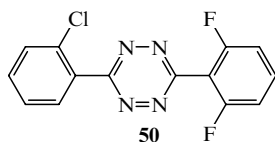
A high insecticidal activity against a large variety of insects has been found for 3-(2-chloro-5-thiazolylmethyl)-4-nitroimino-5-methyl-2,3,5,6(2*H*,5*H*)-tetrahydro-1,3,5-oxadiazine (**47**, experimental insecticide CGA-293343). This agent possesses long-lasting residual activity. The mechanism of biological action of compound **47** resembles that of neonicotinoids.⁸³ The method of preparation of this compound involves the alkylation of 3-methyl-4-nitroiminotetrahydro-1,3,5-oxadiazine (**48**) with either 2-chloro-5-chloromethylthiazole or 5-chloromethyl-2-methylthiothiazole followed by the replacement of the methylthio group by chlorine.⁸⁴



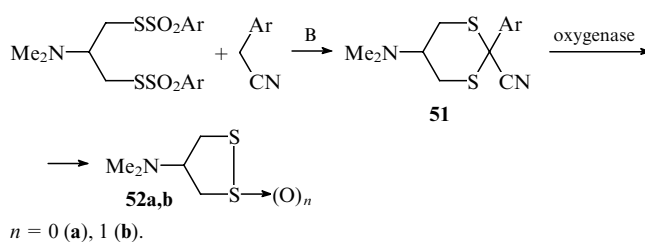
2,4-Diaryl-1,3,4-oxadiazin-5-ones manifest high insectoacaricidal activity. The study of the chemical structure–biological activity relationship using the QSAR programme has shown that in a series of substituted oxadiazines the maximum biocidal activity falls on 4-(2-biphenyl)-2-(2-tolyl)-1,3,4-(4*H*,6*H*)-oxadiazin-5-one (**49**); its LC₅₀ against mite *Tetranychus telarius* is equal to 25 mg litre⁻¹.⁸⁵



Among derivatives of tetrazine, one can mention 3-(2-chlorophenyl)-6-(2,6-difluorophenyl)-1,2,4,5-tetrazine (**50**, SZI-121) as an analogue of clofentezine. This compound at usage rates less than 80 g ha⁻¹ is effective for protection of fruit and citrus trees, vines and vegetables against fruit tree red spider mite *Panonychus ulmi* and spider mite *Tetranychus sp.* in their ovopositional and mobile stages of development. Compound **50** has translaminar and fumigated mode of action and long-lasting residual toxicity.^{86, 87}

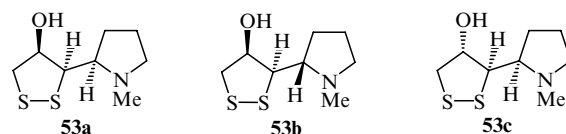


The most detailed study in a series of five- and six-membered sulfur-containing heterocycles has been accomplished for derivatives of substituted 1,2-dithiolanes and 1,3-dithianes. 2-Aryl-2-cyano-5-dimethylamino-1,3-dithianes **51** were synthesised by the reaction of 1,3-bis(arylsulfonylthio)-2-dimethylaminopropanes with CH-acids. These compounds possess high insecticidal activity against rice green leaf hopper and spider mites.⁸⁸

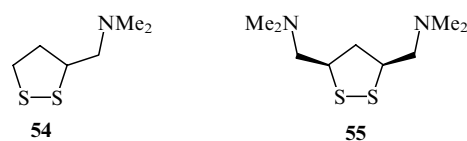


Dithianes **51** are converted into nereistoxin (**52a**) and its *S*-oxide **52b** under the action of liver microsomal oxygenases and therefore they may be considered as propesticides. The nature of the aryl substituent in the 2-position strongly affects the capability of these compounds to penetrate through the covering tissues of insects.⁸⁸

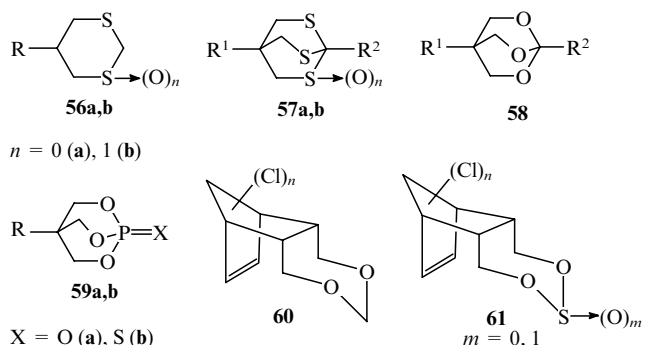
At the end of the 80's, guinesines A, B and C (**53a–c**, respectively) were isolated from a Brazilian tree *Cassipourea guianensis*, which showed fairly strong insecticidal properties.⁸⁹



Modification of the molecules of guinesines resulted in a series of dialkylaminomethyl-1,2-dithiolanes, -1,2,3-trithianes and 2,2-disubstituted 4-dialkylaminomethyl-1,3-dithiane derivatives. Among these compounds, the activity of 3-dimethylaminomethyl-1,2-dithiolane (**54**) and *cis*-3,5-bis(dimethylaminomethyl)-1,2-dithiolane (**55**) was almost the same as that of nereistoxin (**52a**).^{88, 90, 91}

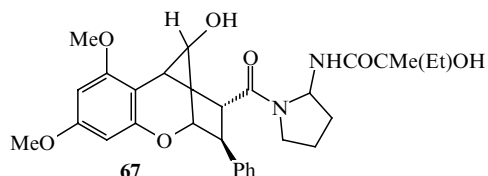
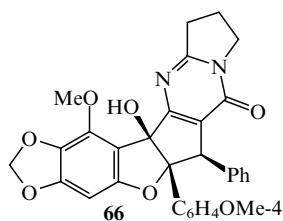


5-Substituted 1,3-dithiane derivatives and their *S*-oxides **56a,b**, 1,4-disubstituted 2,6,7-trithiabicyclo[2.2.2]octanes and their 2-oxides **57a,b**, 1,4-disubstituted 2,6,7-trioxabicyclo[2.2.2]octanes **58**, 4-substituted 2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-oxides and 1-sulfides **59a,b**, chlorinated 2,3:8,7-*endo*-4,6-dioxatricyclo[7.2.1.0^{2,8}]dodec-10-enes **60** and 2,3:8,7-*endo*-4,6-dioxa-5-thiatricyclo[7.2.1.0^{2,8}]dodec-10-ene oxides **61** are competitive inhibitors of the GABA-controlled chloride channels in a nerve cell membrane and show insectoacaricidal activity.^{92–97}

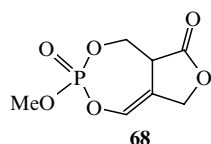


Substituents in the 5-position of compounds **56** and in the 4-position of compounds **57–59** not only substantially determine the neurotoxicity of these substances, but are also essential for their biodegradability under the action of various oxygenases.

Unfortunately, so far no commercial products among compounds **56–61** have been developed.



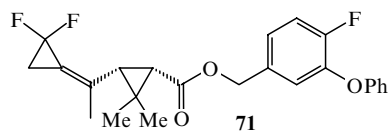
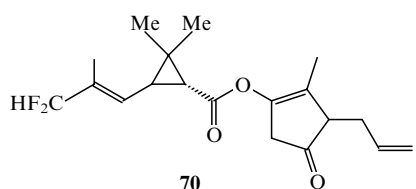
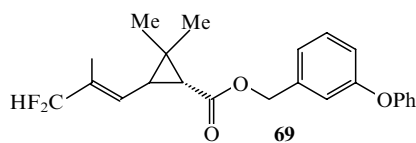
Interestingly, the first analogue of organophosphorus insecticides has been recently found among natural compounds. Antibiotic NK-901093 (**68**), which is an enol cyclophosphate, was isolated from *Streptomyces* sp. At a concentration of 0.1 mg litre⁻¹, this compound causes 100% mortality in mosquitoes and suppresses the activity of cholinesterase at concentrations four orders lower than that of malaoxon.¹¹¹



IV. Pyrethroids and other compounds

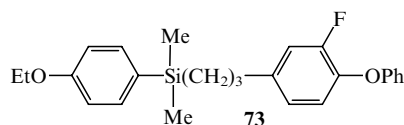
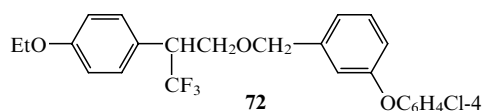
Recent years have been marked by the rapid rise in manufacture of pyrethroids, and the value of their sales has taken the first place among all types of insectoacaricides. Although it is worth mentioning that the real pyrethroid boom had already virtually abated in the 80's. In the 90's, the main emphasis in the research and manufacture of pyrethroids is made on the development of new technologies including the isolation of pure diastereomers and enantiomers for reduction of the usage rates of these compounds and minimisation of their impact on the environment. Apart from that, much attention is paid to the development of numerous multicomponent preparation forms, including mixtures, for their usage not only in farming but in the household, public health and industry.

The scope of the synthetic works on pyrethroids over recent years was not so large. The most interesting result in this field was the synthesis of fluorine- and silicon-containing derivatives of previously known synthetic pyrethroids. In the case of the synthesis of fluorinated pyrethroids, the fluorine atoms and fluorine-containing groups were introduced in both the acidic part of the molecule and the aromatic ring to make these compounds more stable toward hydrolysis and the action of oxygenases. Among these compounds, phenothrin (**69**) and bioallethrin (**70**) analogues containing the difluoroisobutenyl group¹¹² and an analogue of cyfluthrin (**71**) bearing a difluorocyclopropylidene moiety are worth mentioning.¹¹³



Compound **71** causes 100% mortality in *Spodoptera eridania*, *Aphis gossypii* and *Diabrotica undecimpunctata* at concentrations of 0.6, 2.5 and 2.5 mg litre⁻¹, respectively.

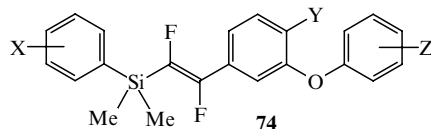
However, only two analogues of pyrethroids devoid of the ester group, viz., experimental insecticides flufenprox (**72**) and silafluofen (**73**), are of certain practical interest.^{114, 115}



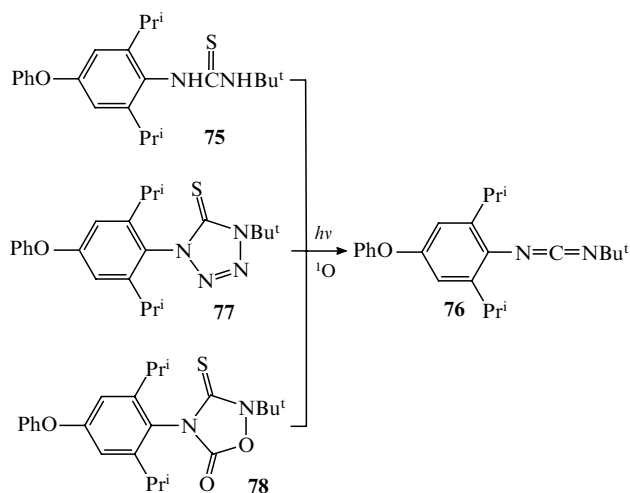
Flufenprox (**72**) has good economical and ecological characteristics, high insecticidal activity in doses of 75–300 g ha⁻¹ against a broad range of pests, and is harmless for warm-blooded animals and bees.

Silafluofen (**73**), which belongs to the group of silaneofans, is used against lepidopterans, dipterans, coleopterans, hemipterans, homopterans, etc., but is ineffective against aphids and whiteflies.

Analogues of silafluofen (**74**) containing the difluorinated double bond possess the high insecticidal activity.¹¹⁶



From the other groups of insectoacaricides, it is worth mentioning thiourea derivatives. Studies of the biological properties of several hundreds of di-, tri- and tetra-substituted thioureas has led to the preparation diafenthion, 1-*tert*-butyl-3-(2,6-diisopropyl-4-phenoxyphenyl)thiourea **75**. This is effective against sucking pests such as mites, aphids and whiteflies on cotton and vegetables. Upon UV irradiation or *in vivo*, compound **75** is converted into the corresponding carbodiimide **76**.^{117, 118} It is the latter that acts as an insecticide. This intermediate blocks the activity of mitochondrial ATPase and therefore is classified as an oxidative phosphorylation decoupler.¹¹⁸



A number of other compounds were also synthesised, which are converted after elimination of a part of the molecule into carbodiimide **76**. These are, for example, 1,4-disubstituted tetra-

zoline-5-thione (77) and 3-thioxo-1,2,4-oxadiazol-5-one (78). Field tests for these compounds have also given good results.¹¹⁹

In the author's opinion, all these studies represent a fine illustration of a propesticidal approach to the development of novel insectoacaricides.

In conclusion, some general tendencies in the manufacture and application of insectoacaricides should be noted. In 1996, the production of active principles of this group of insecticidal preparations had reached 680 000 tons with a total value of \$US 8.7 billion. According to the forecast, in 2001 the value of the insecticide sales will reach 10.5–10.7 billion dollars.

These figures show that in the beginning of the XXIst century (the author assumes that in the near future) the programmes for control of harmful insect and phytophagous mites will be based on the use of the chemical preparations despite certain recent achievements in the development of biological methods for plant protection, first of all, in the selection of transgenic plants resistant to pests. The portion of traditional preparations such as organophosphorus compounds, carbamates and pyrethroids will constitute not less than 80%–85% of all manufactured insectoacaricides. At the same time, the proportion of preparations with new modes of action will be gradually increased.

The wide assortment of preparations makes possible the successful application of technologies of integrated plant protection, which ensure the minimal impact of chemicals on the environment and prevent the development of resistant populations of arthropods.

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Electronic effects of substitution and reconstruction of the coordination polyhedron in adducts of Main Group IV element halides

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Abstract. Nuclear quadrupole resonance and X-ray data on the electronic effects of substitution of acidoligands and reconstruction of the coordination polyhedra in adducts (complexes) of tin(IV), germanium(IV) and silicon(IV) tetrahalides due to the change in the central metal coordination number are surveyed and systematically described. The σ - and π -electron density redistribution over the central metal–halogen bonds resulting from substitution or reconstruction of the coordination polyhedra from pseudooctahedral to trigonal-bipyramidal geometry is discussed. The bibliography includes 55 references.

I. Introduction

Redistribution of electron density upon substitution or reconstruction of the central atom coordination polyhedron in coordination compounds is a fundamental problem of the chemistry and stereochemistry of heteroligand complexes. Whereas the importance of this problem in the coordination chemistry of transition elements is widely known, the electronic effects in the chemistry of main group elements have been studied less extensively. Electronic effects of substitution as well as their steric manifestations are extremely diverse in such compounds, the resulting changes in the metal–halogen bonds being sensitive to details of the electronic structure of the whole adduct, *viz.*, the central metal, ligands and substituents. In most earlier publications, the electronic mechanism of substituent influence was discussed based on the position of ligands in various rows, AO occupancies determined by approximate quantum-chemical calculations and X-ray data. However, all these characteristics related only indirectly to the phenomenon in question, because the contribution of the substituents to the changes in the appropriate parameters is as a rule not unique and sometimes not predominant. Often, the results thus obtained do not allow determination of both the extent of the influence and even its direction. As a result, many important questions of the electronic mechanism of ligand influence in main

group element coordination compounds remain still open. In particular, quantitative data on electron density redistribution over the atomic σ and π orbitals as a result of either substitution of acidoligands or change in the adduct geometry, caused by the change in the central atom coordination number, were very scanty.

The intention of this review is to bring to the attention of researchers a feasibility of quantitative description of electron density redistribution in Main Group IV element coordination compounds using nuclear quadrupole resonance (NQR) spectroscopic data. Here we discuss only static influence of substituents, which reflects processes in a system in the ground state. In this case, a parameter can be used as a measure of substituent (ligand) electronic influence if it satisfies at least two requirements: first, it characterises a system in its ground state and second, it is changed predominantly under this influence. In this respect, NQR spectroscopic parameters seem to be quite suitable, since they are the ground-state characteristics of a system directly relating to the electron density distribution in the vicinity of a quadrupolar nucleus.

NQR spectroscopy investigates interactions between nuclei having nonzero quadrupole moment Q (all the nuclei with spin $I > 1/2$ have such a moment) and their local electric environment. The latter is characterised by the electric field gradient (EFG)

$$q_{ij} = \frac{\partial E_i}{\partial j} = \frac{\partial^2 U}{\partial ij},$$

where E_i is the strength of the electrostatic field, U is the electrostatic potential at the nuclear site and $i, j = x, y, z$. The directly measured spectroscopic parameters are the quadrupole coupling constant (QCC)

$$\text{QCC} = \frac{e^2 Q q_{zz}}{h},$$

where e is the charge on the electron and h is the Planck constant, and the EFG asymmetry parameter

$$\eta = \frac{|q_{xx} - q_{yy}|}{q_{zz}}.$$

Because the values of QCC and η depend directly on the electron density distribution around the nucleus under study, any weak disturbance of the electron density upon introduction of a substituent is clearly reflected in the NQR spectra. The physical

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principles of the NQR phenomenon, the scope and limitations of NQR spectroscopy in application to problems of inorganic and coordination chemistry have been reviewed.¹

X-Ray diffraction analysis is yet another approach to the study of substituent effects. However, one should bear in mind that the changes in interatomic distances depend on numerous factors which form the optimum crystal packing and are not necessarily related to the effects of substitution. Comparison of NQR and X-ray data allows one to determine the changes in effective charge on atoms upon the appropriate bond lengthening, which, in turn, helps to outline the range of variation of interatomic distances under the influence of substituents. The use of the two experimental techniques providing complementary pieces of information, on such important properties of compounds as electron density distribution and spatial arrangement of atoms, permits avoiding indirect estimations in the study of the problem on a quantitative level.

This review presents the results of NQR spectroscopic studies on the σ - and π -electron density redistribution over metal–halogen bonds in tin(IV), germanium(IV) and silicon(IV) halide complexes and adducts resulting from the substitution and/or change in the central atom coordination number. The following series are considered: $M\text{Hal}_4 \rightarrow M\text{Hal}_4\text{L} \rightarrow M\text{Hal}_4\text{L}_2$, $\text{SnHal}_4\text{L}_2 \rightarrow \text{R}_n\text{SnHal}_{4-n}\text{L}_2$ and $[\text{SnHal}_6]^{2-} \rightarrow [\text{RSnHal}_5]^{2-}$, where $M = \text{Sn, Ge and Si}$; $\text{Hal} = \text{Cl, Br and I}$; $\text{R} = \text{Alk and Ph}$; and L are oxygen- and nitrogen-containing ligands.

II. Electronic effects of substitution in adducts of tin(IV) halides

The problem of electron density redistribution over the atomic σ and π orbitals of metal–halogen bonds upon substitution in tin(IV) adducts of the type $\text{SnHal}_4\text{L}_2 ([\text{SnHal}_6]^{2-}) \rightarrow \text{R}_n\text{SnHal}_{4-n}\text{L}_2 ([\text{RSnHal}_5]^{2-})$ seems to be most intriguing. The solution of this problem requires the knowledge of the complete set of NQR spectroscopic parameters for the complexes and adducts of parent tin tetrahalides including the asymmetry parameters η of the halogen atoms. In this respect, iodostannates are most suitable for NQR studies, because the iodine (^{127}I) nuclear spin is $I = 5/2$ and the QCC and η values in the iodo adducts can be found, provided both resonance transition frequencies, ν_1 ($\Delta m = 1/2 - 3/2$) and ν_2 ($\Delta m = 3/2 - 5/2$) are observed.¹ No additional experiments are necessary in this case, whereas they are necessary for determining η in chlorostannates, because only two degenerate quadrupole levels and one transition frequency are available for chlorine nuclei with $I = 3/2$, which precludes simultaneous determination of the QCC and η values from the known relationship

$$\nu = \frac{e^2 Q q_{zz}}{2h(1 + \eta^2/3)^{1/2}}.$$

The EFG asymmetry parameter provides additional information on the electron density distribution around the nucleus in question, because η is a measure of the bonding electron cloud axial asymmetry. Hence the problem of measuring η on the $^{35,37}\text{Cl}$ nuclei with $I = 3/2$, which are most often subject to NQR studies, is considered by spectroscopists as being of current interest, and various attempts were undertaken to solve it. Most determinations of η on the ^{35}Cl atoms were made by Zeeman studies of single crystals.^{1,2} These measurements provide high precision of the η values and permit determination of the orientation of the EFG axes with respect to the crystallographic axes of the specimen. However, this approach substantially reduces the number of the compounds that can be examined, eliminating those air- or moisture-sensitive as well as presenting problems for the crystal growth.

The number of reports on the determination of η in crystalline powders is much less. The majority of the results published by foreign authors were obtained using the CW technique, which as a

rule gives low accuracy of measurements². The advantages of pulsed methods over stationary ones for measuring η in powders were outlined in the review.¹ One approach was based on the Fourier-analysis of slow beats of the spin echo envelope in external magnetic fields of 15–100 G. In powders of chlorine-containing compounds, this provided values of η in reasonable agreement with those available for the appropriate single crystals.³ This approach was applied for determination of η in organic and organoelement compounds.^{4–7} Later, it was modified⁸ to be used for measuring η in a large number of adducts of tin, germanium and silicon tetrachlorides.^{9–12}

The determination of η in compounds in question enables one to escape the σ -approximation, to take into account the electron density distribution over the tin–halogen σ and π orbitals and to juxtapose trends in electron density redistribution upon substitution of different groups for acidoligands. Within the Townes and Dailey theory approximations, the measured NQR spectroscopic parameters (QCC and η) are related to the halogen atom valence p -orbital occupancies Np_i ($i = x, y, z$) and electronic characteristics of metal–halogen bonds as follows:

$$U_p = \frac{e^2 Q q_{zz}}{e^2 Q q_0} = \left| \frac{Np_x + Np_y}{2} - Np_z \right| = \sigma - \frac{\pi}{2}, \quad (1)$$

$$\eta = \frac{q_{xx} - q_{yy}}{q_{zz}} = \frac{3(Np_x - Np_y)}{2Np_z - (Np_x + Np_y)} = \frac{3(\pi_x - \pi_y)}{2U_p}, \quad (2)$$

where $e^2 Q q_{zz}$ is the QCC value at the halogen atom, $e^2 Q q_0$ is the atomic QCC produced by a single electron on the valence p_z orbital of the halogen atom;

$$Np_z = 2 - \sigma,$$

$$Np_x = 2 - \pi_x,$$

$$Np_y = 2 - \pi_y;$$

$$\pi_x + \pi_y = \pi; \quad i + \sigma + \pi = 1,$$

where i , σ and π are the ionic, covalent and π -character of the bond.

Whereas the mutual ligand influence in similar transition metal compounds is known to alter the metal–halogen bonds in such a way that the *trans*-influence is prevailing and is accompanied by a slight change in the *cis*-bonds, the resulting changes in the Sn–Hal bonds due to the introduction of substituents R into $[\text{SnHal}_6]^{2-}$ or SnHal_4L_2 were found to be sensitive to details of the electronic structure of the whole adduct, *viz.*, to the AO energies for the central atom, the halogen atoms and substituents as well as to the oxidation state of the central atom. Depending on the oxidation state of the central metal and its position in the Periodic Table, *cis*-weakening, or *trans*-weakening or *cis*-weakening accompanied by a relatively smaller *trans*-influence can prevail, both strengthening and weakening being possible in principle. Various theoretical approaches have been developed to describe the effects of substituents (ligands) in main group element complexes.

Based on the model of equivalent orbitals applicable to compounds having covalent two-electron two-centre bonds, the mechanism of ligand influence was described as purely inductive.¹³ As a result of substitution, the M – Hal bonds were predicted to undergo changes so as to provide prevailing of *cis*-over *trans*-influence. In the approach using the canonical σ -MO within the perturbation theory approximations, the atomic orbital energies of the halogen ligands and substituents were assumed to be close to each other.¹⁴ According to this approach a *trans*-influence prevailing over relatively weak *cis*-influence was expected as the contribution of the np orbitals of the central atom became more pronounced. A consideration which took into account all the transitions between the occupied and vacant MOs suggested that the central atom valence basis set involved mostly ns and np orbitals rather than the vacant nd -AOs.¹⁵ The resulting

change in the the M—Hal bond character upon substitution was determined in this case by a relationship between the energies of the levels for the valence *ns*- and *np*-AOs of the central atom and *s*-AOs of typical ligands. This means that the influence was expected to be essentially different for the compounds of Groups II–IV (type I) and VII (type II) elements. Thus the substitution $[\text{MHal}_6]^{2-} \rightarrow [\text{RMHal}_5]^{2-}$ in complexes of the Main Group IV element was predicted to result in contraction of the $[\text{MHal}_6]^{2-}$ octahedron along the *z* axis and its expansion in equatorial directions, if substituent R is more electropositive than Hal, whereas the octahedron will be expanded along the *z* axis and contracted in the *x*, *y* directions, if R is more electronegative than Hal.

A model of hypervalent (HV) orbital-deficient bonds¹⁶ applied to tin(IV) compounds¹⁷ suggests that the central atom valence basis involves only *ns* and *np* orbitals. According to this model, in the parent $[\text{SnHal}_6]^{2-}$ complex, the 5*s* orbitals of the tin atom participate in the formation of three equivalent three-center *sp*-hybrid hypervalent (HV-I) bonds Hal—Sn—Hal, each involving only one 5*p* orbital of the tin atom. The σ -level energies of the substituents R in adducts (complexes) $\text{R}_n\text{SnHal}_{4-n}\text{L}_2$ and $[\text{SnHal}_6]^{2-}$ are then close in value to those of the *p* levels of the central atom, while the σ -level energies of the acidoligands are close in value to those of the *s* levels of the tin atom.

In alkyl- and dialkyl-substituted complexes, occupation of a_1^* MOs occurs, which are antibonding with respect to the equatorial ligands. Because the a_1^* MOs contain a remarkable contribution from the *s* orbital of the central atom, the *s*-character of the equatorial bonding orbitals is reduced, so that the corresponding bonds (HV-II) are weakened compared to the bonds HV-I in the parent unsubstituted complex $[\text{SnHal}_6]^{2-}$. On the other hand, alkyl substituents R cannot form stable hypervalent bonds with tin, because R is less electronegative than the tin atom, so that the Alk—Sn bonds are ordinary covalent two-centre two-electron bonds.

Thus, for the adducts and complexes $\text{R}_n\text{SnHal}_3\text{L}_2$ and $[\text{R}_n\text{SnHal}_5]^{2-}$, the model of hypervalent orbital-deficient bonds predicts weakening of the Sn—Hal bonds at the *cis*-position to the alkyl substituent compared to the bonds in the initial SnHal_4L_2 or $[\text{SnHal}_6]^{2-}$ compounds. The weakening can be accompanied by *trans*-influence, presumably strengthening of the Sn—Hal bond at the *trans*-position to the substituent R.

Using NQR, the electronic effects of substitution were observed experimentally: the direction of the *trans*-influence was determined and the relative importance of the effects of *cis*- and *trans*-influence was quantitatively compared. Most clear manifestations of both effects were obtained for pseudooctahedral complexes of the type $[\text{R}_n\text{SnHal}_5]^{2-}$ and molecular adducts $\text{R}_n\text{SnHal}_{4-n}\text{L}_2$ where the tin atom is in its highest oxidation state and either one or two acidoligands (Hal) are substituted for alkyl groups R, which considerably exceed the halogen ligands in donating power. The effects of substitution were especially strong in these compounds, and we discuss here how the substitution influences the σ - and π -electron density distribution in the complexes and molecules of adducts.

Tables 1 and 2 list the NQR spectroscopic parameters measured for the substituted tin(IV) compounds and their unsubstituted precursors, hexahalostannates $\text{Cat}_2\text{SnHal}_6$ (Cat is cation) and pseudooctahedral adducts of tin tetrahalides SnHal_4L_2 . The appropriate Sn—Hal interatomic distances wherever available are also given in these tables. As is seen from Tables 1 and 2, the *cis*- and *trans*-influence of the substituents is clearly reflected in the NQR spectra, which enables one to compare their contribution to the resulting electron density redistribution on a quantitative scale. In Tables 3 and 4, the halogen atom valence p_σ orbital occupancies (N_{p_z}) and p_π orbital occupancy differences ($\Delta N_{p_\pi} = N_{p_x} - N_{p_y}$), estimated from the NQR data, are given for the adducts and complexes of parent unsubstituted and mono- and dialkyl(diphenyl)-substituted tin halides $[\text{R}_n\text{SnHal}_5]^{2-}$, $\text{R}_n\text{SnHal}_3\text{L}_2$, $\text{R}_2\text{SnHal}_2\text{L}_2$. The main sources of inaccuracy in the

determination of the spectroscopic parameters as well as the reliability of interpreting the spectral data were discussed in a review.³ Based on the estimated values of the atomic orbital occupancies, the effective charges (ρ) on the halogen atoms and their variation ($\Delta\rho$) as a result of the introduction of the substituents R were determined

$$\Delta\rho = \frac{\rho(\text{R}_n\text{SnHal}_{4-n}\text{L}_2) - \rho(\text{SnHal}_4\text{L}_2)}{\rho(\text{SnHal}_4\text{L}_2)}. \quad (3)$$

Similarly, the variation of the Sn—Hal bond distances (Δd) was estimated in compounds whose structures were studied

$$\Delta d = \frac{d(\text{R}_n\text{SnHal}_{4-n}\text{L}_2) - d(\text{SnHal}_4\text{L}_2)}{d(\text{SnHal}_4\text{L}_2)}. \quad (4)$$

The values of Δd are also listed in Tables 3 and 4.

The NQR spectra provide evidence for a profound electron density redistribution upon substitution. The negative effective charge on the halogen atoms in the *cis*-position to the substituent R increases in absolute magnitude with respect to the corresponding parent compounds hence yielding the positive values of $\Delta\rho$ (Tables 3 and 4). On the halogen atoms in the *trans*-position to the substituent, the absolute magnitude of the charge falls as compared to that in the parent unsubstituted adduct. The negative values of $\Delta\rho$, found for the *trans*-halogens in all the adducts studied, indicate that the *trans*-influence of substituents R always acts in these compounds as *trans*-strengthening of the Sn—Hal bonds. The only exception was the adduct $\text{EtSnCl}_3(\text{DMSO})_2$ (Table 3), in which strong donor ligands compensate the effect of *trans*-strengthening (and accordingly *trans*-shortening). The introduction of an ethyl group into a $[\text{SnCl}_6]^{2-}$ complex (its singlet NQR spectrum points to the equivalence of all the chlorine atoms) results in the formation of the complex $[\text{EtSnCl}_5]^{2-}$ characterised by an NQR spectrum with a spectroscopic splitting of 6 MHz between the frequencies, assigned to the chlorine atoms in *cis*- and *trans*-positions relative to the substituent R. The effective charges on the appropriate chlorine atoms differ on average by 0.1 e. The difference between the characteristics of the *cis*- and *trans*-bromine atoms in the complex $[\text{BuSnBr}_5]^{2-}$ is even more pronounced: the splitting of the corresponding ^{81}Br NQR frequencies exceeds 50 MHz, whereas the difference in effective charges on the corresponding Br atoms reaches 0.16 e (see Ref. 3).

It is evident that such values of frequency shifts and spectroscopic splittings are mainly due to the intramolecular electronic rather than crystal-field effects. A correlation between the ^{35}Cl NQR frequencies and Sn—Cl bond lengths was examined for a large number of chlorine-containing tin compounds including hexacoordinate tin(IV) complexes of the types $\text{Cat}_2\text{SnHal}_6$ and $\text{Cat}_2\text{R}_n\text{SnHal}_5$ with various cations and anions, electroneutral adducts of types SnCl_4L_2 and $\text{R}_2\text{SnCl}_2\text{L}_2$ and compounds $\text{R}_n\text{SnCl}_{4-n}$, where the tin atom is tetracoordinate and both terminal and bridging chlorine atoms are available.¹⁹ Tin(II) compounds $\text{SnCl}_2 \cdot x\text{H}_2\text{O}$ ($x = 0, 1.5, 2$) were also taken into consideration. The results of the analysis showed that the maximum contribution of the crystal field to the frequency shifts and Sn—Cl bond lengths in these compounds does not exceed 2 MHz and 0.05 Å, respectively. These contributions are evidently less in crystallochemically similar chlorine-containing compounds listed in Tables 3 and 4. Their further decrease occurs on going to more covalent tin(IV) bromo- and iodo compounds. It should be added that the relative changes of the effective charges on atoms are considered as the measure of substituent effects rather than their absolute values. Thus the electronic effect of the ethyl substituent in pentachloroethylstannate was estimated from changes in the effective charges on the chlorine atoms compared to those in the parent hexachlorostannate with the same cation, which implies that the crystal field contributions to the ^{35}Cl NQR frequencies of both pentachloroethyl- and hexachloro-stannate are virtually the same.^{20, 21}

Table 1. ^{35}Cl and ^{81}Br frequencies [$\nu(^{35}\text{Cl})$ and $\nu(^{81}\text{Br})/\text{MHz}$], EFG asymmetry parameters (η) in the NQR spectra of SnHal_4L_2 , $[\text{SnHal}_6]^{2-}$, $\text{R}_n\text{SnHal}_{4-n}\text{L}_2$ and $[\text{RSnHal}_5]^{2-}$ at 77 K and Sn–Hal bond distances (d).^{9–11, 18, 19–22, 23}

Compound	$\nu(^{35}\text{Cl})$	η (%)	$d(\text{Sn}–\text{Cl})/\text{\AA}$	Assignment	$\nu(^{81}\text{Br})$	η (%)	$d(\text{Sn}–\text{Br})/\text{\AA}$	Assignment
$(\text{NMe}_4)_2\text{SnHal}_6^{\text{a}}$	16.683	—	2.424(3)	Cl–Sn–Cl	115.07	—	2.605(1)	Br–Sn–Br
$(\text{NMe}_4)_2\text{RSnHal}_5^{\text{a}}$	12.329	{10.0}	2.516(10)	Cl–Sn–Cl	81.94	{10.0}	2.699(5)	Br–Sn–Br
	18.070	—	2.407(3)	Cl–Sn–Et	133.36	—	2.566(2)	Br–Sn–Bu
$(\text{MeNH}_3)_2\text{SnCl}_6^{\text{a}}$	15.815	—	2.417(3)	Cl–Sn–Cl				
$(\text{MeNH}_3)_2\text{EtSnCl}_5^{\text{a}}$	12.072	11.7(3)	2.507(1)	Cl–Sn–Cl				
	11.537	14.6(3)	2.531(1)	Cl–Sn–Cl				
	10.770	15.4(3)	2.497(1)	Cl–Sn–Cl				
	9.969	17.1(3)	2.549(1)	Cl–Sn–Cl				
	17.032	5.6(3)	2.426(1)	Cl–Sn–Et				
$(\text{PyH})_2\text{SnCl}_6^{\text{a}}$	16.588	—	2.431(1)	Cl–Sn–Cl				
$(\text{PyH})_2\text{EtSnCl}_5^{\text{a}}$	11.322	{14.0}	2.518(1)	Cl–Sn–Cl				
	17.926	—	2.401(2)	Cl–Sn–Et				
L = HMPT				L = HMPT				
<i>trans</i> - SnHal_4L_2	17.91	10.6	2.388(1)	Cl–Sn–Cl	127.75	{10.6}	2.55(1)	Br–Sn–Br
<i>trans</i> - $\text{RSnHal}_3\text{L}_2$	20.02	{0–5.0}	2.379(1)	Cl–Sn–Et	132.60	{> 6.5}	2.529(1)	Br–Sn–Bu
	—	—	2.491(1)	Cl–Sn–Cl	93.82	{10.6}	2.633(1)	Br–Sn–Br
<i>trans</i> - $\text{PhSnCl}_3\text{L}_2$	18.525	{> 6.7}	—	Cl–Sn–Ph				
	14.045	{10.6}	—	Cl–Sn–Cl				
<i>trans</i> - $\text{Me}_2\text{SnHal}_2\text{L}_2$	9.450	{10.6}	2.570(1)	Cl–Sn–Cl	60.61	{10.6}	2.74(1)	Br–Sn–Br
L = THF				L = THF				
<i>trans</i> - SnHal_4L_2	19.02	13.5	—	Cl–Sn–Cl	132.44	{13.5}	—	Br–Sn–Br
$\text{MeSnHal}_3\text{L}_2$	20.17	{> 7.0}	—	Cl–Sn–Me	141.12	{> 6.2}	—	Br–Sn–Me
	15.45	{13.5}	—	Cl–Sn–Cl	104.70	{13.5}	—	Br–Sn–Br
$\text{Me}_2\text{SnBr}_2\text{L}_2$					99.04	{13.5}	—	Br–Sn–Br
L = TMU				L = TMU				
<i>trans</i> - SnHal_4L_2	18.24	7.5	2.391(1)	Cl–Sn–Cl	124.44	{7.5}	—	Br–Sn–Br
<i>trans</i> - SnHal_3L_2	19.35	{> 1.4}	2.374(4)	Cl–Sn–Et				
	13.47	{7.5}	2.491(4)	Cl–Sn–Cl				
<i>trans</i> - $\text{Et}_2\text{SnBr}_2\text{L}_2$					75.71	{7.5}	—	Br–Sn–Br
L = DMSO				L = DMSO				
<i>cis</i> - SnHal_4L_2	18.36	{3.0}	2.382(3)	Cl–Sn–Cl	118.17	{3.0}	—	Br–Sn–Br
	17.045	{14.0}	2.391(3)	Cl–Sn–O	127.73	{14.0}	—	Br–Sn–O
<i>cis</i> - $\text{EtSnCl}_3\text{L}_2$	13.52	14.0	2.456(4)	Cl–Sn–O				
	16.96	3.0	2.398(3)	Cl–Sn–Et				
<i>cis</i> - $\text{Me}_2\text{SnCl}_2\text{L}_2$	10.40	{14.0}	2.51(1)	Cl–Sn–O				
<i>trans</i> - $\text{Me}_2\text{SnBr}_2\text{L}_2$					59.46	{14.0}	2.752(1)	Br–Sn–Br
L = Me_2CO								
<i>cis</i> - SnHal_4L_2	19.75	1.2	—	Cl–Sn–Cl				
	19.135	7.0	—	Cl–Sn–O				
L = DMF								
<i>trans</i> - SnCl_4L_2	17.77	5.7	—	Cl–Sn–Cl				
<i>cis</i> - $\text{Me}_2\text{SnCl}_2\text{L}_2$	11.13	{5.7}	2.47(1)	Cl–Sn–O				
				L = DPSO				
<i>cis</i> - SnBr_4L_2					116.63	—	2.556(1)	Br–Sn–Br
					128.30	—	2.527(2)	Br–Sn–O
<i>cis</i> - $\text{BuSnBr}_3\text{L}_2^{\text{b}}$					90.72	—	2.627(2)	Br–Sn–Br
					102.40	—	2.559(1)	Br–Sn–O
L = py				L = py				
<i>trans</i> - SnHal_4L_2	17.70	15.4	—	Cl–Sn–Cl	122.66	{15.4}	—	Br–Sn–Br
<i>trans</i> - $\text{Me}_2\text{SnHal}_2\text{L}_2$					65.76	{15.4}	2.719(5)	Br–Sn–Br
<i>trans</i> - $\text{Et}_2\text{SnHal}_2\text{L}_2$					64.61	{15.4}	—	Br–Sn–Br
				L = bipy				
<i>cis</i> - SnBr_4L					118.87	{0.0}	2.565(1)	Br–Sn–Br
					129.92	{15.4}	2.540(1)	Br–Sn–N
<i>cis</i> - $\text{Bu}_2\text{SnBr}_2\text{L}_2$					74.69	{15.4}	2.714(1)	Br–Sn–N

Note. Resonance frequencies of chemically equivalent halogen atoms are averaged over crystallographically inequivalent positions for all the compounds except for $(\text{MeNH}_3)_2\text{EtSnHal}_5$. The values expected by analogy with those measured for the related compounds are given in braces. HMPT is hexamethylphosphortriamide; THF is tetrahydrofuran; TMU is tetramethyl urea; DMSO is dimethyl sulfoxide; DMF is dimethylformamide; DPSO is diphenyl sulfoxide; py is pyridine; bipy is bipyridyl.

^a The NQR data at 300 K. ^b The substituent R (Bu) is in *trans*-position to the ligand DPSO.²⁴

Table 2. ^{127}I NQR spectroscopic parameters [ν_1 , ν_2 , e^2Qq_{zz}/h (MHz); η] for adducts SnI_4L_2 and $\text{R}_n\text{SnI}_{4-n}\text{L}_2$ at 77 K and Sn–I bond distances (d).^{12, 18, 25, 26}

Compound	ν_1	ν_2	e^2Qq_{zz}/h	η (%)	$d/\text{\AA}$	Assignment
L = HMPT						
<i>cis</i> - SnI_4L_2	156.15	312.15 ^a	1040.59 ^a	{1.9}	—	I–Sn–I
	164.61	327.69 ^a	1093.11 ^a	{6.0}	—	I–Sn–O
<i>cis</i> - EtSnI_3L_2	166.40	—	—	—	2.634(4)	I–Sn–Et
	111.30	219.17	732.40	11.0	2.886(2)	I–Sn–O
	109.80	—	—	—	2.901(2)	I–Sn–O
<i>trans</i> - $\text{Et}_2\text{SnI}_2\text{L}_2$	70.51	140.26	467.90	6.5	3.016(1)	I–Sn–I
<i>trans</i> - $\text{Ph}_2\text{SnI}_2\text{L}_2$ (see ^b) (I)	86.92	144.00	495.17	41.2	2.957(1)	I–Sn–I
	(II) 88.46	146.60	504.08	41.2	2.938(1)	I–Sn–I
L = TMU						
<i>cis</i> - SnI_4L_2	157.27	314.39	1048.04	1.9	—	I–Sn–I
	164.93	328.35	1095.28	6.0	—	I–Sn–O
L = TPPO ^c						
<i>cis</i> - SnI_4L_2	158.36	—	—	—	2.813(2)	I–Sn–I
	163.42	—	—	—	2.782(2)	I–Sn–O
L = bipy						
<i>cis</i> - SnHal_4L	153.68	—	—	—	2.816(2)	I–Sn–I
	169.29	—	—	—	2.788(2)	I–Sn–N
L = DMSO						
<i>cis</i> - SnI_4L_2	150.65	—	—	—	—	I–Sn–I
	166.55	—	—	—	—	I–Sn–O
<i>cis</i> - $\text{Et}_2\text{SnI}_2\text{L}_2$	70.83	119.30	409.07	39.1	2.941(1)	I–Sn–O
	79.96	156.34	523.00	13.3	2.982(1)	I–Sn–O
$\text{Ph}_2\text{SnI}_2\text{L}_2$	103.17	192.00	647.32	24.3	—	—
	107.02	212.04	707.80	8.6	—	—
L = py						
<i>trans</i> - SnI_4L_2	162.66	—	—	—	—	I–Sn–I
$\text{Et}_2\text{SnI}_2\text{L}_2$	80.92	149.36	504.35	25.7	—	I–Sn–I
	82.01	162.38	542.13	8.8	—	I–Sn–I
$\text{Ph}_2\text{SnI}_2\text{L}_2$	98.11	187.68	630.03	18.9	—	I–Sn–I
L = DPPO						
<i>cis</i> - SnI_4L_2	154.41	305.00	1018.70	9.8	2.806(1)	I–Sn–I
	163.72	—	—	—	2.781(1)	—
	164.58	—	—	—	2.776(1)	—
	167.22	—	—	—	2.773(1)	—
<i>cis</i> - EtSnI_3L_2	130.50	—	—	—	2.869(1)	I–Sn–I
	136.50	268.00	895.10	12.4	2.840(1)	I–Sn–I
					2.821(1)	I–Sn–O

Note. Resonance frequencies of chemically equivalent iodine atoms are averaged over crystallographically inequivalent positions. The values expected by analogy to those measured for the related compounds are given in braces.

^a Calculated. ^b The unit cell comprises two crystallographically independent molecules of the adduct. ^c Triphenylphosphine oxide.

As is seen from Tables 3 and 4, the prevailing effect of substitution is, in agreement with the earlier conclusions,¹⁷ weakening of the *cis*-Sn–Hal bonds relative to the substituent R as compared to the Sn–Cl bonds in the corresponding non-substituted complexes (adducts). The elongation of the Sn–Hal bond by 0.1 Å is accompanied by an increase in the effective negative charge on the chlorine, bromine and iodine atoms by *ca.* 0.08, 0.1 (see Ref. 18) and 0.12 e (see Ref. 12), respectively. It is noteworthy that according to the X-ray data the elongation of the *cis*-Sn–Hal bond relative to the substituent R is the same for all the monoalkyl-substituted adducts of any halogen element, amounting approximately to 0.1 Å. The similar bond elongation is accompanied by an increment of the negative charge on the corresponding halogen atom, which points to an increase in *cis*-weakening due to the alkyl group in the order Cl < Br < I.^{12, 18}

Phenyl substituents also weaken the appropriate Sn–Hal bonds, although to a lesser extent. The effective charges born by the iodine atoms in dialkyl- and diphenyl-substituted adducts $\text{R}_2\text{SnI}_2\text{L}_2$ were estimated¹² to differ, on average, by 0.08 e. In adducts of mono-substituted tin halides, both *cis*-weakening and *trans*-strengthening are also more pronounced in alkyl-substituted adducts than in phenyl analogues (Tables 1 and 3). Variations of the effective charges on the halogen atoms in *cis*- and *trans*-positions to the substituent R as well as their valence p_π orbital occupancies resulting from substitution can clearly be compared on a quantitative scale. As follows from comparison of the absolute magnitudes of $\Delta\rho$ (Table 3), a negative charge increment on the halogen atoms, *i.e.*, the effect of *cis*-weakening of the Sn–Hal bond as a result of substitution, is 2–3 times as strong as that of *trans*-strengthening. Comparison of the corresponding

Table 3. Changes in the Sn–Hal bond characteristics in the adducts of tin tetrahalides as a result of substitution $\text{SnHal}_4\text{L}_2 \rightarrow \text{RSnHal}_3\text{L}_2$.

Compound	Np_σ	ΔNp_π	$-\rho/e$	$\Delta\rho$ (%)	Δd (%)	Assignment
(NMe ₄) ₂ SnCl ₆	1.696	0.0 ^a	0.696	—	—	Cl–Sn–Cl
(NMe ₄) ₂ EtSnCl ₅	1.670	0.0 ^a	0.670	–3.7	–0.7	Cl–Sn–Et
	1.768	0.015	0.753	+8.2	+3.8	Cl–Sn–Cl
(NMe ₄) ₂ SnBr ₆	1.642	0.0 ^a	0.642	—	—	Br–Sn–Br
(NMe ₄) ₂ EtSnBr ₅	1.585	0.0 ^a	0.585	–8.9	–1.5	Br–Sn–Et
	1.733	0.017	0.716	+11.5	+3.6	Br–Sn–Br
(MeNH ₃) ₂ SnCl ₆	1.712	0.0 ^a	0.712	—	—	Cl–Sn–Cl
(MeNH ₃) ₂ EtSnCl ₅	1.684	0.012	0.672	–5.6	+0.4	Cl–Sn–Et
	1.772	0.017	0.755	—	—	Cl–Sn–Cl
	1.780	0.020	0.760	+8.0	+4.3	Cl–Sn–Cl
	1.794	0.020	0.774	???	($\Delta A.E.$)	Cl–Sn–Cl
	1.809	0.021	0.788	—	—	Cl–Sn–Cl
(PyH) ₂ SnCl ₆	1.698	0.0 ^a	0.698	—	—	Cl–Sn–Cl
(PyH) ₂ EtSnCl ₅	1.673	0.0 ^a	0.673	–3.6	–1.2	Cl–Sn–Et
	1.785	0.019	0.766	+9.7	+2.8	Cl–Sn–Cl
L = TMU						
SnCl ₄ L ₂	1.659	0.017	0.642	—	—	Cl–Sn–Cl
EtSnCl ₃ L ₂	1.645	>0.003	<0.642	<0.0	–0.7	Cl–Sn–Et
	1.748	0.012	0.736	+14.6	+4.2	Cl–Sn–Cl
L = DMSO						
SnCl ₄ L ₂	1.662	0.007	0.655	—	—	Cl–Sn–Cl
	1.676	0.029	0.647	—	—	Cl–Sn–O
EtSnCl ₃ L ₂	1.688	0.006	0.682	+4.1	+0.7	Cl–Sn–Et
	1.743	0.023	0.720	+11.2	+2.7	Cl–Sn–O
L = HMPT						
SnCl ₄ L ₂	1.663	0.023	0.640	—	—	Cl–Sn–Cl
EtSnCl ₃ L ₂	1.630	0.097	0.620 ^b	–3.2	–0.4	Cl–Sn–Et
				+4.3		Cl–Sn–Cl
PhSnCl ₃ L ₂	1.655	<0.015	<0.640	<0.0	—	Cl–Sn–Ph
	1.735	0.019	0.716	+11.9	—	Cl–Sn–Cl
SnBr ₄ L ₂	1.589	0.028	0.561	—	—	Br–Sn–Br
BuSnBr ₃ L ₂	1.579	>0.018	<0.561	<0.0	–0.8	Br–Sn–Bu
	1.698	0.020	0.678	+20.8	+3.2	Br–Sn–Br
L = THF						
SnCl ₄ L ₂	1.639	0.031	0.607	—	—	Cl–Sn–Cl
MeSnCl ₃ L ₂	1.624	>0.017	<0.607	<0.0	—	Cl–Sn–Me
	1.707	0.025	0.682	+12.3	—	Cl–Sn–Cl
SnBr ₄ L ₂	1.571	0.037	0.534	—	—	Br–Sn–Br
MeSnBr ₃ L ₂	1.552	>0.018	<0.534	<0.0	—	Br–Sn–Me
	1.661	0.029	0.632	+18.3	—	Br–Sn–Br

^a In the absence of the experimental data, it was assumed that $\eta = 0$; from symmetry considerations, the real η -value should not exceed 5%–10%.

^b At $\eta = 4\%$.

values for ΔNp_π shows that the equatorial π -bonds in monoalkyl-substituted adducts remain virtually undisturbed by *cis*-weakening, whereas *trans*-strengthening seems to involve both σ - and π -bonds. In most of the $\text{RSnHal}_3\text{L}_2$ compounds, *trans*-strengthening of the Sn–Hal bond occurs only if η is non-zero, hence revealing disturbance of the halogen π -system. In chlorine-containing adducts, the η -values, at which *trans*-strengthening takes place, show the tendency to an increase as the donating power of either substituent R (provided the ligand L remains the same) or ligand L (provided the substituent R remains the same) decreases. Thus, *trans*-strengthening in the adduct $\text{PhSnCl}_3(\text{HMPT})_2$ can only be observed when the η -value for the appropriate chlorine atom reaches 6.7%, whereas in its ethyl analogue $\text{EtSnCl}_3(\text{HMPT})_2$, it is observed at $\eta = 0$ and reaches 3% at $\eta = 4\%$. However, *trans*-strengthening in the adduct

Table 4. Changes in the Sn–Hal bond characteristics in the adducts of tin tetrahalides as a result of substitution $\text{SnHal}_4\text{L}_2 \rightarrow \text{R}_2\text{SnHal}_2\text{L}_2$.

Compound	Np_σ	ΔNp_π	$-\rho/e$	$\Delta\rho$ (%)	Δd (%)	Assignment
L = HMPT						
SnCl ₄ L ₂	1.663	0.023	0.640			Cl–Sn–Cl
Me ₂ SnCl ₂ L ₂	1.822	0.012	0.810	+26.6	+7.6	Cl–Sn–Cl
SnI ₄ L ₂	1.543	0.006	0.537			I–Sn–I
	1.514	0.019	0.495			I–Sn–O
Et ₂ SnI ₂ L ₂	1.791	0.009	0.782	+51.5	+7.8 ^a	I–Sn–I
Ph ₂ SnI ₂ L ₂ (I)	1.754	0.059	0.695	+34.7	+5.7 ^a	I–Sn–I
(II)	1.750	0.060	0.689	+33.5	+5.0 ^a	I–Sn–I
SnBr ₄ L ₂	1.589	0.028	0.561			Br–Sn–Br
Me ₂ SnBr ₂ L ₂	1.805	0.014	0.791	+41.0	+7.4	Br–Sn–Br
L = TMU						
SnI ₄ L ₂	1.540	0.006	0.534			I–Sn–I
	1.512	0.019	0.493			I–Sn–O
SnBr ₄ L ₂	1.604	0.018	0.586			Br–Sn–Br
Et ₂ SnBr ₂ L ₂	1.759	0.011	0.748	+27.6		Br–Sn–Br
L = DMF						
SnCl ₄ L ₂	1.670	0.012	0.658			Cl–Sn–Cl
Me ₂ SnCl ₂ L ₂	1.793	0.008	0.785	+19.3		Cl–Sn–O
L = DMSO						
Et ₂ SnI ₂ L ₂	1.798	0.046	0.752	+52.5 ^b	+5.0 ^c	I–Sn–O
	1.762	0.020	0.742	+50.5 ^b	+6.4 ^c	I–Sn–O
Ph ₂ SnI ₂ L ₂	1.695	0.046	0.649	+31.6 ^b		—
	1.682	0.018	0.665	+34.9 ^b		—
SnBr ₄ L ₂	1.629	0.007	0.622			Br–Sn–Br
	1.586	0.037	0.549			Br–Sn–O
Me ₂ SnBr ₂ L ₂	1.807	0.017	0.790	+35.0	+7.7 ^d	Br–Sn–Br
SnCl ₄ L ₂	1.662	0.007	0.655			Cl–Sn–Cl
	1.676	0.029	0.647			Cl–Sn–O
Me ₂ SnCl ₂ L ₂	1.802	0.017	0.785	+21.3	+5.0	Cl–Sn–O
L = bipy						
SnBr ₄ L	1.630	0.004	0.630			Br–Sn–Br
	1.577	0.041	0.536			Br–Sn–N
Bu ₂ SnBr ₂ L	1.757	0.024	0.733	+36.7	+6.8	Br–Sn–N
L = THF						
SnBr ₄ L ₂	1.571	0.037	0.534			Br–Sn–Br
Me ₂ SnBr ₂ L ₂	1.679	0.028	0.651	+21.9		Br–Sn–Br
L = py						
Et ₂ SnI ₂ L ₂	1.761	0.038	0.723			I–Sn–I
	1.757	0.014	0.742			I–Sn–I
Ph ₂ SnI ₂ L ₂	1.708	0.035	0.673			I–Sn–I
SnBr ₄ L ₂	1.601	0.038	0.563			Br–Sn–Br
Et ₂ SnBr ₂ L ₂	1.790	0.020	0.770	+36.8		Br–Sn–Br
Me ₂ SnBr ₂ L ₂	1.786	0.020	0.766	+36.1		Br–Sn–Br

^a With respect to $\text{SnI}_4(\text{Ph}_3\text{PO})_2$. ^b With respect to $\text{SnI}_4[(\text{Me}_2\text{N})_2\text{CO}]_2$.

^c With respect to $\text{SnI}_4(\text{bipy})$. ^d With respect to $\text{SnBr}_4(\text{Ph}_2\text{SO})_2$.²³

$\text{EtSnCl}_3(\text{THF})_2$ is only possible at $\eta > 7\%$. Although the contribution of the π -system to chemical bonding in tin adducts is small, the above tendency is clearly seen from the NQR data.

As a whole, the electronic effects of substitution in the adducts with known structure were found to correlate to their structural manifestations, although in the adducts of mono-substituted tin chlorides, a shortening of the Sn–Hal bond in the *trans*-position to the substituent R was small and comparable with the standard deviation values. In $(\text{MeNH}_3)_2\text{EtSnCl}_5$, no shortening of the *trans*-bond Sn–Hal compared to the parent unsubstituted complex was found by X-ray analysis,¹⁹ whereas the absolute value of

the effective charge on the *trans*-ligand decreased by more than 5%, the appropriate frequency shift exceeding 1 MHz. The frequency shifts at the chlorine atoms in *trans*-positions to the substituent observed in the NQR spectra of all compounds studied notably exceeded the errors of measurement, so that the effect of *trans*-strengthening was readily revealed in terms of a decrease in the effective charge on the corresponding chlorine atom. The NQR parameters are more sensitive to the influence of substituents than the interatomic distances (Tables 3 and 4); this is however not unexpected, considering that the substituent influence is governed by the electronic effects, whereas the NQR parameters directly reflect the electron density variations on the atom under study.

It is worthwhile to compare redistribution of the electron density in adducts of mono-substituted tin halides with different mutual arrangement of the ligands L. For instance, in Tables 1 and 3, the data are summarised for the adducts *cis*-EtSnCl₃(DMSO)₂ (**1**) and *trans*-PhSnCl₃(HMPT)₂ (**2**), whose strong donor ligands L are competitive in donating power with the substituents R. One can see that *cis*-weakening of the Sn–Hal bonds in the adduct **1**, where the ligands DMSO are in *cis*-position to each other, is less pronounced than that in the ethyl-substituted adducts with weaker donor ligands L. Moreover, in agreement with X-ray data, *trans*-strengthening of the Sn–Hal bond in **1** gives way to *trans*-weakening. By contrast, *trans*-strengthening of the Sn–Hal bond exists in the molecule **2** with *trans*-position of the HMPT ligands relative to each other, as follows from the NQR frequency shift, and *cis*-weakening in this adduct is stronger than in **1**, although the phenyl group is a weaker ‘influencing’ substituent than the ethyl group.

Introduction of the second substituent R to give an adduct R₂SnHal₂L₂ increases the *cis*-lengthening (weakening) of the Sn–Hal bond in an approximately additive manner. As a result, in the adducts of dialkyltin dichloride, dibromide and diiodide the effects exceed 25%, 40% and 50%, respectively, the appropriate Sn–Hal bond elongation being ~ 0.2 Å. Whereas the *cis*-weakening effect of the phenyl substituents is less than that due to the ethyl groups, the effects due to different alkyl groups are approximately the same, as one can see from the data for Me₂SnBr₂(py)₂, Et₂SnBr₂(py)₂ and Bu₂SnBr₂(bipy)₂ (Table 4). It thus follows that the variations from 22% to 41% in *cis*-weakening of the Sn–Br bonds in the adducts of dialkyldibromostannates are caused by different contributions of the ligands L into the combined effect of *cis*-weakening: THF < TMU < DMSO ≈ py ≈ bipy < HMPT.

In studies of adducts of dialkyl(diphenyl)diiodostannates it was found^{12,25} that the elongation of the Sn–I bond with respect to that in the parent adduct was accompanied by a dramatic increase in η at the iodine sites. Such an increase was observed in five of six adducts studied by NQR (Table 5), which implies that the iodine valence $5p_{\pi}$ orbitals were notably disturbed as a result of the substitution, which gives rise to an essential increase in the occupancy difference $\Delta Np_{\pi} = Np_x - Np_y$. NQR spectroscopic and X-ray diffraction data for the two adducts were correlated in order to understand the reason for this disturbance.²⁶

As one can see from Table 5, the largest increase in η upon replacement of two iodine atoms by the groups R is observed in the adducts Ph₂SnI₂(HMPT)₂ (**3**) and Et₂SnI₂(DMSO)₂ (**4**). The ¹²⁷I NQR spectrum of the adduct **3** consists of two sets of lines corresponding to two crystallographically inequivalent iodine sites having close spectroscopic characteristics. The introduction of the phenyl groups resulted in the elongation of the Sn–I bonds by 0.165 Å on average with respect to those in the nonsubstituted adduct SnI₄(TPPO)₂ whose structure is known and spectroscopic characteristics are similar to those in the yet as structurally unstudied adducts SnI₄(HMPT)₂ and SnI₄(TMU)₂ (Table 2). As the comparison of the iodine valence orbital occupancies in substituted and nonsubstituted adducts shows (Table 5), the substitution results in an increase in the iodine valence $5p_{\sigma}$ orbital occupancies (Np_z), which is a natural consequence of the *cis*-weakening of the Sn–I bonds. The latter is however accompanied by a notable increase in the iodine valence $5p_{\pi}$ orbital occupancy difference ($\Delta Np_{\pi} = Np_x - Np_y$) from 0.019 in nonsubstituted SnI₄(TMU)₂ to 0.06 in the adduct **3**.

The obvious suggestion accounting for such an increase in η in compound **3** is that secondary non-valence intra- or intermolecular contacts exist in this compound that involve the iodine atoms. The results of the X-ray study do not, however, support this suggestion: no secondary contacts were found in the structure of **3**.²⁶

In the crystals of the adduct **4**, two crystallographically inequivalent iodine positions (characterised by substantially different spectroscopic parameters) were identified by NQR. According to the X-ray diffraction data, the coordination polyhedron around tin is an octahedron with *trans* ethyl groups and *cis* DMSO molecules (Fig. 1a). Both DMSO molecules occupy disordered positions, so that the sulfur atom of one DMSO molecule occupies the positions at the opposite sides of the O(1)C(5)C(6) plane, whereas in the other molecule, both sulfur and oxygen atoms are sited at disordered positions. Table 6 lists the bond lengths and angles for the prevailing configuration of the

Table 5. ¹²⁷I NQR spectroscopic parameters for adducts R₂SnI₂L₂ and SnI₄L₂ at 77 K and the Sn–I bond characteristics.²⁶

Compound	e^2Qq_{zz}/h /MHz	a/e	η (%)	Np_z	$\Delta Np_{\pi} = Np_x - Np_y$ ($Np_x = 2$)	$-\rho/e$	$d/\text{\AA}$
<i>cis</i> -Et ₂ SnI ₂ (DMSO) ₂	409.1		39.1	1.798	0.046	0.752	2.941
	523.0		13.3	1.762	0.020	0.742	2.982
						0.690 ^a	
Ph ₂ SnI ₂ (DMSO) ₂	647.3		24.3	1.695	0.046	0.649	
	707.8		8.6	1.682	0.018	0.665	
<i>trans</i> -Et ₂ SnI ₂ (HMPT) ₂	467.9		6.5	1.791	0.009	0.782	3.016
<i>trans</i> -Ph ₂ SnI ₂ (HMPT) ₂ (I) (II)	495.2		41.2	1.754	0.059	0.695	2.957
	504.1		41.2	1.750	0.060	0.689	2.938
	1048.0	a	1.9	1.540	0.006	0.534	
<i>cis</i> -SnI ₄ (TMU) ₂	1095.3	e	6.0	1.512	0.019	0.493	
<i>cis</i> -SnI ₄ ·bipy		a					2.816
		e					2.788
Et ₂ SnI ₂ (py) ₂	504.35		25.7	1.761	0.038	0.723	
	542.1		8.8	1.757	0.014	0.742	
Ph ₂ SnI ₂ (py) ₂	630.03		18.9	1.708	0.035	0.673	

Note. Here and in tables below: a is axial, e is equatorial halogen atoms; for the remaining notations see Table 3. ^a See text.

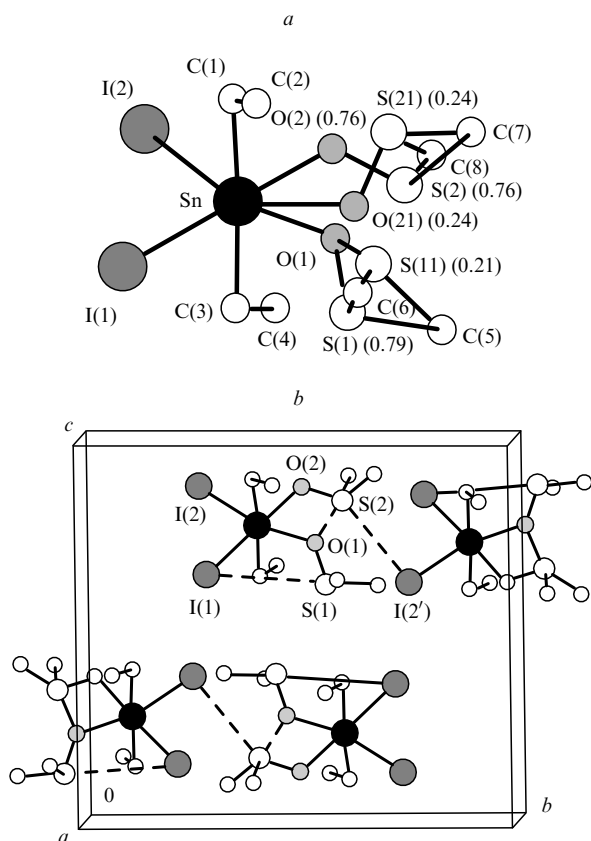


Figure 1. Structure of the adduct $\text{Et}_2\text{SnI}_2(\text{DMSO})_2$:²⁶ (a) molecular structure of $\text{Et}_2\text{SnI}_2(\text{DMSO})_2$, illustrating disorder in the DMSO ligands; occupancies of the atomic positions are given in parentheses; (b) crystal structure of the adduct showing non-valence contacts (dotted lines); only prevailing conformation retained.

adduct molecule. In the structure of the adduct **4**, the intramolecular $[\text{S}(2) \cdots \text{O}(1) = 3.06 \text{ \AA}$, $\text{S}(1) \cdots \text{I}(1) = 4.11 \text{ \AA}]$, and intermolecular $[\text{S}(2) \cdots \text{I}(2') = 3.79 \text{ \AA}]$ contacts (Fig. 1 b) were found, hence revealing at least one of the reasons for the increase in the value of η (39.1%) in this adduct.

On the plot giving the effective charge on the iodine atom as a function of the respective Sn–I bond lengths (Fig. 2), deviation of the point 7, corresponding to the I(1) site in the adduct **4** from the correlation line is a maximum. Note that the effective charges were evaluated assuming that the occupancy of one of the iodine $5p_\pi$ orbitals (Np_x) was equal to 2.²⁶ As Fig. 2 shows, such an assumption results in a good correlation between $-\rho$ and the Sn–I bond lengths for all the points in the adducts discussed except that for the I(1) atom in compound **4**. The effective charge

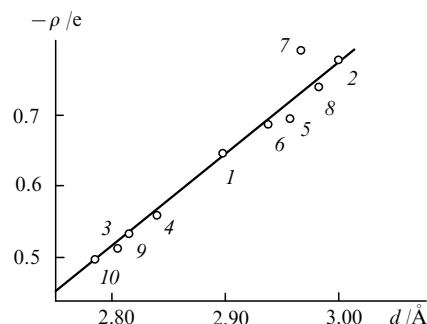


Figure 2. Correlation between the effective charges on the iodine atom ($-\rho$) and interatomic Sn–I distances (d):¹² (1) $\text{EtSnI}_3(\text{HMPT})_2$, (2) $\text{Et}_2\text{SnI}_2(\text{HMPT})_2$, (3) $\text{SnI}_4(\text{Ph}_2\text{SO})_2$, (4) $\text{EtSnI}_3(\text{Ph}_2\text{SO})_2$, (5, 6) $\text{Ph}_2\text{SnI}_2(\text{HMPT})_2$, (7, 8) $\text{Et}_2\text{SnI}_2(\text{DMSO})_2$, (9, 10) $\text{SnI}_4(\text{TMU})_2$.

on this atom (for the same values of experimentally measured QCC and η) for the point 7 to fit the correlation line should be equal to -0.69 e (Table 5), which gives the following iodine valence orbital occupancies: $Np_z = 1.778$, $Np_x = 1.979$ and $Np_y = 1.933$. Thus, the deviation of the point 7 from the correlation serves as indirect evidence that the assumption $Np_x = 2$ underestimates the Sn–I π -bonding character for the I(1) atom involved in secondary contact to sulfur. This contact is associated with the transfer of $\sim 0.042 \text{ e}$ from the iodine valence $5p_\pi$ orbitals.

The probable reason for the increased η -value (39.1%) in the adduct **3**, where no shortened contacts were found, was sought in the analysis of contributions of the iodine valence $5p$ orbital occupancies into the measured value of η . It was shown that despite similar values of the asymmetry parameters at the iodine sites in **3** and the I(1) site in **4** the difference $\Delta Np_\pi = Np_x - Np_y$ in the latter adduct is less than in the former one. As has been mentioned above, the alkyl substituents weaken the respective Sn–I bonds to a greater extent than the phenyl groups, thus producing higher occupancy of the iodine $5p_\sigma$ orbitals. A sharp increase in the experimentally measured η -value occurs, at the fixed $\Delta Np_\pi = Np_x - Np_y$ difference, as the σ -electron density at the iodine atom (Np_z) increases (Fig. 3), i.e., the enhanced *cis*-weakening of the Sn–I bond due to substitution results, at a given ΔNp_π difference, in an increase in the asymmetry parameter η caused by the increased contribution to the latter of the iodine valence $5p_\sigma$ orbitals. Indeed, the closely similar values of η in **3** and at the I(1) site in **4** are associated with a relatively smaller iodine $5p_\pi$ orbital occupancy difference in the latter adduct, since the alkyl substituents favour an increase in σ -electron density on the iodine atoms to a larger extent than the phenyl groups do.

Thus, an increase in the η -value in the adduct **4** (Table 5) is caused by the combined contribution of the iodine valence $5p_\sigma$ orbitals, whose occupancy increases upon substitution, and the shortened I $\cdots$ S contacts responsible for an increase in ΔNp_π . As to the increased ΔNp_π difference in the adduct **3**, this is most

Table 6. Bond lengths (d) and bond angles (α) in the adduct **4**.²⁶

Bond	$d/\text{\AA}$	Angle	α/deg	Angle	α/deg
Sn–I(1)	2.982(1)	I(1)–Sn–I(2)	100.40(4)	(1)–Sn–O(2)	80.2(3)
Sn–I(2)	2.941(1)	I(1)–Sn–O(1)	95.4(2)	O(1)–Sn–C(1)	88.9(3)
Sn–O(1)	2.220(6)	I(1)–Sn–O(2)	173.9(2)	O(1)–Sn–C(3)	92.0(4)
Sn–O(2)	2.253(8)	I(1)–Sn–C(1)	90.7(3)	O(2)–Sn–C(1)	85.0(4)
Sn–O(21)	2.16(2)	I(1)–Sn–C(3)	84.6(3)	O(2)–Sn–C(3)	99.7(4)
Sn–C(1)	2.164(10)	I(2)–Sn–O(1)	163.9(2)	C(1)–Sn–C(3)	175.3(4)
Sn–C(2)	2.174(10)	I(2)–Sn–O(2)	83.8(2)		
		I(2)–Sn–C(1)	87.7(3)		
		I(2)–Sn–C(3)	92.7(3)		

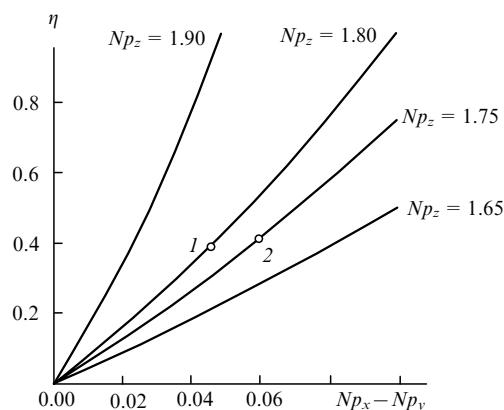


Figure 3. Measured value of the EFG asymmetry parameter (η) at the iodine atom as a function of its valence π -orbital occupancy difference ($Np_x - Np_y$) for various σ -orbital occupancies (Np_z);²⁶ (1) is the point corresponding to the point (7) and (2), to the points (5) and (6) on the plot of Fig. 2.

probably associated with the interaction of the iodine π -system with those of the phenyl rings. This suggestion is supported by the fact that in the $\text{Et}_2\text{SnI}_2(\text{HMPT})_2$ adduct, which is a dialkyl analogue of **3** comprising no cyclic fragments in the ligands and substituents, the alkyl groups did not give rise to an increase in ΔNp_π and consequently in the EFG asymmetry parameter η . However, replacement of the ethyl by phenyl substituents affected dramatically the asymmetry parameter η , although no proper structural manifestations could be registered by X-ray diffraction. This is one of a few examples illustrating a possibility to detect, using NQR, the electronic effects, whose structural manifestations lie below the sensitivity of X-ray experiments. Yet another example was given above in the effects of *trans*-strengthening. The accuracy of their determination in chlorides is, as a rule, comparable to the standard deviations, whereas the corresponding variations of the NQR parameters notably exceed the errors of measurement. It is however to be noted that there are many other systems in which π - π interactions were clearly revealed by X-ray studies. For instance, the π - π interactions between the iodine atoms and phenyl rings were earlier found by X-ray in several imidazopyridinium salts.²⁷

The NQR and X-ray data yield complementary pieces of valuable information. A correlation between them on a quantitative scale contributes to the further progress in understanding the electronic effects of substitution in adducts and complexes of tin(IV) halides, augmenting the current view by information on relative importance of the σ - and π -electron systems in electron density redistribution.

III. Electronic characteristics of M – Hal bonds in hexa- and pentacoordinate adducts of tin(IV) tetrachlorides; similarities and differences

In this section, the M – Hal bond reorganisation in adducts of tin tetrachlorides resulting from the change in the central metal coordination number is discussed. The data on electron density redistribution due to spatial rearrangement of adducts, especially those of silicon and germanium, are scanty. The literature on ^{35}Cl NQR studies of hexa- and pentacoordinate adducts of tin tetrachloride is more extensive. However, *cis*–*trans* isomerism of hexacoordinate tin(IV) adducts complicated comparative studies of the bond electronic characteristics in these compounds, because no reliable spectroscopic criteria of either isomerism or assignment of the ^{35}Cl NQR frequencies in *cis*-isomers to axial–equatorial chlorine atoms were available.

NQR studies of pseudooctahedral adducts SnCl_4L_2 have received major attention. The subjects of investigations were the structures of the compounds,^{28–34} charge distribution over acceptor molecules,^{33–39} relation of the ligand donating power to the strength of the produced adducts judging from spectroscopic data⁴⁰ and identification of isomers based on their NQR spectra.^{40–42} A bibliography on these problems covering the period since 1980 to the beginning of the 90's may be found in a review.⁴³

Studies on isomerism of pseudooctahedral adducts of tin tetrachloride show⁴⁰ that the frequency splitting in the NQR spectra of *cis*-isomers (*i.e.*, the difference between the frequencies of equatorial and axial chlorine atoms) cannot serve as a reliable criterion of isomerism, because its magnitude decreases as the donating power of ligands L increases. For strong adducts, this prevents the spectroscopic identification of *cis*- and *trans*-isomers. An unambiguous identification of isomers is further complicated where the NQR spectra of *trans*-isomers are affected by crystal-field effects, which enhance the frequency splitting, and mask their difference from the spectra of *cis*-isomers. Temperature dependences of the NQR frequencies of equatorial and axial chlorine atoms do not always clarify the situation.^{41,42} For the isomers with established *cis*-configuration, the assignment of resonance frequencies to equatorial–axial atoms is also ambiguous. According to the X-ray data available on a relatively few *cis*- SnCl_4L_2 adducts, the number of adducts whose axial Sn–Cl bond distances are shorter than the equatorial ones is approximately the same as that whose axial Sn–Cl bond distances exceed equatorial. The identification of a large number of SnCl_4L_2 isomers was made⁴⁰ assuming that in NQR spectra of both *cis*- and *trans*-isomers the ^{35}Cl frequencies of the atoms making a linear Cl–Sn–Cl fragment are close to each other if the donating powers of ligands L are similar. As a result, the higher ^{35}Cl frequencies in the NQR spectra of *cis*-isomers were erroneously assigned to linear Cl–Sn–L fragments.

Thus, a considerable body of experimental data showed that neither frequency splittings and line multiplicity nor temperature dependence of the NQR frequencies can be recognised as reliable criteria for identification of isomers. However, the symmetry considerations suggest that the EFG asymmetry parameters at axial–equatorial chlorine sites may possibly serve as such criteria, although the values of η and QCC cannot be simultaneously found, without additional experiments, from only one transition frequency for nuclei with $I = 3/2$ having two degenerate quadrupole levels. Conventional Zeeman NQR experiments with single crystals are however complicated and tedious, serious limiting factors being duration of experiments and problems of growing large single crystals of tin tetrachloride adducts, most of which are hygroscopic.

Attempts at experimental determination of η at the chlorine atoms in powder samples were undertaken⁸ using a modified approach³ based on Fourier analysis of slow beats of the spin-echo envelope in an external magnetic field. The experiment was run according to the scheme: NQR spectrometer $\longleftrightarrow$ programmer and digitiser $\longrightarrow$ box-car integrator $\longrightarrow$ computer. The programmer and digitiser were adapted to the tube levels of NQR signals. Instead of the conventional Fourier transform used in NMR spectroscopy, the data processing involved expansion of a signal to harmonics followed by numerical integration for determining the expansion coefficients. As a result, the accuracy of the analysis increased, whereas its duration remained shorter than the time of signal accumulation. The Fourier transform programme was used which yielded a graphic representation of both the accumulated spectrum of slow beats and its expansion into harmonics. This easy-to-grasp form of representation of the results enabled the authors to monitor the data processing checking the operation for errors. The accuracy of η measurements performed by this procedure even on weak ^{35}Cl signals was fairly high.

In subsequent experiments, the results of determination of η in a number of *cis*- and *trans*-isomers of SnCl_4L_2 adducts con-

firmed¹¹ that the EFG asymmetry parameters can actually be used for identification of isomers (Tables 7 and 8). Thus the magnitudes of η on axial chlorine atoms in *cis*-isomers appeared to be zero unless lattice contributions raised its value by several percent. On equatorial Cl atoms of both isomers, the η -values were usually noticeably higher, varying around 10% in the majority of the compounds.

For comparison, the results of Zeeman analysis of single crystals at 297 K, 293 K and 235 K available for several hexacoordinate adducts, are also listed in Tables 7 and 8.^{44–46} They are in reasonable agreement with those obtained with powder samples: the magnitudes of orbital occupancies and effective charges on the chlorine atoms derived from both experiments are consistent with each other. The approach for measuring η in powder samples simplified the experiment and markedly cut its time. The important benefit to the user consists in avoiding a tedious long-term procedure of growing large single crystals required for the NQR Zeeman experiments.

The determination of the total set of NQR spectroscopic parameters (the transition resonance frequencies ν , quadrupole coupling constant QCC and EFG asymmetry parameter η) for a number of adducts, which became possible due to the use of powder samples, revealed the regularities of electron density redistribution between axial–equatorial bonds (Fig. 4) which thereafter allowed identification of *cis*- and *trans*-isomers of some adducts that had not been studied structurally based only on the NQR frequency measurements.¹⁰

The ³⁵Cl NQR frequencies assigned to the axial chlorine atoms in the spectra of all the *cis*-isomers examined¹⁰ appeared to be higher and the σ -electron density on the respective Cl atoms lower than those on the equatorial chlorine atoms. The frequency ranges assigned to axial and equatorial Cl atoms did not virtually overlap, so that the corresponding frequencies in the spectra of *cis*-isomers were found in the intervals (MHz) $17.5 < \nu_e < 19.8 < \nu_a < 22.0$, whereas the region covered by the ³⁵Cl frequencies in the spectra of *trans*-isomers was slightly shifted downwards: $17.2 < \nu_e < 19.4$. The effective charges on the Cl atoms were practically insensitive to the kind of isomerism of the adduct, their magnitudes being approximately the same on both

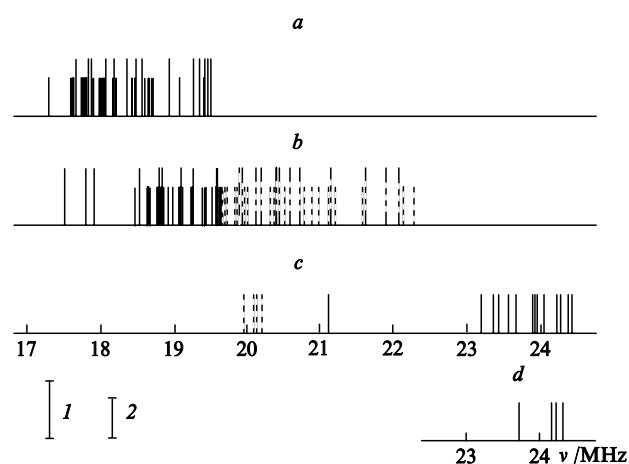


Figure 4. The diagrams of ³⁵Cl NQR spectra of pseudooctahedral adducts: *trans*-SnCl₄L₂ (a), *cis*-SnCl₄L₂ (b), trigonal-bipyramidal adducts SnCl₄L (c) and parent tin tetrachloride (d). The ³⁵Cl frequencies with measured (1) and unknown (2) magnitudes of η ; the dotted bars are axial, the solid bars are equatorial chlorine positions.

axial and equatorial chlorine sites and in both types of isomers (Tables 7 and 8).

The results of the study cited (Ref. 10) show that the *cis*-isomer of adduct SnCl₄L₂ can be identified by the presence in its NQR spectrum of the ³⁵Cl signals at frequencies above 19.8 MHz, which should be assigned to the axial Cl–Sn–Cl fragments. More than 80% of *trans*-isomers examined so far gave NQR spectra with the ³⁵Cl average frequencies below 18.3 MHz, while 80% of *cis*-isomers had them above 19.3 MHz. It is to be emphasised however that the above regularities in electron density distribution are only valid for the molecular adducts, whose chlorine atoms are bonded only to the central atom and are not involved in secondary inter- or intramolecular interactions.

Table 7. ³⁵Cl NQR spectroscopic parameters for *trans*-isomers of hexacoordinate adducts of tin tetrachloride at 77 K and the M–Cl bond characteristics.⁹

L	ν /MHz	η (%)	e^2Qq_{zz}/h /MHz	Np_σ	ΔNp_π	$-\rho/e$	$ \sum\rho /e$
Diox	19.41	6.1 ± 1.5	38.80	1.639	0.014	0.625	2.500
DMF	17.77	5.7 ± 1.0	35.52	1.670	0.012	0.658	2.632
TMU	18.36	8.4 ± 0.5	36.68	1.656	0.019	0.637	2.568
	18.16	6.7 ± 1.9	36.29	1.662	0.015	0.647	
THF	19.39	15.8 ± 3.0	38.62	1.628	0.037	0.591	2.426
	19.25	13.4 ± 1.1	38.38	1.634	0.031	0.603	
	18.91	12.2 ± 1.1	37.73	1.641	0.028	0.613	
	18.54	12.8 ± 1.2	36.98	1.648	0.029	0.619	
DEE	19.44	13.6 ± 3.1	38.76	1.630	0.032	0.598	2.390
	19.47	13.6 ± 3.1	38.82	1.629	0.032	0.597	
	19.341 ^a	11.4	38.600				
	19.440 ^a	11.6	38.793				
HMPT	17.77	10.8 ± 2.1	35.47	1.665	0.023	0.642	2.558
	18.04	10.4 ± 1.4	36.02	1.660	0.023	0.637	
py	17.76	15.4 ± 2.6	35.38	1.660	0.033	0.627	2.512
	17.64	15.4 ± 2.6	35.14	1.662	0.033	0.629	
DBS	18.48	15.2 ± 4.1	36.81	1.647	0.034	0.613	2.464
	18.18	15.5 ± 3.4	36.22	1.653	0.034	0.619	
acac	19.94(2)	5.5 ± 0.9	39.86	1.630	0.013	0.617	2.493
	19.48	5.2 ± 1.0	38.94	1.639	0.012	0.627	
	18.28	10.5 ± 2.1	36.49	1.655	0.023	0.632	

Note. Diox is dioxane, DEE is diethyl ether, DBS is dibenzyl sulfide, acac is acetylacetonate; $|\sum\rho|$ is the total effective charge on the chlorine atoms in the adduct. ^a The results of Zeeman analysis of a single crystal at 235 K.⁴⁴

Table 8. ^{35}Cl NQR spectroscopic parameters for *cis*-isomers of hexacoordinate adducts of tin tetrachloride at 77 K and the M – Cl bond characteristics.⁹

L	a/e	ν /MHz	η (%)	e^2Qq_{zz}/h /MHz	Np_{σ}	ΔNp_{π}	$-\rho$ /e	$ \sum \rho $ /e
POCl_3	a	21.13	2.3 ± 0.5	42.26	1.612	0.006	0.606	2.425
	e	19.79	11.1 ± 2.0	39.50	1.627	0.027	0.600	
	e	19.03	11.7 ± 2.4	37.97	1.640	0.027	0.613	
	a ^a	20.924	1.2 ± 0.1	41.847	1.617	0.003	0.614	2.475
	e ^a	19.093	8.8 ± 0.4	38.134	1.642	0.020	0.622	
$\text{P}_2\text{O}_3\text{Cl}_4$	e ^a	18.852	9.2 ± 0.1	37.651	1.646	0.021	0.625	
	a	22.05	4.8 ± 1.6	44.08	1.592	0.013	0.579	2.351
	a	21.87	5.6 ± 1.6	43.72	1.594	0.015	0.579	
	e	19.77	12.8 ± 3.0	39.43	1.625	0.031	0.594	
	e	18.49	19.6 ± 2.1	36.74	1.643	0.044	0.599	
Me_2O^b	a	20.287	2.7	40.569	1.627	0.007	0.620	2.520
	e	18.807	4.9	37.600	1.651	0.011	0.640	
MeCN	a	20.67	5.6 ± 1.5	41.32	1.616	0.014	0.602	2.477
	a	19.87	3.4 ± 1.5	39.73	1.643	0.008	0.635	
	e	19.59	7.3 ± 2.2	39.14	1.634	0.017	0.617	
	e	19.20	7.8 ± 2.2	38.36	1.641	0.018	0.623	
	a ^c	20.466	3.1	40.93	1.623	0.008	0.615	2.504
	a ^c	19.752	2.5	39.45	1.637	0.006	0.631	
	e ^c	19.513	5.3	39.01	1.638	0.013	0.625	
	e ^c	19.207	4.9	38.40	1.644	0.011	0.633	
Bu^tCN^c	a	20.039	2.8	40.07	1.632	0.007	0.625	2.523
	a	19.426	1.3	38.85	1.644	0.003	0.641	
	e	18.981	7.8	37.92	1.645	0.018	0.627	
	e	18.859	8.1	37.68	1.648	0.018	0.630	
Me_2C	a	20.09	1.2 ± 0.8	40.17	1.632	0.003	0.629	2.524
	a	19.48	1.2 ± 0.8	38.96	1.644	0.003	0.641	
	e	19.43	7.3 ± 1.3	38.82	1.637	0.017	0.620	
	e	18.84	6.6 ± 1.2	37.65	1.649	0.015	0.634	
MeOH	a	20.32	2.1 ± 0.4	40.64	1.627	0.005	0.622	2.525
	a	19.87	3.1 ± 0.5	39.73	1.634	0.0075	0.627	
	e	17.87	13.1 ± 1.5	35.63	1.661	0.028	0.633	
	e	17.50	12.2 ± 0.1	34.91	1.669	0.026	0.643	
EtOH	a	20.57	3.8 ± 1.5	41.13	1.620	0.009	0.611	2.455
	a	20.12	3.9 ± 1.2	40.23	1.629	0.010	0.619	
	e	17.75	19.4 ± 3.5	35.27	1.657	0.042	0.615	
	e	17.50	23.2 ± 3.2	34.69	1.659	0.049	0.610	
$\text{C}_4\text{H}_8(\text{CN})_2$	a	20.30	1.8 ± 0.5	40.60	1.623	0.004	0.623	2.502
	e	19.06	7.1 ± 1.8	38.08	1.644	0.016	0.628	
SeOCl_2^a	a	17.030	39.5 ± 0.2	33.219	1.657	0.080	0.577	2.394
	e	19.551	6.9 ± 0.3	39.069	1.636	0.016	0.620	
$\text{BrCH}_2\text{COOMe}$	a	21.91	1.7 ± 0.5	43.82	1.598	0.005	0.598	2.480
	a	18.57	1.7 ± 0.5	37.14	1.660	0.004	0.660	
	e	19.59(2)	9.0 ± 1.6	39.13	1.632	0.021	0.611	
$\text{ClCH}_2\text{COOMe}$	a	21.82	1.1 ± 0.5	43.64	1.601	0.003	0.601	2.487
	a	18.53	1.7 ± 0.5	37.06	1.660	0.004	0.660	
	e	19.51(2)	9.0 ± 0.8	38.97	1.634	0.021	0.613	

Note. The results of Zeeman analysis of single crystals: ^a at 297 K;⁴⁵ ^b at 293 K;⁴⁴ ^c at 235 K.⁴⁶

For the latter compounds, the results of X-ray study are consistent with those of NQR measurements: their axial Sn – Cl bond distances were found to be shorter than the equatorial ones. However, it is clear that the EFG asymmetry parameter on the chlorine atom will increase, if this atom is involved in additional (inter- or intramolecular) interactions, as it is observed in $\text{SnCl}_4(\text{SeOCl}_2)_2$.⁴⁵ The respective ^{35}Cl frequency in the NQR spectrum of the adduct decreased, and the ratios between the axial – equatorial resonance frequencies and Sn – Cl bond distances were inverted (Table 8).

The spectroscopic regularities found for the isomeric chloro adducts are not universal. Tin tetrabromide and tetraiodide adducts show different positional order of the NQR frequencies assigned to axial and equatorial halogen atoms due to different relationships between the electron-donating (withdrawing) properties of ligands L and halogens and relatively lesser contribution

to the EFG of crystal-field effects as compared to the contribution of their own valence orbitals. This is illustrated in the results of NQR studies of hexacoordinate adducts SnBr_4L_2 .²³ Although the ^{81}Br frequency ranges assigned to axial and equatorial Br atoms in the NQR spectra of *cis*-isomers also did not overlap (Table 9), their mutual positions were inverted with respect to those in the ^{35}Cl NQR spectra of the chloro analogues, *i.e.*, the ^{81}Br NQR frequencies of axial bromine atoms were lower than those of equatorial in all the *cis*-isomers studied: $112 < \nu_a < 126$ MHz; $128 < \nu_e < 142$ MHz. In agreement with the NQR data, the results of X-ray studies available for the *cis*- SnBr_4L_2 adducts gave axial Sn – Br bond distances exceeding the equatorial ones.²³ In the spectra of *trans*-isomers, the ^{81}Br NQR frequency range was relatively larger than the corresponding ^{35}Cl frequency range in the spectra of chloro adducts, the former interval covering almost the entire $(\nu_e + \nu_a)$ frequency range of *cis*-isomers:

Table 9. ^{81}Br frequencies in the NQR spectra of isomers of hexacoordinate adducts of tin tetrabromide at 77 K.²³

L	ν /MHz	L	a/e	ν /MHz
<i>trans</i> -Isomers		<i>cis</i> -Isomers		
TMU	125.30(2)	bipy	a	119.07
	123.68		a	118.67
	123.47		e	128.78
DMF	124.57	$\text{NC}(\text{CH}_2)_4\text{CN}$		
	122.18		a	130.95(2)
DPF	125.22		a	140.96
	124.72		e	141.29
DBS	127.63	DESO	a	118.24
	127.18		e	127.07
Diox	136.20	DPSO		
py	122.66		a	116.63
2,3-Mepy	119.54(2)		e	128.34
	117.26			
	115.74	DMSO	a	118.17
TPPO	127.91		e	127.73
	121.14			
HMPT	127.73	CH_3OH	a	120.90
Et_2O	135.31		a	125.75
	135.58		e	135.55
Me_2O	135.82	$\text{C}_2\text{H}_5\text{OH}$	e	140.46
	136.47			
	136.72		a	113.83(2)
THF	137.27	$(\text{C}_2\text{H}_5)_2\text{CO}$	a	140.51
	128.28		e	141.44
	131.26			
	134.30			
	135.93		a	112.57
			e	133.62

Note. DPF is diphenylformamide; DESO is diethyl sulfoxide; relative intensities of resonance lines are given in parentheses.

$115 < \nu_e < 138$ MHz. Thus, the ^{81}Br NQR frequency ranges in the spectra of *cis*- and *trans*-isomers of the SnBr_4L_2 adducts were found to overlap. This implies that, unlike in the related chloro adducts, the EFG asymmetry parameters at the Br nuclei in the bromo adducts should be measured for the spectroscopic identification of isomerism. The mutual position of the ^{81}Br frequency ranges assigned to axial–equatorial bromine atoms indicates the prevailing electronic influence of ligands on the electron density redistribution in *cis*- and *trans*-isomers of the adducts SnBr_4L_2 .

As a whole, the NQR results on isomers of hexacoordinate adducts SnHal_4L_2 show^{9, 11, 18, 23} that the measurement of the EFG asymmetry parameters along with examination of the spectroscopic shifts, splittings and temperature dependence of the resonance frequencies made it possible to identify the type of isomerism of the adducts from their NQR spectra, even though the latter exhibit complicated patterns of the shifts and splittings. The average NQR frequency shifts at halogen atoms in adducts with respect to their frequencies in parent SnHal_4 can serve as a measure of the strength of the adducts formed provided the resulting increase in the halogen σ -electron density in the acceptor is mainly due to intramolecular electronic effects, the contributions of the crystal-field effects being much less significant.

Table 10 lists the ^{35}Cl NQR spectroscopic parameters for trigonal-bipyramidal adducts of tin(IV) having the coordination number 5. The corresponding spectra differ notably from those for pseudooctahedral adducts (Tables 7 and 8). They comprise the triplets from equatorial Cl atoms at frequencies slightly different from those of the parent tetrachloride, and the singlets from axial chlorine atoms, shifted considerably to lower frequencies, which indicates that the electron density in such adducts is mainly transferred from the ligands L to the axial chlorine atoms.

In both trigonal-bipyramidal and pseudooctahedral adducts, the asymmetry parameters on equatorial chlorine atoms exceed those on the axial atoms and vary within similar limits. Accordingly, the corresponding valence $3p_\pi$ orbital occupancy differences are also close to each other. The main difference between these two types of adducts consists of the magnitudes of the $3p_\sigma$ orbital occupancies (Np_z) at equatorial chlorine sites. In trigonal-bipy-

Table 10. ^{35}Cl NQR spectroscopic parameters for pentacoordinate adducts of tin tetrachloride at 77 K and the M–Cl bond characteristics.⁹

L	a/e	ν /MHz	η (%)	Np_σ	ΔNp_π	$-\rho/e$	$ \sum \rho /e$
MeNO_2	e	24.39	10.6 ± 0.7	1.540	0.031	0.509	2.145
	e	24.26	14.0 ± 1.2	1.537	0.041	0.496	
	e	24.01	8.4 ± 0.4	1.550	0.025	0.525	
	a	20.21	4.5 ± 0.6	1.626	0.011	0.615	
4-MeC ₆ H ₄ COCl	e	23.34	14.2 ± 1.0	1.555	0.040	0.515	2.192
	e	23.89(2)	9.6 ± 1.0	1.551	0.028	0.523	
	a	19.91	1.5 ± 0.5	1.635	0.004	0.631	
PhMe	e	23.85	12.0 ± 1.0	1.548	0.035	0.513	2.189
	e	23.66	9.2 ± 1.0	1.556	0.026	0.530	
	e	23.39	13.3 ± 1.0	1.555	0.038	0.517	
	a	20.18	0.9 ± 0.5	1.631	0.002	0.629	
2,5-Me ₂ C ₆ H ₃ OMe	e	23.90	13.0 ± 3.0	1.546	0.038	0.508	2.192
	e	23.56	12.5 ± 3.0	1.553	0.036	0.517	
	e	23.19	10.5 ± 3.0	1.563	0.030	0.533	
	a	20.11	0.0	1.634	0.0	0.634	
$\text{C}_5\text{H}_5\text{COCl}$	e	24.22	5.5 ± 2.0	1.551	0.016	0.535	2.205
	e	21.38(2)	4.6 ± 1.5	1.548	0.014	0.534	
	a	21.04	0.9 ± 0.5	1.604	0.002	0.602	
SnCl_4^a		24.30	2.9 ± 0.5	< 1.557	> 0.02	< 0.54	< 2.15
		24.23	2.9 ± 0.5				
		24.14	2.9 ± 0.5				
		23.72	2.9 ± 0.5				

^a Data from Ref. 47.

amid adducts, the absolute values of Np_z are by 0.1 lower than those in the pseudooctahedral adducts, whereas the spectroscopic and electronic characteristics of their Sn—Cl axial bonds differ insignificantly. As is seen from Tables 7, 8 and 10, the overall effective charge $|\sum \rho|$ on all the chlorine atoms in the octahedral adducts is markedly larger than that in the parent tetrachloride SnCl_4 , while in trigonal-bipyramidal adducts, the corresponding difference is small. This supports a conventional idea of relatively larger extent of charge transfer in octahedral adducts. The NQR data on pseudooctahedral adducts show that the overall σ -electron density on chlorine atoms in *trans*-isomers is on average slightly higher than that in *cis*-isomers.

IV. Penta- and hexacoordinate adducts of silicon and germanium tetrachlorides

The ^{35}Cl NQR spectroscopic parameters and M—Cl bond characteristics in adducts MCl_4L (M = Si, Ge) are summarised in Table 11, which clearly demonstrates the similarities of the spectral patterns to those of the related tin compounds: the NQR spectra of the adducts of all three elements consist of triplets from equatorial atoms, slightly shifted relative to the frequencies of parent tetrachlorides MCl_4 , and lower-frequency singlets from axial chlorine atoms. However, the electronic characteristics of equatorial M—Cl bonds in adducts of different central metals M are markedly different. Thus η on the equatorial chlorine atoms was found to increase considerably in the order: $\text{Sn} < \text{Ge} < \text{Si}$. In silicon adducts, this increase was accompanied by a fall of the ^{35}Cl frequencies with respect to both the germanium and tin adducts and CCl_4 , which can be accounted for by an increase in the π -character of the Si—Cl bonds. The participation of the chlorine

$3p_\pi$ orbitals in bond formation results in their reduced occupancies Np_x and Np_y , whose sign in equation (1) is opposite to that of the $3p_\sigma$ orbital occupancy Np_z . This causes a decrease in both U_p and frequency with respect to those for the purely σ -bonded chlorine atom. In the latter case, the value of e^2Qq_{zz}/h becomes a measure of the chlorine valence $3p_\sigma$ orbital occupancy. One cannot make an independent estimation of the M—Cl bond σ - and π -characters, *i.e.*, determine three unknowns, σ , π_x and π_y from two equations (1) and (2). A spatial arrangement of ligands is however possible where the central atom M can interact with only one chlorine p_π orbital ($3p_x$), the occupancy of the other ($3p_y$) remaining undisturbed ($Np_y = 2$). Denoting $\pi_x = \pi$, we obtain equation (2) in the form

$$\eta = \frac{3\pi}{2U_p}, \quad (5)$$

so that η becomes a measure of the M—Cl π -bonding. One can now determine both parameters, σ and π , from equations (1) and (5). Such an arrangement is often the case in trigonal-bipyramidal adducts MCl_4L . The estimation of their M—Cl bond σ - and π -characters (Table 11) shows that in the silicon adducts the decrease in the equatorial ^{35}Cl frequency and increase in η result from substantial increase in the Si—Cl π -bonding. In the germanium adducts, the π -bonding is relatively weaker, whereas in SnCl_4L the η values exhibit a further considerable fall. They comprise a significant contribution from external charges, which is more pronounced than in analogous germanium and silicon adducts because of the larger Sn—Cl bond ionicity. This is supported by relatively higher values of η on axial Cl atoms in comparison with equatorial in the SnCl_4L adducts than in related silicon and germanium adducts.

Table 11. ^{35}Cl NQR spectroscopic parameters for pentacoordinate adducts of silicon and germanium tetrachlorides at 77 K and the M—Cl bond characteristics.⁴⁷

Compound	a/e	ν /MHz	η (%)	e^2Qq_{zz}/h /MHz	Np_σ	ΔNp_π	$-\rho$ /e	$ \sum \rho $ /e
$\text{SiCl}_4 \cdot \text{Me}_3\text{N}$	e	21.50	42.1 ± 7.2	41.78	1.566	0.107	0.459	2.081
	e	21.30(2)	36.6 ± 4.0	41.68	1.574	0.093	0.481	
	a	18.86	1.7 ± 0.5	37.77	1.654	0.004	0.650	
$\text{SiCl}_4 \cdot \text{TMU}^a$	e	21.65	43.1 ± 4.1	42.02	1.562	0.110	0.452	2.248
	e	21.16	38.8 ± 2.6	41.30	1.575	0.097	0.478	
	a	18.45	7.5 ± 2.0	36.86	1.656	0.017	0.639	
	a	17.34	1.7 ± 0.5	34.68	1.682	0.003	0.679	
SiCl_4		20.464	2.9 ± 0.5	40.77	< 1.59	> 0.07	< 0.52	< 2.08
		20.415	2.9 ± 0.5					
		20.408	2.9 ± 0.5					
		20.273	2.2 ± 0.5					
$\text{GeCl}_4 \cdot \text{Me}_3\text{N}$	e	24.83(2)	25.3 ± 3.9	48.92	1.516	0.075	0.441	1.948
	e	24.66	24.1 ± 3.3	48.85	1.519	0.071	0.448	
	a	20.59	2.0 ± 0.9	41.17	1.623	0.005	0.618	
$\text{GeCl}_4 \cdot \text{TMU}$	e	25.09	26.4 ± 5.0	49.06	1.510	0.079	0.431	1.914
	e	24.86	25.3 ± 4.2	49.19	1.514	0.076	0.438	
	e	24.34	27.0 ± 3.8	48.10	1.522	0.079	0.443	
	a	20.67	5.6 ± 1.0	41.33	1.616	0.014	0.602	
$\text{GeCl}_4 \cdot \text{HMPA}$	e	24.92	31.8 ± 5.0	49.02	1.506	0.095	0.411	1.890
	e	24.66	28.0 ± 4.3	48.69	1.515	0.083	0.432	
	e	24.57	28.0 ± 4.3	48.51	1.516	0.083	0.433	
	a	20.53	3.4 ± 0.5	41.05	1.622	0.008	0.614	
GeCl_4		25.745	2.2 ± 0.5	51.32	< 1.51	> 0.04	< 0.47	< 1.89
		25.739	2.2 ± 0.5					
		25.715	2.2 ± 0.5					
		25.450	2.2 ± 0.5					
		25.745 ^b	—	—	—	—	—	—
		25.735 ^b	7.8					
		25.713 ^b	3.7					
		25.449 ^b	3.4					

Note. ^a The ligand TMU is located in the equatorial plane of the adduct. ^b The results of Zeeman analysis of a single crystal at 77 K.⁴⁸

Table 12. ^{35}Cl and ^{81}Br Frequencies (ν) in the NQR spectra of pseudooctahedral adducts of silicon and germanium tetrachlorides and EFG asymmetry parameters (η) at 77 K.

L	e/a	ν /MHz	η (%)
SiCl₄L₂			
<i>trans</i> -py	e	19.15	6.6 ± 0.6
<i>trans</i> -TPPO	e	18.29	
<i>cis</i> -4,4'-Me ₂ - α,α -bipy	e	19.03(2)	13.0 ± 1.0
	a	18.4	2.0 ± 0.7
GeCl₄L₂ (see Ref. 49)			
<i>trans</i> -py	e	20.45	6.7 ± 1.0
<i>trans</i> -HMPT	e	21.10	7.8 ± 1.2
<i>trans</i> -DMF	e	20.67	8.2 ± 0.8
	e	20.32	{5.7}
<i>cis</i> -DMSO	e	20.82	{13.0}
	a	19.69	
<i>cis</i> -DESO	e	20.56	
	a	19.59	
GeBr₄L₂ (see Ref. 49)			
<i>trans</i> -py	e	139.78	
HMPT	—	135.09	
		146.46	
DMF	—	138.43	
		145.46	

Only a few results of NQR studies are currently available on pseudooctahedral adducts of silicon and germanium tetrahalides (Table 12), most important being the value of the asymmetry parameter η on the chlorine atoms in the only *cis*-isomer of the adduct SiCl₄L₂. This enables one to assign the ^{35}Cl NQR frequencies to equatorial and axial chlorine atoms and find that their positional order on a frequency scale is inverted with respect to that in analogous tin adducts: unlike in the latter, the lower-frequency components in the spectra of silicon adducts are assigned to axial Cl atoms. Unfortunately, lack of data on *cis*-isomers does not allow one to conclude whether this order is typical of silicon adducts.

Table 13 lists the M—Hal bond characteristics and effective charges on halogen sites in all the spectroscopically examined pseudooctahedral (MCl₄L₂) and trigonal-bipyramidal (MCl₄L)

Table 13. Average effective charges ($-\rho$) on chlorine atoms and chlorine valence $3p$ orbital occupancies ($Np_\sigma = Np_z$, $\Delta Np_\pi = Np_x - Np_y$) in adducts MCl₄L and MCl₄L₂.

M	Atom	a/e	Np_σ	ΔNp_π	$-\rho$ /e
MCl₄L₂					
Sn	Cl	e	1.645	0.025	0.620
	Cl	a	1.624	0.007	0.617
Ge	Cl	e	1.614	0.021	0.593
	Cl	a	1.641	0.0	0.641
Si	Cl	e	1.641	0.023	0.618
	Cl	a	1.662	0.005	0.657
MCl₄L					
Sn	Cl	e	1.550	0.029	0.521
	Cl	a	1.627	0.005	0.622
Ge	Cl	e	1.510	0.080	0.430
	Cl	a	1.619	0.009	0.610
Si	Cl	e	1.572	0.102	0.470
	Cl	a	1.654	0.004	0.650

adducts of silicon and germanium tetrachlorides. The corresponding characteristics for SnCl₄L₂ and SnCl₄L averaged over all the known examples are also included in the table. One can see that the chlorine $3p_\pi$ orbital occupancy differences at equatorial sites ($\Delta Np_\pi = Np_x - Np_y$) in all the hexacoordinate adducts MCl₄L₂ (M = Si, Ge, Sn), are close to each other, the main difference between the adducts consisting in the chlorine $3p_\sigma$ orbital occupancies. The absolute magnitudes of the effective charge ρ on the equatorial chlorine atoms vary in the order: Sn $\sim$ Si > Ge. When the adduct of pseudooctahedral configuration is compared to that of trigonal-bipyramidal geometry, one can find that the axial M—Cl bond characteristics differ insignificantly in both types of the adducts, whereas the equatorial bonds are markedly different, the difference being determined by the nature of the central atom. The effective negative charge on the equatorial chlorine atom increases in absolute value as the coordination number of the central atom increases (Table 14). In the tin adducts, this increase in the charge is nearly fully induced by the increase in chlorine $3p_\sigma$ orbital occupancy, whereas in the germanium and especially in the silicon adducts, it is provided by both the increased chlorine $3p_\sigma$ orbital occupancy and reduced ΔNp_π . This may be accounted for by the increased local symmetry of the Cl site in a crystal as well as the M—Cl bond elongation accompanying an increase in the coordination number. In germanium tetrachloride adducts, the contributions of the $3p_\sigma$ - and $3p_\pi$ -systems to the effective charge increment on the Cl atom amount in absolute magnitude to 0.104 and 0.059, respectively; in the silicon adducts, the contribution of the chlorine $3p_\pi$ orbitals to the respective increment exceeds that of the $3p_\sigma$ orbitals (0.079 and 0.069, respectively).

Table 14. Average values of effective charges on equatorial chlorine atoms and chlorine valence $3p$ orbital occupancies in adducts MCl₄L and MCl₄L₂ and variations of their absolute magnitudes ($\delta\rho$, δNp_σ , $\delta\Delta Np_\pi$) due to the change MCl₄L $\rightarrow$ MCl₄L₂.

Adduct	$-\rho(\text{Cl})/\text{e}$	Np_σ	ΔNp_π	$\delta\rho/\text{e}$	δNp_σ	$\delta\Delta Np_\pi$
SiCl ₄ L → SiCl ₄ L ₂						
SiCl ₄ L	0.470	1.572	0.102	+0.148	+0.069	−0.079
SiCl ₄ L ₂	0.618	1.641	0.023			
GeCl ₄ L → GeCl ₄ L ₂						
GeCl ₄ L	0.430	1.510	0.080	+0.163	+0.104	−0.059
GeCl ₄ L ₂	0.593	1.614	0.021			
SnCl ₄ L → SnCl ₄ L ₂						
SnCl ₄ L	0.521	1.550	0.029	+0.099	+0.095	−0.004
SnCl ₄ L ₂	0.620	1.645	0.025			

Thus, the NQR data available on the trigonal-bipyramidal SiCl₄L and GeCl₄L adducts provide evidence that the $3p_\pi$ -systems of the equatorial Si—Cl and Ge—Cl bonds contribute considerably to the bond formation, the estimated π -character amounting on average to 0.1 and 0.08, respectively. It should be noted however that the NQR data enable one to compare an extent of participation of the equatorial chlorine $3p_\pi$ electrons in the M—Cl bonding, whereas the question of the mechanism of the π -interaction remains open. In addition, the magnitude of ΔNp_π may not be a measure of the M—Cl bond π -character in pseudooctahedral adducts SiCl₄L₂ and GeCl₄L₂, if the electron density is withdrawn from both chlorine $3p_\pi$ orbitals; in this case, the true extent of the π -character will be higher than that estimated from ΔNp_π . This also holds for the parent tetrachloride molecules having slightly distorted tetrahedral structures.⁴⁸

The variation of the chlorine valence p orbital occupancies upon adduct formation was discussed based on the results of PM3 calculations of model acceptor molecules and adducts MCl₄L and MCl₄L₂ (M = Si, Ge, Sn).^{37,38} The M—Cl bond π -character was

identified by the authors with the magnitude of ΔNp_π determined in the parent tetrachlorides by the NQR experiments.⁴⁷

For SiCl_4 and GeCl_4 , such an estimation gave $\pi = 0.007$, which resulted in the considerably overestimated absolute value of the negative effective charge on the chlorine atom: $\rho(\text{Cl}) = 0.618$ and 0.525 e in SiCl_4 and GeCl_4 , respectively. Hence, the entire charge on the chlorine atoms $|\sum \rho(\text{Cl})|$ was 2.472 e in SiCl_4 and 2.1 e in GeCl_4 , which notably exceeded in absolute magnitude the appropriate charges in adducts MCl_4L , namely, 1.983 e in $\text{SiCl}_4 \cdot \text{NMe}_3$ and 1.912 e in $\text{GeCl}_4 \cdot \text{NMe}_3$.

The contradictions arisen were accounted for^{37,38} by the difference between the symmetry of free MCl_4 molecules (T_d) and the symmetry of the same molecules in the adducts (D_{3h} in MCl_4L and D_{4h} in MCl_4L_2). The results of PM3 calculations showed that the total effective charge on the chlorine atoms $|\sum \rho(\text{Cl})|$ in hypothetical MCl_4 molecules, whose symmetry and $\text{M}-\text{Cl}$ bond distances are the same as those in the corresponding adducts, was reduced as a result of the molecular spatial rearrangement only (the charge transfer being ignored) up to 2.184 e in SiCl_4 and 1.988 e in GeCl_4 . However, it is to be noted that similar characteristics ($|\sum \rho(\text{Cl})|$) of the MCl_4 molecules in the adducts $\text{SiCl}_4 \cdot \text{NMe}_3$ and $\text{GeCl}_4 \cdot \text{NMe}_3$ estimated from the orbital occupancies using the PM3 approach^{37,38} decrease accordingly:

Atom	a/e	Np_z	$Np_x + Np_y$	$Np_x - Np_y$	$-\rho/\text{e}$	$\sum \rho(\text{Cl})/\text{e}$
$\text{SiCl}_4 \cdot \text{Me}_3\text{N}$						
Cl	a	1.579	3.911	0.016	0.490	1.504
Cl	e	1.440	3.898	0.044	0.338	—
$\text{GeCl}_4 \cdot \text{Me}_3\text{N}$						
Cl	a	1.481	3.903	0.019	0.384	1.176
Cl	e	1.381	3.883	0.055	0.264	—

One can see that the calculated η values at the equatorial Cl atoms in the adducts in question (16.4% in $\text{SiCl}_4 \cdot \text{NMe}_3$ and 20.7% in $\text{GeCl}_4 \cdot \text{NMe}_3$)^{37,38} do not reflect even qualitatively the trends observed in experiments (see the measured magnitudes of η in Table 11).⁴⁷ Hypothetical molecules MCl_4 having the D_{4h} symmetry and $\text{M}-\text{Cl}$ bond distances characteristic of those in pseudooctahedral adducts MCl_4L_2 were calculated to give the largest values of η at the chlorine atoms, namely, $\eta \approx 31\%$ in SiCl_4 , 37% in GeCl_4 and 33% in SnCl_4 .^{37,38} Meanwhile, the experimental Z values at chlorine atoms did not exceed 15% in any of the measured MCl_4L_2 adducts (Tables 7 and 8), unless this atom is involved in secondary inter- or intramolecular interactions, as in the adducts $\text{SnCl}_4(\text{SeOCl}_2)_2$ and $\text{SnCl}_4(\text{EtOH})_2$ (Table 8). Moreover, the average values of η at the equatorial chlorine atoms in the adducts SiCl_4L_2 and GeCl_4L_2 are notably lower than in the related trigonal-bipyramidal adducts SiCl_4L and GeCl_4L .

There is no question that spatial reconstruction of an acceptor molecule upon complexation is accompanied by electron density redistribution. However, the orbital occupancies calculated within the PM3 approximations do not account for the inconsistency between the effective charges on the chlorine atoms in free acceptor molecules and their adducts,^{37,38} nor the reasons for the increase in the π -character of the $\text{M}-\text{Cl}$ equatorial bonds in the adducts MCl_4L ($\text{Sn} < \text{Ge} < \text{Si}$) found in NQR experiments.⁴⁷

But no inconsistency arises if one takes into account that the T_d symmetry of the parent tetrachloride molecules allows for the participation of both chlorine $3p_\pi$ orbitals in bond formation, whereas one can measure by NQR only the difference between their occupancies. Let us take the values of Np_x and Np_y in SiCl_4 (fitting the measured NQR frequencies and η), which give rise to the $\text{Si}-\text{Cl}$ bond π -character typical of the equatorial $\text{Si}-\text{Cl}$ bonds in the adducts SiCl_4L (for example, $\pi = 0.093$, $Np_x = 1.957$, $Np_y = 1.950$). One can find herefrom that the corresponding effective charges on the Cl atoms in the SiCl_4

molecules ($\rho = -0.49$ e, $\sum \rho(\text{Cl}) = -1.96$ e) are consistent with those in the SiCl_4L adducts ($-2.1 > \sum \rho(\text{Cl}) > -2.3$ e, see Table 11), hence allowing for the charge transfer from the ligand L to the acceptor SiCl_4 .

The problem of electron density distribution in Main Group IV element chloro complexes has received much attention in Refs 34–39. The results of semiempirical quantum-chemical calculations were reported, and their conformity to the data obtained using the NQR, Mössbauer and X-ray fluorescence spectroscopies were discussed. It was found that upon complexation, the positive charge on the central atom of the acceptor molecule increases with respect to that in the free MCl_4 molecule, which is in agreement with the results of other publications.⁴³ It was however noted that according to the X-ray fluorescence spectroscopy data ($\text{Cl}K_\alpha$ -shifts), the electron density on the chlorine atoms in the adducts MCl_4L_2 either remains unchanged or decreases as compared to free MCl_4 . The reader is referred to a review⁴³ where the criticism of this conclusion was given.

The quantum-chemical calculations of the trigonal-bipyramidal adducts $\text{SiCl}_4 \cdot \text{NMe}_3$ (**5**), $\text{SiCl}_4 \cdot \text{CO}(\text{NMe}_2)_2$ (**6**) and pseudooctahedral $\text{SiCl}_4 \cdot (\text{py})_2$ adduct (**7**) were made within the MNDO approximations.^{49–52} The changes in silicon, nitrogen, oxygen and chlorine valence p orbital occupancies as well as the effective charges on the appropriate atoms were considered as functions of the reaction coordinate of complexation, the considered separation between the components of the adducts varying from infinity ($d = 200$ Å) to 1.5 Å. As the calculated heats of formation showed, the most energetically favourable structures of **5** and **6** were those with the ligand L in axial and equatorial positions of the bipyramid, respectively, which is in agreement with their ³⁵Cl NQR spectral patterns (Table 11).

When the shape of the SiCl_4 molecule changes from tetrahedral to that in the adduct **5** (at $d = 200$ Å), the effective charge on the silicon atom decreases in absolute magnitude by 0.116 e, and that on the equatorial chlorine atom, by 0.059 e, whereas the absolute magnitude of the negative charge on the axial chlorine atom increases by 0.061 e. When the components of **5** approach each other to reach $d = 2.25$ Å, at which distance the heat of adduct formation is a minimum, the effective charge on silicon begins to grow. At the same time, the negative charge on nitrogen decreases and that on chlorine, increases in absolute value, the increment being larger on the equatorial Cl atoms. It was estimated^{50,52} that the formation of **5** results in the transfer of electron density of 0.2 e from the donor (mainly, from the nitrogen lone pair p_x orbital) to the acceptor (mainly, to the equatorial chlorine p_σ orbitals) molecule, which is in good agreement with experiment.⁴⁷ However, low sensitivity of this semiempirical method to the chlorine $3p_\pi$ orbital occupancies was noted. The calculated differences between the equatorial chlorine $3p_x$ and $3p_y$ orbital occupancies in the adduct **5** were negligibly small, whereas the experimental asymmetry parameters η on these atoms were large, the corresponding ΔNp_π values contributing considerably to the effective charge values (Table 11). Thus, the estimation of the effective charge on chlorine atoms from the calculated orbital occupancies^{50,52} is not quite reliable.

A similar calculation for the adduct **6**^{51,52} with a tetramethyl-urea ligand occupying an equatorial position shows that the formation of **6** also results in the transfer of the charge from the donor to chlorine atoms of the acceptor molecule, but in this case, the electron density is mainly transferred to the axial chlorines. The donor atoms are carbon of the carbonyl group, one of the nitrogen atoms and hydrogens from the dimethylamino groups, both p_σ and p_π orbitals of the carbonyl group contributing to the charge transfer. An increase in positive charge on silicon and in negative charge on oxygen upon adduct formation is caused presumably by polarisation of the $\text{Si}-\text{Cl}$ and $\text{Si}-\text{O}$ bonds.^{51,52} The p_σ orbital occupancies of the axial (1.591 e) and equatorial (1.523 e) chlorine atoms in **6**, found by the MNDO calculations, are in agreement with the observed trends (Table 11), while the

values of Np_x and Np_y at the equatorial chlorine atoms showed, as in **5**, poor agreement with experiment.⁴⁷

The results of MNDO calculations of **5**, **6** and pseudooctahedral **7** adducts were summarised⁵² to conclude that the formation of all the three adducts results in an increase in positive charge on the silicon atom, the conclusion being supported by the Mössbauer and X-ray fluorescence spectroscopy data^{34–36} available on the adducts of Main Group IV element tetrachlorides. The increasing charges, positive on silicon and negative on nitrogen, gave the authors⁵² grounds to believe that the electrostatic interactions resulting in polarisation of the bonds contribute considerably into the electron density distribution upon complexation. The electrostatic interactions initiate the charge transfer: the estimated total charge located on the acceptor fragment of the adduct was negative (-0.523 e in **7**) and that on the donor fragments, positive ($+0.206$ e per pyridine ring in **7**).

In order to compare the chlorine orbital occupancies calculated within the MNDO approximations with those derived from the NQR experiment the assumption was made⁵² (in the absence of the published η values) that the values of η at the equatorial chlorine atoms in pseudooctahedral adducts SiCl_4L_2 are similar to those for trigonal-bipyramidal adducts SiCl_4L . Thus, the value $\eta = 0.4$, which is the average for the SiCl_4L adducts, was used to estimate Np_x (at $Np_y = 2$) at the equatorial Cl atoms in **7**. This gave $Np_x = 1.909$ and $\Delta Np_\pi = 0.09$, the latter being considerably overestimated compared to the correct value $\Delta Np_\pi = 0.015$ derived from the recently measured η in $\text{SiCl}_4 \cdot 2\text{py}$. As was noted above, the values of ΔNp_π at the equatorial chlorine atoms, derived from the NQR spectra of SiCl_4L_2 and GeCl_4L_2 , are markedly lower than those in analogous trigonal-bipyramidal adducts. But even this correct magnitude of ΔNp_π exceeded considerably the value $\Delta Np_\pi = 0.004$ (and hence $\eta = 0.016$) found by the MNDO calculations.⁵² Therefore, for the pseudooctahedral adduct **7**, the MNDO approach also gave an η value in poor agreement with experiment (Tables 11 and 12).

It was however reported⁵³ that the results of calculations of η can be in much better agreement with the experiment if one takes into account that the EFG (q_{zz} , q_{xx} , q_{yy}) at the quadrupole atom is produced not by its entire valence p shell, but its less diffuse part which can be determined by *ab initio* calculations of a large

number of molecules in the split valence basis set 6-31G* using full optimisation of the molecular geometry.

It is reasonable to discuss how the differences in the M–Cl bond characteristics influence the formation by silicon, germanium and tin tetrachlorides of pentacoordinate adducts with ligands of various donating power. Before discussing this problem, the bonding in the parent tetrachlorides should be considered in more detail. Note once more that the values of η measured in tetrahedral MCl_4 molecules and octahedral adducts MCl_4L_2 using spin-echo technique and powder samples^{9,47} were in agreement with those measured with single crystals of similar compounds,^{44–46,48} whereas earlier experiments^{54,55} using continuous-wave techniques for measuring η with powder samples of MCl_4 (M = Si, Ge, Sn), yielded the asymmetry parameters η , whose values were an order of magnitude higher than those given in Tables 10 and 11, which is unlikely on symmetry grounds. An independent estimation of the M–Cl bond σ - and π -characters from equations (1) and (2) is impossible in these molecules, because η at chlorine sites is equal to zero ($Np_x = Np_y$), and two unknowns, σ and π , remain in equation (1). The probable intervals for the values of M–Cl bond σ - and π -characters in MCl_4 were found based on the data obtained for the adducts MCl_4L .⁴⁷ The magnitude of the entire effective charge $|\sum \rho(\text{Cl})|_{\text{MCl}_4}$, born by all the chlorine atoms in the parent molecule MCl_4 , was varied with respect to the related value for the adducts $|\sum \rho(\text{Cl})|_{\text{MCl}_4\text{L}}$, assuming that the latter is at least no less than the former: in fact, an increase in the entire effective charge on the chlorine atoms $|\sum \rho(\text{Cl})|_{\text{MCl}_4}$, depending on the amount of charge transferred from the donor L, is normally observed upon adduct formation.

For the silicon compounds, the results of varying the difference $\Delta = |\sum \rho(\text{Cl})|_{\text{SiCl}_4\text{L}} - |\sum \rho(\text{Cl})|_{\text{SiCl}_4}$ showed that the strengthening of the equatorial Si–Cl bonds by virtue of both σ and π orbitals is expected in the adduct with respect to SiCl_4 as Δ varies in the interval $0 < \Delta < 0.18$ e (Table 15). This implies that if the extent of charge transfer from the ligand L is small (due, for instance, to the weak donating power of ligands L), the adduct formation will be accompanied by an additional charge transfer from the equatorial chlorine atom σ and π orbitals to the axial ones. When the extent of charge transfer is increased, so that Δ varies in the interval $0.18 < \Delta < 0.21$ e, weakening of the equa-

Table 15. Variation of chlorine valence $3p_z$ orbital occupancies (δNp_σ) and equatorial M–Cl bond π -character ($\delta\pi$) in adducts MCl_4L in relation to the difference Δ between the total effective charges on the chlorine atoms in the adduct and parent tetrachloride MCl_4 .

Compound	$\sum \rho(\text{Cl}) / \text{e}$	$-\rho(\text{Cl}) / \text{e}$	a/e	Np_σ	π	Δ / e	δNp_σ	$\delta\pi$
SiCl_4L	2.07	0.473	e	1.571	0.098			
		0.650	a	1.654	0.004			
SiCl_4	2.07	0.517	—	1.591	0.074	0.0	–0.020	+0.024
	1.96	0.490	—	1.582	0.092	0.11	–0.011	+0.006
	1.924	0.481	—	1.579	0.098	0.146	–0.008	0.0
	1.89	0.472	—	1.576	0.104	0.18	–0.005	–0.06
	1.86	0.465	—	1.573	0.109	0.21	–0.002	–0.11
	1.836	0.459	—	1.571	0.113	0.234	+0.00	–0.015
GeCl_4L	1.77	0.442	—	1.566	0.124	0.30	+0.005	–0.026
	1.89	0.425	e	1.512	0.087			
GeCl_4		0.614	a	1.622	0.008			
	1.89	0.472	—	1.512	0.040	0.0	0.00	+0.047
SnCl_4L	1.84	0.460	—	1.508	0.048	0.05	+0.004	+0.039
	1.607	0.402	—	1.489	0.087	0.283	+0.023	0.0
	1.53	0.382	—	1.482	0.100	0.36	+0.030	–0.013
SnCl_4	2.15	0.511	e	1.543	0.032			
		0.615	a	1.626	0.011			
	2.15	0.537	—	1.557	0.020	0.0	–0.014	+0.012
	2.052	0.513	—	1.545	0.032	0.098	–0.002	0.0
	1.96	0.490	—	1.537	0.047	0.19	+0.006	–0.015
	1.88	0.470	—	1.531	0.061	0.27	+0.012	–0.029

torial Si—Cl bonds through the π -mechanism is expected, *i.e.*, increase in the electron density will partly localise on the equatorial chlorine atom $3p_\pi$ orbitals of the acceptor molecule being withdrawn from their $3p_\sigma$ orbitals until Δ reaches 0.21 e, after which the weakening will occur through the σ -system also.

The variation of Δ should evidently proceed within reasonable limits. The situation where the π -bonding in SiCl_4 exceeds the equatorial Si—Cl bond π -character in the adducts seems improbable. From the other side, the assumption of pure σ -bonds in SiCl_4 leads to the conclusion that the total σ -electron density in the acceptor molecule decreases considerably upon adduct formation, which is also unlikely. It thus follows that the most probable limits for variation of Δ , associated with the formation of the adducts SiCl_4L , are $0 < \Delta < 0.30$ e.

Similarly, strengthening of the equatorial Ge—Cl bonds in the adducts GeCl_4L with respect to GeCl_4 is first expected as the extent of charge transfer increases within $0 < \Delta < 0.22$ e, which is then followed by their weakening at $\Delta > 0.22$ e. But unlike the silicon adducts, the Ge—Cl bond strengthening involves the π -system only, whereas the chlorine $3p_\sigma$ orbital occupancy can only increase, whatever small extent of charge transfer may be in the germanium adducts (Table 15). The range for variation of Δ associated with the formation of the adducts GeCl_4L ($0 < \Delta < \sim 0.40$ e) is here larger than for the silicon adducts. As to the adducts SnCl_4L , their equatorial Sn—Cl bonds weaken at $\Delta > 0.13$ e.

Thus, the NQR data, if not providing the undisputable absolute magnitudes of the electronic characteristics, reveal considerable difference between the equatorial M—Cl bonds in trigonal-bipyramidal adducts of silicon, germanium and tin tetrachlorides. This difference determines specific changes in their σ - and π -components when going to the adducts of pseudooctahedral configuration. Several characteristic distinctions, depending on the nature of the central atom M and donating power of ligand L, were revealed when the electron density redistribution due to formation of pentacoordinate adducts by the parent MCl_4 molecules was compared using the NQR data.

V. Conclusion

The NQR spectroscopic data refine our understanding of the electronic effects due to substitution and spatial rearrangement of the coordination polyhedra in adducts and complexes of tin, germanium and silicon tetrachlorides. They provide information on the relative contribution of the σ - and π -systems to the electron density redistribution. The results of NQR studies of adducts and complexes of monoalkyl(phenyl)-substituted chloro, bromo and iodostannates enabled one to estimate and compare the contributions of their σ -electron systems to weakening of the Sn—Cl bonds in *cis*-positions relative to the substituents. An estimation of the effective charges on the halogen atoms in *cis*- and *trans*-positions to the substituents made it possible to compare quantitatively the contributions of *cis*-weakening and *trans*-strengthening to the resulting electron density redistribution in the adduct due to replacement of the acidoligands; participation of the halogen π -electron system in the M—Cl bond *trans*-strengthening was revealed. The NQR spectra provide evidence that the length of the chain in the alkyl groups of the substituent influences insignificantly the overall *cis*-weakening of the Sn—Cl bonds. This permitted one to estimate the contribution of the ligands L to the Sn—Cl bond weakening in the presence of the alkyl groups in dialkylidibromostannates. An examination of dependence of the EFG asymmetry parameters at the iodine atoms in the adducts of type $\text{R}_2\text{SnI}_2\text{L}_2$ on the iodine valence orbital occupancies showed that an increase of the halogen σ -electron density due to *cis*-weakening leads to an increase in η at a fixed $\Delta N p_\pi = N p_x - N p_y$ difference.

Comparison of the NQR and X-ray diffraction data enabled one to correlate on a quantitative basis the change in the Sn—Hal

bond lengths with the effective charge increments on the appropriate halogen atoms. The NQR spectroscopic parameters directly determined by the electron density distribution at the halogen atoms were found to be more sensitive to the electronic effects than the interatomic distances. However, X-ray data on the spatial arrangement of atoms and atomic groups, especially in isomers, appeared to be very important for the correct assignment of resonance lines and hence correct interpretation of the NQR spectra. However, examples are known where the electronic effects registered by NQR gave structural evidences below the accuracy of X-ray experiments. Thus the structural effects of *trans*-strengthening in adducts and complexes of monoalkyl(phenyl)tin trichlorides were small, so that the corresponding *trans*-shortening was comparable with the standard deviation values, whereas the electronic effects involved were registered by NQR with an accuracy notably exceeding the errors of measurement. Similarly, no structural evidence for any intermolecular (interligand) interactions were found by X-ray in the adduct $\text{Ph}_2\text{SnI}_2(\text{HMPT})_2$, whose ^{127}I NQR spectral patterns were consistent with a considerable disturbance of the iodine valence π -electron system caused seemingly by the π - π interactions between the iodine atom and phenyl rings of the substituents.

The measurement of the EFG asymmetry parameters at chlorine atoms in pseudooctahedral adducts SnCl_4L_2 enabled one to find a spectroscopic criterion of *cis*–*trans* isomerism of the adducts. The type of isomer could be identified, using this criterion, by measuring the ^{35}Cl NQR frequencies only. The identification of isomers led to better understanding of the electronic reorganisation of the adducts as a result of their rearrangement from pseudooctahedral to trigonal-bipyramidal geometry. It was found that the transformation $\text{SnCl}_4\text{L}_2 \rightarrow \text{SnCl}_4\text{L}$ is accompanied by an insignificant change in the axial Sn—Cl bond character. The equatorial Sn—Cl bond π -system also remains undisturbed by this transformation. The main influence was exerted on the equatorial halogen atom valence $3p_\sigma$ orbitals, whose occupancies decreased on average by 0.1 e.

The measurement of η at chlorine atoms in analogous adducts of germanium and silicon tetrachlorides demonstrated both similarities and differences between the M—Cl bond characteristics. According to the NQR data, the equatorial M—Cl (M = Sn, Ge, Si) bond π -character considerably increases in the trigonal-bipyramidal adducts in the order $\text{Sn} < \text{Ge} < \text{Si}$ ($0.03 < 0.08 < 0.1$, respectively). On going from these adducts to the adducts of pseudooctahedral configuration, the axial M—Cl bond exhibits only minimal changes. However, the electron density redistribution over the σ - and π orbitals of the equatorial M—Cl bonds strongly depends on the nature of the central atom: an increase in the coordination number of the latter results in an increase in absolute magnitude of the effective charges on the equatorial chlorine atoms. In tin adducts, this increase is completely provided by the increased halogen $3p_\sigma$ orbital occupancy, whereas in the silicon adducts, the charge increment, caused by the reduced chlorine $3p_\pi$ orbital occupancy difference (0.079), exceeds that contributed by its $3p_\sigma$ orbital (0.069).

The difference between the bonds of tin, germanium and silicon tetrachlorides causes the different character of σ - and π -electron density redistribution upon formation of trigonal-bipyramidal adducts with ligands L of various donating powers.

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Radical pairs in redox reactions involving sterically hindered quinones and phenols[†]

A I Prokof'ev

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Abstract. The review summarises the results of studies on the redox reactions involving sterically hindered quinones and pyrocatechols (phenols) occurring in glassy and single-crystal matrices. Exposure of these systems to light results in the transfer of a hydrogen atom or an electron from the phenol to the quinone accompanied by the formation of radical pairs, *viz.*, two paramagnetic species existing in the triplet state. Studies of the transformations in single-crystal matrices enabled separation of the mechanisms of electron and hydrogen atom transfer. Synchronous transfer of two hydrogen atoms from two sterically hindered phenol molecules to *o*-benzoquinone is also possible. The bibliography includes 39 references.

I. Introduction

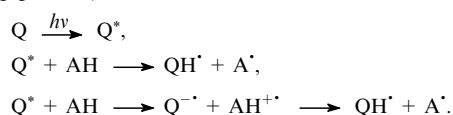
The simplest quinones can be considered as model systems that mimic biologically important quinoid compounds (plastoquinones, ubiquinones, vitamin K, flavin adenine dinucleotide, *etc.*). Therefore, studies of the photochemistry of quinones are of undeniable interest due to elucidation of their role as electron acceptors in photosynthesis. For example, photoreduction of quinones results in semiquinone radicals, which are active species in electron transfer reactions in biological systems. Studies of photoreduction reactions in the liquid phase make use of methods of flash photolysis with optical detection of intermediate products and chemically induced dynamic polarisation of electrons and nuclei, while studies of these reactions in the solid state are carried out with the use of ESR spectroscopy. Although the ESR data obtained in the solid state are essentially depleted due to unaveraged rotational dipole–dipole electron–nucleus interactions, studies of solid-state processes and the identification of the radical species formed in these processes are still of special interest.

The present review generalises the results of studies dealing with the solid-state photoreduction of quinones and quinone-like systems with sterically hindered phenols.

A characteristic feature of sterically hindered phenols and their derivatives is that they are readily involved in redox reactions to give relatively stable radicals. The application of radio-

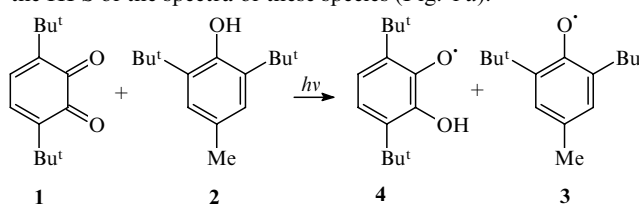
frequency spectroscopic methods gave strong impetus to the studies on the structure and reactivity of phenoxyl-type radicals and promoted progress in the chemistry of this class of compounds; this resulted in the synthesis of metal complexes with paramagnetic ligands.^{1,2} The rather high stability of phenoxyl radical species and the relative simplicity of their ESR spectra made it possible to solve diverse structural and kinetic problems based on the analysis of the hyperfine structure (HFS) of the spectra.^{2–4} Taken together, all this has made the sterically hindered phenols–quinones system a convenient model for studying the photooxidation by the ESR method.

UV irradiation of aromatic ketones in the presence of hydrogen or electron donors results in the reduction of carbonyl groups.^{5–7} In a discussion of the elementary act of transfer of an H atom from a hydrogen donor (AH) to an excited quinone (Q*), Porter suggested in 1958 two possible variants of this process: (1) transfer of a hydrogen atom as a whole (one-step process) and (2) transfer of an electron followed by transfer of a proton (two-step process).⁸



In certain cases, it was possible to detect the formation of both neutral and radical-ion intermediates in these systems and to demonstrate the independence of their formation and dark decay. This fact implies that the solid-state reactions of this type are quite unusual.

Irradiation of a solution of 3,6-di-*tert*-butyl-1,2-benzoquinone (**1**, 3,6-Q) and 2,6-di-*tert*-butyl-4-methylphenol (**2**) in toluene or CCl₄ results in the phototransfer of an H atom from the phenol **2** to the quinone **1** accompanied by the formation of 2,6-di-*tert*-butyl-4-methylphenoxyl (**3**) and 3,6-di-*tert*-butyl-2-hydroxyphenoxyl (**4**, 3,6-SQH[•]) radicals, as indicated unambiguously by the HFS of the spectra of these species (Fig. 1 *a*).



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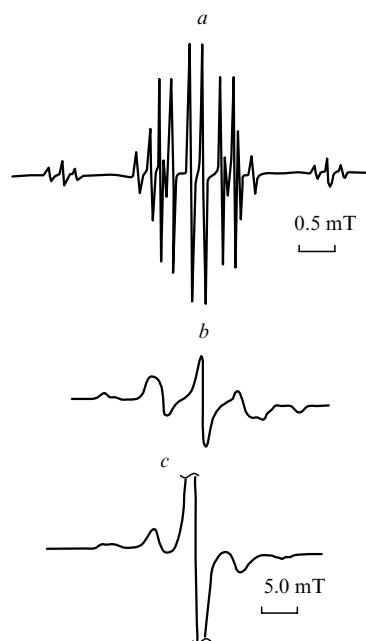


Figure 1. ESR spectra of a solution of 3,6-di-*tert*-butyl-1,2-benzoquinone (1,3,6-Q) and 2,6-di-*tert*-butyl-4-methylphenol (2) in CCl_4 (UV irradiation, 30 °C) (a) and of radical pairs (3,6-Q + NEt_3) (b) and (3,6-Q + phenol 2) (c) in solid phase (toluene, 77 K).

On the other hand, irradiation of quinone **1** in the presence of amines results in semiquinone (SQ) radical anions.⁹

HFS of the ESR spectra of biradicals formed upon photolysis of the quinone **1**–phenol **2** system at 77 K points to their triplet state (Fig. 1 b,c). A similar pattern is also observed for the efficient dipole–dipole interaction of unpaired electrons of two mono-radical species located in a solid phase at a distance of up to 7–10 Å from each other (radical pairs).

A theoretical consideration of systems in a triplet state enables an experimental determination of the zero splitting parameters (D and E) from the lines of the fine structure corresponding to the allowed transitions ($\Delta m_S = 1$).¹⁰ The parameter D (in mT) in the point dipole approximation depends on the distance between the radical centres: $D = 3g\beta/r_{\text{av}}^3$, where g is the spectroscopic splitting factor, β is the Bohr magneton, and r_{av} is the average distance between the unpaired electrons. In this approximation, r is defined as $r_{\text{av}}(\text{\AA}) = 14.06 D^{-1/3}$. As regards the parameter E , $E \neq 0$ in the absence of axial symmetry, while $E = 0$ in the case of axial symmetry where the system should have, at least, a three-fold axis.

The recorded absorption ($\Delta m_S = 1$, $g = 2$) due to reorientation of one electron spin in the external magnetic field (H) and in the field of the other electron of the radical pair (RP) is anisotropic in principle. Therefore, two components are distinguished for chaotically oriented RP, which correspond to RP oriented along the direction of H , i.e., parallel ($D_{\parallel}$) and perpendicular ($D_{\perp}$); in this case, $D_{\parallel} \approx 2D_{\perp}$.

In addition, the ESR spectra of triplet systems often display forbidden transitions ($\Delta m_S = 2$) in the range $g = 4$ (half-field signal); the intensity of these increases with a decrease in the distance between the electron spins. The signal with $\Delta m_S = 2$ is intrinsically isotropic, as it originates from simultaneous reorientation of two electrons of the RP in the field H .

Detailed analysis of the ESR spectra of single crystals of phenols doped with quinones and similar compounds and subjected to photolysis made it possible to reveal fundamentally new types of solid-state reactions, viz., synchronous transfer of two hydrogen atoms from a single-crystal phenol matrix to a quinone, relay transfer of a hydrogen atom in the system 2,6-di-*tert*-butylphenol–2,6-di-*tert*-butyl-1,4-quinonediazide, and tunnel transfer of a hydrogen atom in the dark decay of RP in a single

crystal of 2,6-di-*tert*-butylphenol doped with 2,6-di-*tert*-butylquinoneimine.

The effects of abnormal relaxation of RP detected due to the different saturation of certain lines of the fine structure proved to be useful in the study on the chemical polarisation of nuclei in liquid solutions of the above systems. In certain cases, X-ray diffraction analysis of single crystals of phenols made it possible to determine specific ways of reverse transfer of a hydrogen atom in the dark decay of the RP. Analysis of kinetic curves of the RP decay showed the possibility of intramolecular migration of a hydrogen atom in semiquinone radicals.

Thus, detailed investigations into the spectral and relaxation characteristics of RP can provide additional information regarding the nature of the RP and the mechanism of processes resulting in their formation.

II. Radical pairs of phenoxy radicals in frozen solutions

Specific features of solid-state phototransfer of a hydrogen atom in frozen solutions have been studied for the system 2,4,6-tri-*tert*-butylphenol (**5**)–3,6-di-*tert*-butyl-1,2-benzoquinone (**1**) as an example.¹¹ The ESR spectra of the radical pairs formed upon photolysis of the phenol **5** and the quinone **1** in Nujol at 77 K (Fig. 2) attest to the formation of two types of RP, viz., RP_1 with $r_{\text{av}} = 5.4 \text{ \AA}$ and RP_2 with $r_{\text{av}} = 6.3 \text{ \AA}$. The lines corresponding to the $D_{\perp}$ component of RP_1 coincide with the lines of the $D_{\parallel}$ component of RP_2 . A study of the static saturation of these types of RP showed that the RP_1 lines are saturated with much greater difficulty than the RP_2 lines (Fig. 3) because of efficient relaxation in RP_1 due to stronger spin–spin interaction of unpaired electrons. It was shown that the accumulation of RP_1 and RP_2 during photolysis by filtered light ($\lambda = 365\text{--}460 \text{ nm}$) occurs in parallel, but the ratio of their maximum concentrations at 77 K is 1 : 4. The presence of two types of RP in this system is due to the formation of ‘sandwich’ donor–acceptor complexes (Fig. 4) between the quinone **1** and the phenol **5** (NMR data) in which

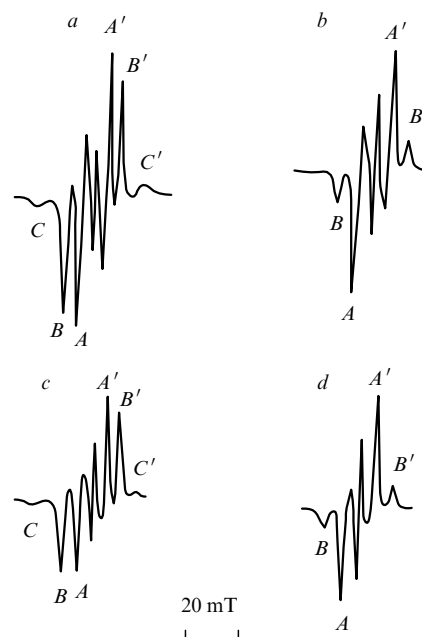


Figure 2. ESR spectra of radical pairs formed after 10-min irradiation of frozen solutions of 3,6-Q and 2,4,6-tri-*tert*-butylphenol (**5**) in Nujol at 77 K with light at a wavelength of 365–450 nm (a, b) and after 6 min of annealing the samples at 133 K (c, d).

The spectra were recorded at a microwave irradiation power of 150 (a, c) and 0.2 mW (b, d).

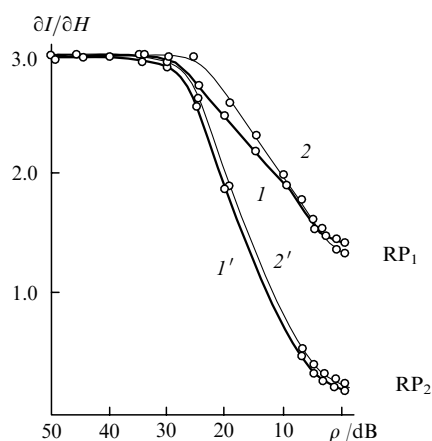


Figure 3. Dependence of saturation of RP_1 (1, 2) and RP_2 (1', 2') formed upon irradiation of solutions [3,6-Q + 2,4,6-tri-*tert*-butylphenol (5)] (1, 1') and (3,6-Q + OH-deuterated 2,4,6-tri-*tert*-butylphenol) (2, 2') in Nujol on the microwave irradiation power (ρ).

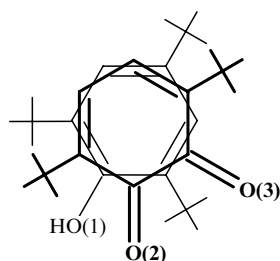
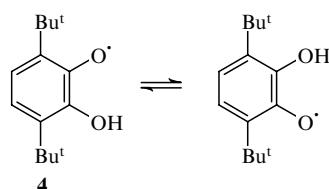


Figure 4. Tentative structure of the complex of the quinone 1 with the phenol 5.

the distances between the oxygen atoms of the OH group of the phenol 5 and two carbonyl groups of the quinone 1 [O(1)...O(2) and O(1)...O(3)] differ noticeably. In addition, account of the electric dipole interaction between the oxygen atoms of the OH group of the phenol 5 and the carbonyl groups of the quinone 1 in the sandwich complex (Fig. 4) shows that the relative depth of the proton trap at the O(2) atom is greater than that at the O(3) atom by 0.2 kcal mol⁻¹. As a result, the ratio between the equilibrium concentrations of RP_1 and RP_2 is approximately equal to 1:4, which is consistent with the experimental data. The hydroxyphenoxyl radical 4 formed is characterised by intramolecular migration of a hydrogen atom between the oxygen atoms at a frequency of $\nu \approx 10^9$ s⁻¹ (at 300 K) or $\nu \approx 10^3$ s⁻¹ (at 77 K), which is much slower than the ESR time scale (10^{-6} – 10^{-10} s).¹²



As a result, the spectra of RP_1 and RP_2 are recorded separately.

Studies of the dark decay of RP_1 and RP_2 showed that both types of pairs decay in the same way and that the kinetics of this process is stepwise, which is probably caused by the heterogeneity of the matrix. The similarity of the character of accumulation and decay of RP_1 and RP_2 is apparently due to intramolecular migration of the H atom in the hydroxyphenoxyl radical, which causes the kinetic interrelation between the states determining the existence of both pairs. It should be noted that multiple cycles of generation and subsequent dark decay of the pairs do not result in the consumption of the starting reagents, which suggests that only two processes occur in these and similar systems, *viz.*, photo-

Table 1. The values of fine structure constants D (mT) for neutral and radical-ion (D^i) pairs formed upon irradiation of the system quinone 1 – pyrocatechol 6 with light at $\lambda = 480$ –650 nm in various solvents.

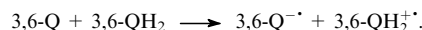
Solvent	D_1 (C,C') ^a	D_2 (B,B') ^a	D^i	ΔD^i (see ^b)
3-Methylhexane	25.7	14.6	22.5	0.5
1,1,2,2-Tetrachloroethane	24.2	14.2	21.1 ^c	0.9
Toluene	24.9	14.3	–	0.5
Carbon tetrachloride	23.1	12.5	22.9	–
Pentane	25.5	14.2	22.0	0.9
Hexane	24.5	13.4	21.5	1.6
Heptane	24.7	13.9	20.9	0.9
Octane	23.5	12.4	21.4	0.7
Nonane	23.5	13.1	20.3	0.7
Decane	23.2	12.3	21.3	1.2
Tridecane	23.8	13.1	20.5	1.4
Benzene	23.3	13.2	21.0	0.6
Chlorobenzene	23.0	13.4	21.7	1.1
Bromobenzene	24.5	13.9	21.0	0.5
Dichloroethane	24.1	13.8	20.5	0.8
<i>m</i> -Ethyltoluene	21.5	12.1	22.4	1.2
Tetramethylsilane	23.8	13.3	20.9	1.3
Decalin	23.3	12.6	–	0.9

^a D_1 and D_2 are dipole–dipole coupling constants for neutral RP with the perpendicular components C,C' and B,B'. ^b ΔD^i is the change in D^i after 30 min of dark annealing at 77 K. ^c In this case it was possible to measure E , which was found to be 0.47 mT.

transfer of the hydrogen atom from the phenol to the quinone and its reverse transition in the dark process.

A detailed study of the dependence of the structure of RP formed in the system quinone 1–3,6-di-*tert*-butyl-1,2-dihydroxybenzene (6, 3,6-QH₂) in glassy frozen solutions at 77 K on the solvent nature (Table 1) and the wavelength of the incident light was carried out.^{13,14} Irradiation of this system with light at $\lambda = 365$ –500 nm results in the phototransfer of a hydrogen atom with formation of three types of neutral RP,[‡] which differ in their fine structure parameters. The kinetic characteristics of accumulation and decay of all of these types of RP are identical due to the intramolecular migration of the H atom in the phenoxyl radical 3,6-SQH[•], and hence, the difference between the accumulation and decay curves of the RP disappears.

However, irradiation of this system with light at $\lambda = 480$ –650 nm gives, in addition to the types of pairs specified above, one more type which has an intermediate D value and corresponds to a radical-ion pair formed due to the phototransfer of an electron:



The kinetic stability of this type of RP is much smaller (Fig. 5) than that of neutral ones.

An important feature of radical-ion pairs is the absence of an induction period in their accumulation curves; this made it possible to draw the conclusion that the formation of the neutral and radical-ion pairs occurs independently, *i.e.* the two processes occur in parallel.^{14,15} The main argument for the suggested mechanism of the formation of neutral and radical-ion pairs is the increase in the relative photoyield of ionic RP in comparison

[‡] In solution, the quinone 1 and the pyrocatechol 6 give donor–acceptor complexes;¹³ in this case, the phototransfer of an H atom formally results in four types of RP (generally, four localisation variants of two H atoms on four O atoms are possible in each hydroxyphenoxyl radical; however, the parameters D of two of these variants are equal).

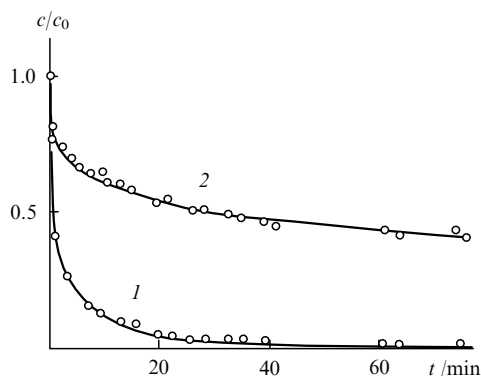


Figure 5. Kinetic curves of decay of ionic (1) and neutral (2) radical pairs in 3-methylhexane.

with that of the neutral ones (Fig. 6) with an increase in the wavelength of the incident light (λ). Similar results were obtained for the photoreduction of *p*-benzoquinone in an ethanolic solution at room temperature.¹⁶ The long-wave threshold for the generation of neutral semiquinone radicals is 450 ± 10 nm, while that of radical ions is 580 ± 10 nm.¹⁶ Hence, the transfer of a hydrogen atom requires irradiation in a shorter wavelength range than that required for the electron transfer. This feature of ionic RP is apparently due to the formation of donor–acceptor complexes in which the single-electron phototransfer is facilitated.¹⁷

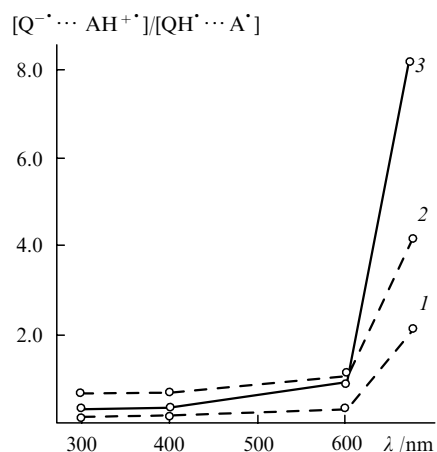


Figure 6. Dependence of the relative photoyield of radical-ion pairs $[Q^{\bullet-} \cdots AH^{\bullet+}]/[QH^{\bullet} \cdots A^{\bullet}]$ in different solvents on the wavelength of the exciting light. The abscissa axis represents the value of λ corresponding to the maximum of the transmission band of a set of light filters (the half-width of the transmission band was 50 nm); (1) toluene; (2) 1,1,2,2-tetrachloroethane; (3) 3-methylhexane.

III. Characteristic features of photoreduction of quinones in single crystals of organic hydrogen donors

Doping of single-crystalline phenolic compounds with sterically hindered quinones enabled the development of new interesting systems characterised by specific behaviour when exposed to photoirradiation. Single crystals of 3,6-QH₂ doped with 3,6-Q (10^{-2} mol litre⁻¹) were obtained¹⁸ and the ESR spectra of radical pairs formed upon irradiation of this system ($\lambda = 425\text{--}475$ nm) at 77 K were studied. Figure 7 shows the ESR spectra of single-crystalline 3,6-QH₂ doped with 3,6-Q (Fig. 7a) and a polycrystalline sample obtained from a melt of

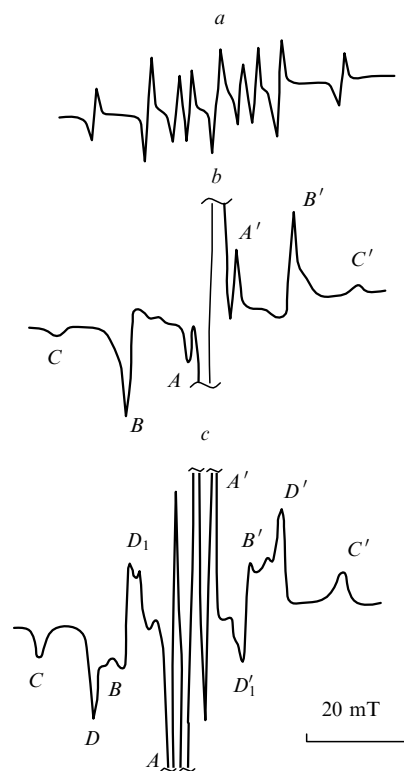


Figure 7. ESR spectra of a single crystal of 3,6-QH₂ doped with 3,6-Q (10^{-2} mol litre⁻¹) (a) and a polycrystalline sample obtained from a melt of the corresponding single crystals (b, c); (a) is the single-crystal sample 10 min after irradiation with light at a wavelength of 425–475 nm; (b) is the polycrystalline sample 10 min after the irradiation; (c) is the polycrystalline sample during irradiation in the ESR spectrometer resonator.

The components *A* and *A'* can be assigned to RP with $D = 7.5 \pm 0.2$ mT and $r_{av} = 7.2$ Å; *B* and *B'*, to the perpendicular components $D_{\perp}$; *C* and *C'*, to the parallel components $D_{\parallel}$. The additional short-lived components *D*, *D'* and *D₁*, *D₁'* belong to RP with $E = 0$. The parallel components of the short-lived RP coincide with those for the stable RP.

the corresponding single crystals (Fig. 7b,c). The calculated value of parameter $D = 28.6 \pm 0.4$ mT for this system corresponds to the mean distance between the unpaired electrons, $r_{av} = 4.6$ Å.

The equality between the $D_{\parallel}$ components of short-lived and stable RP suggests that their r_{av} are approximately equal to 4.6 Å. The essential difference in the stability of the RP in question enables one to assign the short-lived RP to radical-ionic ones ($AH^{\bullet+} + Q^{\bullet-}$) formed upon phototransfer of an electron. Stable RP ($A^{\bullet} + SQH^{\bullet}$) result from the phototransfer of an H atom. As in glassy frozen solutions (see Section II), the long-wave threshold of the formation of stable RP is 460 ± 15 nm, while that of radical-ionic RP is 560 ± 15 nm. It should be noted that irradiation of a sample with light at $\lambda = 475$ nm for 2 h virtually does not give stable RP. Analysis of the ESR spectra of radical pairs shows that the fraction of the radical-ion pairs is 99.9%, and their subsequent dark decay occurs without conversion into stable neutral RP.¹⁵ These data confirm the conclusions on the independence of two photoreduction mechanisms of excited 3,6-Q made for glassy frozen solutions.

Single crystals of 3,6-QH₂ were studied by the X-ray diffraction method.¹⁹ They were found to have a tetragonal structure (space group $I4_1/a$). Analysis of packing of the 3,6-QH₂ molecules in the crystal indicates that they form a helix relative to a four-fold axis (4₁) (Fig. 8) with a rotation angle of 90° relative to each other.

The X-ray diffraction data were compared with those of ESR spectroscopy by calculating the zero splitting parameters (*D* and *E*) for the case where one 3,6-QH₂ molecule is replaced by 3,6-Q

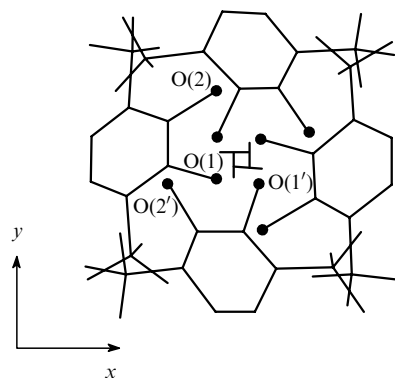


Figure 8. Fragment of a projection of the unit cell of 3,6-QH₂ on the *xy* plane.

and two identical 3,6-SQH[•] radicals are formed upon irradiation. The values of *D* were calculated for various pairs of adjacent molecules using the method described in Ref. 20. The spin densities on various atoms in the 3,6-SQH radical were taken from Ref. 21 where they are given with an accuracy of 15%. The transfer of the H atom (Fig. 8) can occur through the channels O(1)–O(1') and O(1)–O(2'). The calculated values of *D* are 33.55 mT for the channel O(1)–O(1') and 33.4 mT for the channel O(1)–O(2'). These values are virtually identical and differ from the experimental one by 14% (*D*_{exp} = 28.6 mT). Since the spin density distribution in 3,6-SQH[•] was estimated to the same accuracy, the agreement between the theoretical and experimental *D* values may be considered as satisfactory. By comparing the theoretical and experimental angular dependences *D*(θ), where θ is the angle between the axis *x* (Fig. 8) and the direction of the external magnetic field *H* (the crystal rotates around a four-fold axis), it was shown that the O(1)–O(2') channel of the transfer of the H atom is more efficient.¹⁹

The interest in the photoprocesses in single-crystal matrices is caused by the fact that single crystals of sterically hindered phenols doped with quinones have diverse crystal structures and unit cell parameters, which depend on the structure of the phenol. In turn, this determines the specific features of the photo- and dark processes of the H atom transfer in each particular case.

It is known that in some redox processes, the transfer of two electrons can occur within one elementary act.²² Studies^{13,23,24} of the transfer of H atoms in single crystals of sterically hindered phenols doped with quinones showed the possibility of synchronous transfer of two H atoms from the phenol single-crystal matrix to quinones. The ESR spectra that appear upon photoirradiation ($\lambda = 285\text{--}470$ nm) of single-crystalline 2,6-di-*tert*-butyl-4-methylphenol doped with 3,6-Q are given in Fig. 9. Visually, the single crystals of the phenol **2** have a two-fold axis (axis *z*) and two faces parallel to this axis; the axis *y* is chosen along these faces. The spectral pattern shown in Fig. 9*a* corresponds to the direction of the external magnetic field *H* along the axis *z*. Six groups of lines of the fine structure of the RP formed comprise HFS lines, which indicates unambiguously the interaction of the unpaired electrons with the protons of two equivalent methyl groups in the phenoxyl radicals **3** present in the pair. Each component of the fine structure contains seven lines with a binomial intensity distribution, $a_{\text{H}}^{\text{Me}} = 0.53$ mT. Such a pattern can only be caused by the transfer of two H atoms from two matrix molecules of the phenol **2** to the quinone **1**:

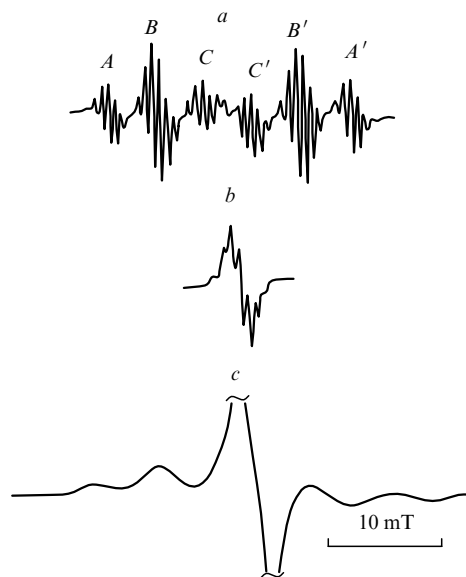
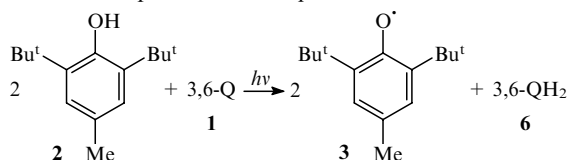


Figure 9. ESR spectra of a single crystal of the phenol **2** doped with 3,6-Q (10^{-3} mol litre⁻¹) (a) (*b* is the forbidden signal of single-crystalline phenol **2** ($\Delta m_S = 2$) in half-field) and polycrystalline sample (*c*).

The isotropic forbidden signal ($\Delta m_S = 2$) also contains seven lines (Fig. 9*b*) from two equivalent methyl groups. The HFS constant in this system is half that in the original radical existing in solution ($a_{\text{H}}^{\text{Me}} = 10.7$ mT), which also proves the existence of two phenoxyl radicals **3** in the triplet state. In other words, along with the dipole–dipole interaction of two unpaired electrons giving fine structure lines, their strong isotropic exchange interaction due to overlapping of the wave functions of the unpaired electrons is observed.²⁵ The presence of six groups of fine structure lines (*A, A', B, B'* and *C, C'*) in the single-crystalline phenol **2** suggests the possibility of three orientations of the three RP with respect to the external magnetic field *H*; on the other hand, only one type of RP with $D = 15.8 \pm 0.3$ mT ($r_{\text{av}} = 5.4$ Å) is observed in the polycrystalline matrix of this sample (Fig. 9*c*).

The spectral pattern is completely the same in the system phenol **2**–3,5-di-*tert*-butyl-1,2-benzoquinone (3,5-Q). Thus, one can state that the transfer of two H atoms from two molecules of the phenol **2** to the quinone 3,5-Q accompanied by the formation of two phenoxyl radicals **3** existing as a pair also occurs in this case.

The photoirradiation of the same single-crystalline phenol matrix doped with 2,6-di-*tert*-butyl-1,4-benzoquinone (**7**, 2,6-Q) results in a spectral pattern where the fine structure components of the three types of RP contain HFS from only one methyl group (a quadruplet with a 1:3:3:1 intensity ratio, $a_{\text{H}}^{\text{Me}} = 0.53$ mT) (Fig. 10). This indicates unambiguously that the transfer of only one H atom occurs.

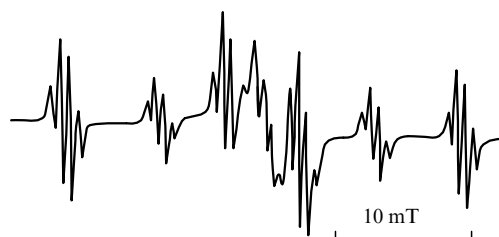
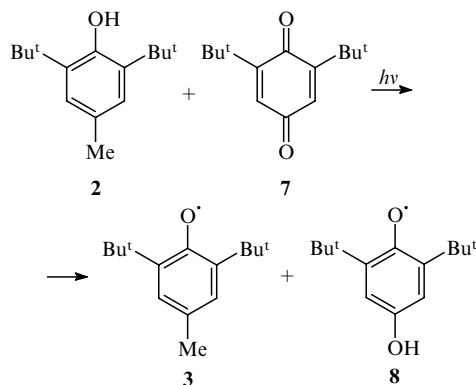


Figure 10. ESR spectrum of irradiated single crystal of the phenol **2** doped with 2,6-di-*tert*-butyl-1,4-benzoquinone.



It should be noted that the D parameter (13.4 mT) in this polycrystalline sample is noticeably smaller than that in the sample doped with 3,6-Q; this suggests that the relative arrangement of molecules of the corresponding quinones and the phenol **2** in these systems is different in principle.

The question arises as to the mechanism of phototransfer of two H atoms in the system phenol **2**–3,6-Q. It was shown that the RP accumulation in this system is proportional to the radiation intensity, *i.e.*, the transfer of two H atoms is not a two-quantum process. In addition, the long-wave threshold frequency of the RP formation in the single-crystalline phenol **2** doped with 3,6-Q is in the range from 290 to 330 nm, while in glassy frozen solutions where the transfer of one H atom occurs the long-wave threshold frequency of the RP formation is 560–630 nm; this indicates that a much smaller energy (by a factor of 1.7–2.2) is required for the phototransfer of one H atom. Let us note that the long-wave threshold frequency of the RP formation in the system single crystal of the phenol **2**–2,6-Q where phototransfer of one H atom occurs is noticeably higher: $\lambda = 390$ –445 nm. These data altogether support the one-quantum mechanism of phototransfer of two H atoms in the system single crystal of phenol **2**–3,6-Q (or 3,5-Q). Nevertheless, the principal proof of a one-quantum process is that the RP yields, or, in other words, the efficiencies of phototransfer of one and two H atoms in all three systems (phenol **2**–3,6-Q, phenol **2**–3,5-Q and phenol **2**–2,6-Q) are all almost the same. In the case of the two-quantum process, the efficiency of phototransfer of two H atoms would be much lower.

It was found in a study of the kinetics of RP decay in all the three systems that it is exponential and is the same in the systems phenol **2**–3,6-Q and phenol **2**–3,5-Q ($k = 10^4 \text{ s}^{-1}$, $E_a = 23.8 \text{ kJ mol}^{-1}$) but differs strongly from the kinetics of RP decay in the system phenol **2**–2,6-Q ($k = 10^8 \text{ s}^{-1}$, $E_a = 22.8 \text{ kJ mol}^{-1}$). Apparently, the decay of RP occurs due to the reversible dark transfer of H atoms.

Thus, it has been shown that the phototransfer of two H atoms requires much higher excitation energy and that this act occurs due to the absorption of one quantum of light.

IV. Other quinoid systems in hydrogen atom transfer reactions in single-crystalline phenols

The interest in the use of 2,6-di-*tert*-butyl-1,4-quinonediazide (2,6-QN) as a potential acceptor of an H atom from phenolic hydrogen donors is due to the fact that the photoirradiation of 2,6-QN results in its dissociation into a carbene **9** (2,6-SQN) and molecular nitrogen.^{26–28}

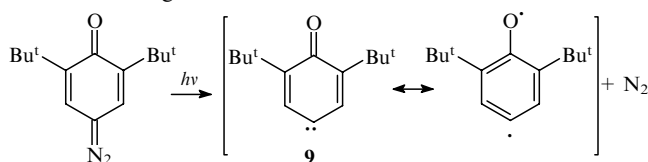


Figure 11 *a* shows a part of the ESR spectrum of the carbene **9** in single-crystalline phenol **2** doped with 2,6-QN upon irradiation

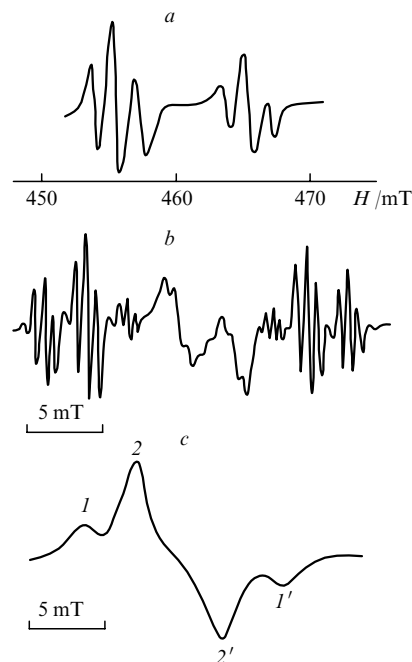
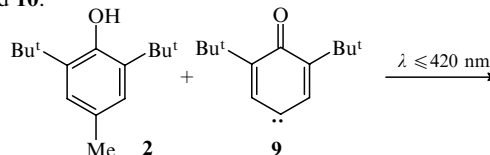


Figure 11. ESR spectra of the carbene **9** (*a*), the radical pair appearing upon irradiation of a single crystal of the phenol **2** doped with 2,6-QN (77 K) (*b*) and a polycrystalline sample obtained from a melt of single crystals of the phenol **2** and 2,6-QN (*c*); (*I*, *I'*) are perpendicular components of RP_1 ; (*2*, *2'*) are perpendicular components of RP_2 .

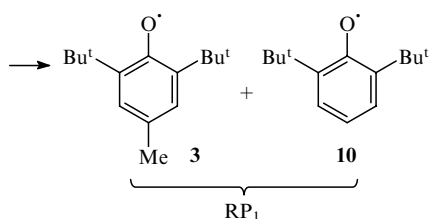
with light at a wavelength of $\lambda = 530 \pm 20 \text{ nm}$ at 77 K. In this case, two triplets (1:2:1) are observed which correspond to the interaction of unpaired electrons with benzene ring protons.⁸ This spectrum corresponds to the high-field transition $\Delta m_S = \pm 1$. Depending on the sample rotation angle, four sets of triplets, which reflect four orientations of the 2,6-QN molecules in a single crystal, are observed.²⁷ Depending on the conditions, it is possible to observe two types of radical pairs in the system phenol **2**–2,6-QN, *viz.*, RP_1 ($D = 13.2 \text{ mT}$, $r_{av} = 6.0 \text{ \AA}$) and RP_2 ($D = 3.9 \text{ mT}$, $r_{av} = 8.9 \text{ \AA}$) (Fig. 11 *b,c*). The fine structure parameters were determined from the spectra of polycrystalline samples.

The radical pairs RP_1 and RP_2 appear upon irradiation with light at $\lambda \leq 420 \text{ nm}$ and $\lambda \leq 350 \text{ nm}$, respectively.

In the short-term (30 s) irradiation at 77 K, only the spectrum of RP_2 and the carbene is observed. After a period of three days, the signal of the carbene disappears, but the intensity of the signal of RP_2 ($D = 3.9 \text{ mT}$) increases. The rate of RP_1 formation at the beginning of photolysis with light at $\lambda \geq 310 \text{ nm}$ at 77 K is practically zero and its increase is observed after some time; this is apparently due to the transfer of an H atom from the phenol **2** to the carbene **9** with the formation of two phenoxyl radicals, *viz.*, **3** and **10**.

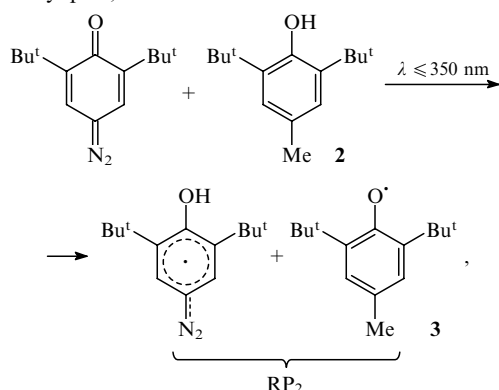


§ The magnitude of D for the system phenol **2**–2,6-Q is comparable with the magnetic field strength in the ESR spectrometer.



The characteristic time of RP_1 accumulation ($D = 13.2$ mT) is 30 min at 110 K. As the temperature is increased to 300 K, the RP_2 species disappear and only the RP_1 species remain.

These data suggest that there are two different processes of the H atom phototransfer. Specifically, these include the phototransfer of itself (the formation of RP_2) resulting in the formation of a 'primary' pair,



and the reaction of the carbene with the matrix (the formation of RP_1).

The eight groups of lines containing a multiplet (1 : 4 : 6 : 4 : 1) correspond to different orientations of RP_1 relative to the external magnetic field H in the single crystal. The relative intensity of the lines corresponding to each type of pairs depends on the photo-reaction efficiency, *i.e.* on the orientation of the 2,6-QN molecules relative to the direction of the incident light.

The photoselection effect in the photolysis of 2,6-QN has been studied in detail.²⁸ The line positions vary as the crystal is rotated relative to the external magnetic field, but the hyperfine coupling (HFC) remains unchanged and corresponds to the interaction of the unpaired electrons of the carbene **9** with four equivalent protons ($a_H = 0.6$ mT). The hyperfine structure (multiplet) originates from the interaction of the unpaired electrons of RP_1 with three protons of the methyl group in the radical **3** and the H atom at the *para* position of 2,6-di-*tert*-butylphenoxyl (radical **10**).

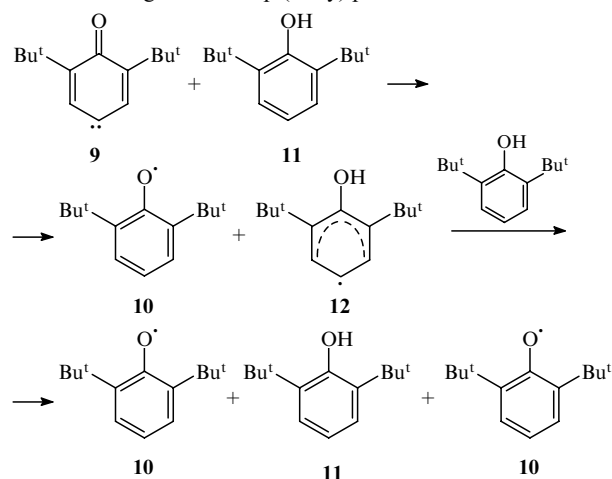
This conclusion was confirmed by a study of photoreactions that occur in the matrix of the phenol **2** with a deuterated OH group. In this case the multiplet is transformed into a quadruplet due to the HFC only with the hydrogen atoms of the methyl group.²⁸

The particular channels of the H atom phototransfer were determined from X-ray diffraction data²⁴ on the phenol **2** crystal structure and with consideration of the spin density distribution in the phenoxyl radicals formed.

The experimental results obtained allow one to assume a different mechanism of the RP_1 and RP_2 formation as well. The radical pair RP_2 (the 'primary' RP) eliminates N_2 to give the 'secondary' RP_1 ; the difference between the r_{av} of the unpaired electrons is due to the change in the spin density distribution in the radical partners of the phenoxyl radical **3** and the relative change in the distances between the radicals in the corresponding pairs.

The formation of symmetric RP was observed in the photolysis of single-crystalline 2,6-di-*tert*-butylphenol (**11**) doped with 2,6-QN.²⁹ Two types of RP were detected in the ESR spectra of this system due to different orientations of the RP in the crystal. Owing to the specific features of the 2,6-di-*tert*-butylphenol crystal lattice, the phototransfer of an H atom can involve two

possible different RP orientations relative to the external magnetic field. The small magnitude of the fine structure parameter D (4.3 mT) in this case suggests a large distance between the radical centres. X-Ray diffraction data and calculations of the D and E hyperfine structure parameters and data on the spin density distribution in phenoxyl radicals suggest that the RP are formed in this case through a two-step (relay) process.^{30, 31}



The carbene **9** formed in the photolysis abstracts the *para*-hydrogen atom from the nearest 2,6-di-*tert*-butylphenol molecule to give a phenoxyl radical (**10**) and a phenyl radical (**12**). In turn, the phenyl radical abstracts an H atom from the nearest 2,6-di-*tert*-butylphenol molecule. In this manner, an RP is formed from rather remote phenoxyl radicals. Experiments with OH-deuterated single crystals confirmed the formation of such RP with identical hyperfine structures, which proves the validity of the suggested relay scheme of the H atom transfer.

The ESR spectra of the radical pairs formed upon photolysis of single-crystalline phenol **2** doped with 2,6-di-*tert*-butyliminoquinone ($\lambda = 350$ nm) and those of the corresponding polycrystalline sample are given in Fig. 12. The spectrum of the polycrystal (Fig. 12*b*) implies the formation of only one type of RP ($D = 12.2 \pm 0.2$ mT). The observed combination of the fine structure lines suggests different orientation of radical pairs relative to the external magnetic field due to the crystal structure of the phenol **2**.²⁸

The nature of the radicals that form RP in a single crystal of the phenol **2** doped with 2,6-di-*tert*-butylquinoneimine was established using computer modelling based on the set of HFS

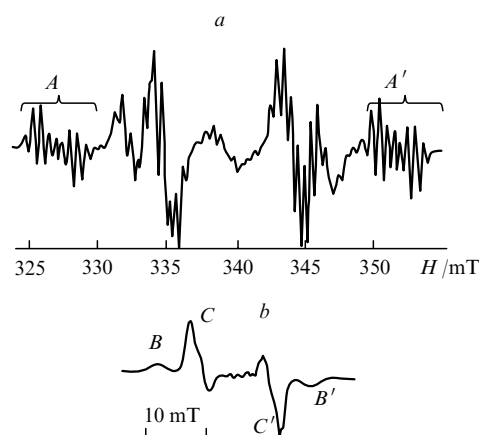
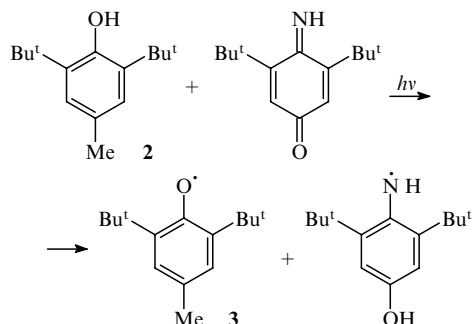


Figure 12. ESR spectra of the radical pairs formed upon photolysis of a single crystal of the phenol **2** doped with 2,6-di-*tert*-butyliminoquinone (*a*) and the corresponding polycrystalline sample (*b*).

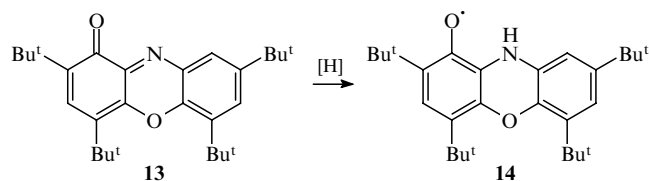
lines (Fig. 12 *a*).^{30,31} It was found that the HFS is due to the interaction between the unpaired electrons and four equivalent protons, which implies the phototransfer of the H atom and formation of the corresponding phenoxyl and aminyl radicals.



The multiplet is formed by three protons of the methyl group and the proton of the aminyl radical. The long-wave threshold frequency of the RP formation in this system is 430 ± 10 nm, which corresponds to the quinoneimine absorption band. The interpretation of the RP spectra was confirmed completely by experiments with single crystals of deuterated phenol 2.³⁰

The exponential character and an unexpectedly large kinetic isotope effect ($k_H/k_D = 10^3$) of the dark RP decay allow one to assume the tunnel character of the H atom reverse transfer.³²

The redox properties of 2,4,6,8-tetrakis-*tert*-butylphenoxazin-1-one (**13**) are rather similar to those of sterically hindered *o*-quinones. The phenoxazinyl radical **14** formed in the reduction of phenoxazinone **13** manifests high stability and very characteristic ESR spectrum with a hyperfine coupling constant $a_N = 0.9$ mT.³³



The high spin density on the nitrogen nucleus makes it possible to obtain additional information on the structure of paramagnetic complexes incorporating this ligand and on the structural changes in RP formed upon phototransfer of the hydrogen atom in single crystals of 3,5-QH₂ doped with the phenoxazinone **13**.³⁴

Figure 13 presents the optical absorption spectra of 3,5-QH₂ and the phenoxazinone **13**. The ESR spectra of single-crystalline 3,5-QH₂ doped with the phenoxazinone **13** contain only a combination of lines of the original pyrocatechol and phenoxazinone, *i.e.*, no additional bands are present.

On irradiation of single-crystalline phenol **2**, RP of various types appear in the absorption band of the phenoxazinone (Fig. 14 *a, b*). Analysis of the spectral pattern obtained suggests

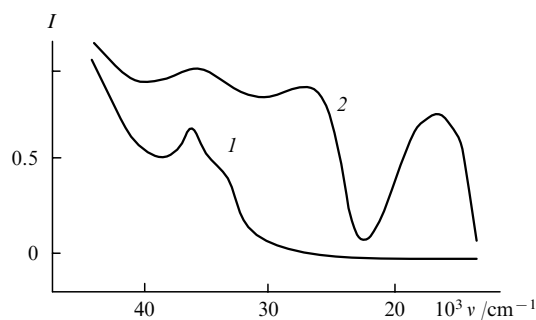


Figure 13. Optical absorption spectra of 3,5-QH₂ (*I*) and phenoxazinone **13** (*2*).

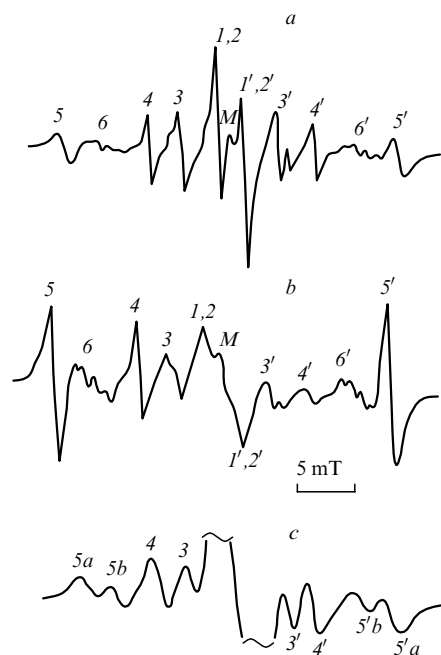
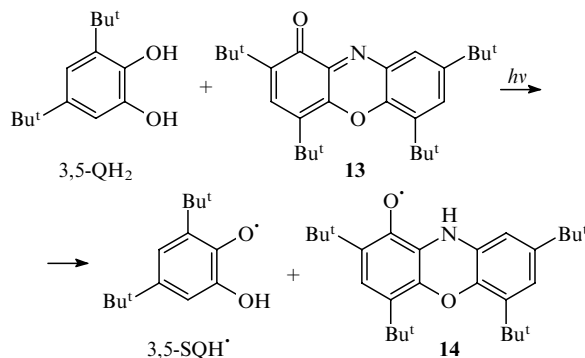


Figure 14. ESR spectra of the radical pairs formed upon photolysis of a single-crystalline 3,5-QH₂ doped with the phenoxazinone **13** (*a, b*) and polycrystalline sample (*c*). Microwave power /mW: (*a*) 1, (*b*) 50.

that there are six types of RP with different spectral characteristics (*D*) and hence with different distances between the radical centres. The radical pairs RP₁–RP₄ appear upon irradiation with light at $\lambda \leq 600 \pm 20$ nm, RP₅ at $\lambda \leq 520 \pm 20$ nm and RP₆ at $450 \leq \lambda \leq 550$ nm. The observed RP have the following dipole–dipole coupling constants: $D_1 = D_2 = 1.6$, $D_3 = 8.0$, $D_4 = 13.0$, $D_5 = 25.0$ and $D_6 = 0.7$ mT. The values of D_3 , D_4 and D_5 were determined from the spectra of polycrystalline samples (Fig. 14 *c*), and those of D_1 and D_2 , from studies of the dependence of these parameters on the angle relative to the external field.

Studies of the dark decay of RP₁–RP₆ at 77 K showed that the kinetic curves are satisfactorily linearised in the $I/I_0 - \log(t/t_0)$ coordinates,³⁴ which indicates that there is a set of different rates of reverse transfer of the H atom from the radical **14** to the 3,5-SQH[•] radical. This situation is typical of processes occurring in solids and is determined by the structural features of the RP formed in this system. In the case under consideration, the distribution of the RP decay rates can be determined by the small changes (~ 0.1 Å) in the position of the phenoxazinone **13** in the crystal lattice of 3,5-QH₂. Moreover, the presence of six types of RP and, hence, the difference in their kinetic behaviour can be due to different arrangement of hydrogen atoms at the oxygen atoms of the 3,5-SQH[•] radical (non-equivalent shielding of the oxygen atoms by the *tert*-butyl groups) and in the radical **14**.



Photolysis of the system 3,5-QH₂–phenoxazinone **13** in the region from 450 to 550 nm at 77 K gives rise to RP₆ with additional HFS caused by the nitrogen nucleus of the radical **14** (Fig. 14); the intensity of the signal is small under these conditions.

The existence of reversible temperature evolution of RP₃ and RP₆ in the temperature range from 20 to 77 K has also been shown.³⁴ Only the ESR spectrum of RP₃ (Fig. 15a) was observed during irradiation of a single crystal at 55 K. The spectrum of RP₆ was observed when the irradiation was terminated and the temperature was decreased to 20 K (Fig. 15b); the components of this spectrum contain HFS from the ¹⁴N nucleus ($a_N = 0.9$ mT). This temperature-reversible transformation is caused by spin density redistribution in the radical **14** as a result of H atom intramolecular transfer between the nitrogen and oxygen atoms (Fig. 16).

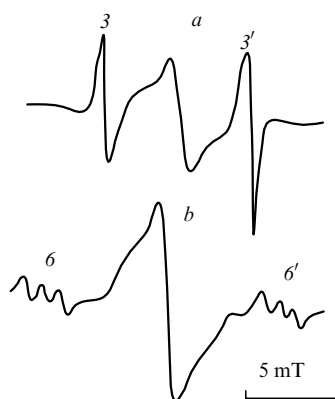
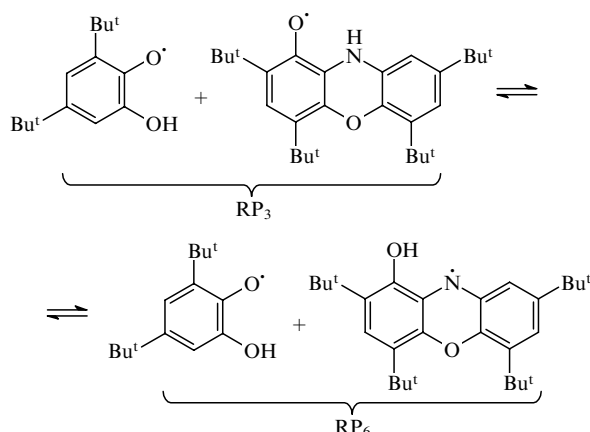


Figure 15. ESR spectra of the radical pairs RP₃ and RP₆ at 55 K (a) and 20 K (b).

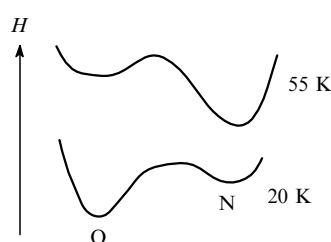


Figure 16. Potential energy curve for the migration of an H atom between the oxygen and nitrogen atoms in the radical **14**.

V. Anomalous relaxation in the ESR spectra of radical pairs

The ESR spectra of radical pairs sometimes show anomalies which can provide additional information on the interaction of the spin centres.

For example, anomalies have been reported³⁵ such as changes in the widths of the fine structure lines for the RP formed upon the hydrogen atom phototransfer in single-crystalline 3,5-QH₂ doped with 3,5-Q (system A) and in single-crystalline 3,3',5,5'-tetrakis-*tert*-butyl-6,6'-dihydroxydiphenylmethane doped with 2,6-Q (system B). Figure 17 shows the ESR spectra of the system A obtained upon irradiation with light at $\lambda > 720$ nm. It can be seen that at low power of the microwave field (0.02 mW), the fine structure components have identical intensities, while at high power (2 mW), the high-field component has a considerably higher intensity implying shorter relaxation time.

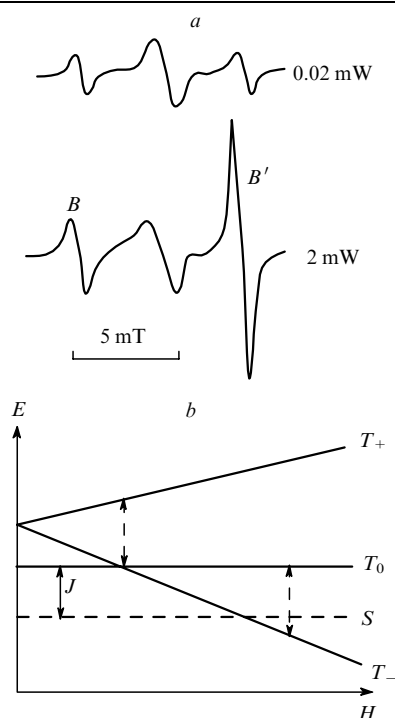


Figure 17. ESR spectra (a) and diagram of magnetic levels of the radical pair energy (b) for the system 3,5-QH₂–3,5-Q.

The times of spin–lattice (T_1) and spin–spin (T_2) relaxations for the low- and high-field components were determined from the saturation curves using the technique described in Ref. 36 and based on a model of non-interacting Bloch packets:

$$T_1 = 5.7 \times 10^{-4}, \quad T_2 = 6.6 \times 10^{-7} \text{ s (low-field component);}$$

$$T_1 = 1.2 \times 10^{-4}, \quad T_2 = 2.8 \times 10^{-7} \text{ s (high-field component).}$$

The system B was found to behave similarly.

In the systems studied, the ESR spectra at low power of the microwave field are centrosymmetric at any orientations of single crystals relative to the external magnetic field. Therefore, a mechanism of interaction of triplet levels was suggested³⁹ which dictated nonsymmetrical relaxation of the fine structure components but did not result in their asymmetry relative to the centre of the spectrum. Additional relaxation channels according to the scheme shown in Fig. 17b were considered:

$$T_0 \rightarrow S \rightarrow T_- \text{ (high-field component) – channel 1;}$$

$$T_+ \rightarrow S \rightarrow T_0 \text{ (low-field component) – channel 2.}$$

For these channels, the distances between the levels S – T_- and S – T_+ are different. In the cases $J \ll g\beta H$ or $J \gg g\beta H$ (J is the distance between the T_0 and S levels), this difference is insignificant, and the rates of relaxation through the channels 1 and 2 are

the same. However, if the magnitudes of J and $g\beta H$ are comparable (Fig. 17), differences in the relaxation $S \rightarrow T_-$ and $T_+ \rightarrow S$ can be expected and, hence, the rates of relaxation through the channels 1 and 2 should differ.

The rates of the spin–lattice relaxation can be represented as:

$$\frac{1}{T_1(B)} = \frac{1}{T_0(B)} + \frac{1}{\tau_1},$$

$$\frac{1}{T_1(B')} = \frac{1}{T_0(B')} + \frac{1}{\tau_2},$$

where $T_0(B)$ and $T_0(B')$ are the times of spin–lattice relaxations through the channels 1 and 2, respectively; τ_1 and τ_2 are the times of relaxation through the channels 1 and 2, respectively. The difference between $1/\tau_1$ and $1/\tau_2$ can explain the effect of abnormal asymmetrical relaxation provided that $1/T_0(B) \leq 1/\tau_1$ and $1/T_0(B') \leq 1/\tau_2$, i.e., where the relaxation channels 1 and 2 under consideration contribute significantly to the relaxation rate.

Thus, the asymmetrical relaxation effect can take place if the singlet–triplet coupling is comparable with the Zeeman coupling, but is still different from the latter. These results can be useful in studies of the effect of a magnetic field on the rates of chemical reactions involving radical pairs as transition states.³⁷

VI. Conclusion

The processes of solid-state hydrogen and electron transfer under photoirradiation considered above provide unique information on the nature of the elementary act in organic matrices which represent potential hydrogen donors. The advantage of studying solid-state systems, particularly single crystals, is that it provided the possibility of ESR in-depth studies of the structural features and kinetic behaviour of radicals which exist as radical pairs as a function of the features of the matrix and its crystal structure.

It was found that solid-state transfer of a hydrogen atom and an electron is possible not only under photoirradiation but also under elastic-wave impact on mechanical mixtures of the corresponding pyrocatechols and quinones or on the same mixtures in the presence of polymeric materials.^{38,39}

The results summarised in this work were obtained with direct participation of Professor Ya S Lebedev, whose top professionalism, authority, and sharp scientific intuition much favoured the development of chemical physics of solid-state processes in general and of the hydrogen atom and electron transfer in particular.

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^a — *Dokl. Chem. Technol., Dokl. Chem. (Engl. Transl.)*

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

^c — *Russ. J. Chem. Phys. (Engl. Transl.)*

^d — *Russ. J. Phys. Chem. (Engl. Transl.)*

Cyanoacetamides and their thio- and selenocarbonyl analogues as promising reagents for fine organic synthesis

V P Litvinov

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Abstract. Published data on the use of cyanoacetamides, cyanothio- and -selenoacetamides in fine organic synthesis and the prospects of application of these compounds in combinatorial synthesis are analysed and generalised. The bibliography includes 653 references.

I. Introduction

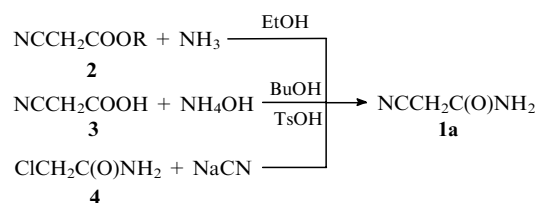
Cyanoacetic acid derivatives are important intermediates for preparation of various organic and, especially, heterocyclic compounds possessing diverse biological activities and many other practically useful properties. In this group of compounds, cyanoacetamides and their thio- and selenocarbonyl analogues are of particular interest as very promising reagents for cascade heterocyclisation, which will undoubtedly become one of the main approaches to the targeted synthesis of heterocycles in the near future, and for combinatorial chemistry experiencing nowadays a sharp rise (see, for example, Refs 1–26). This new methodology based on automatic, high-tech synthetic methods enables synthesis of a large number (up to several thousand) of novel organic compounds as subjects for biological screening.

The present review systematises for the first time published data on the reactivity of cyanoacetamides and their thio- and selenocarbonyl analogues (for selected aspects of the chemistry of these compounds, see reviews^{27–34}). The presence of several reactive centres in the molecules of these reagents provides ample opportunities to synthesise a great variety of novel compounds under relatively mild conditions and using rather simple laboratory equipment. Syntheses of many polyfunctional heterocyclic compounds, including those prepared by multicomponent condensations, are based on cyanoacetamides and their S- and Se-containing analogues. The reactions involving these reagents occur, as a rule, with high regioselectivity (often, stereoselectively) and their course can easily be controlled by changing reaction conditions and varying substituents in the molecules of initial compounds. All this makes cyanoacetamides and their S- and Se-analogues very useful reagents for combinatorial synthesis aimed at the design of novel biologically active compounds with a targeted mode of action.

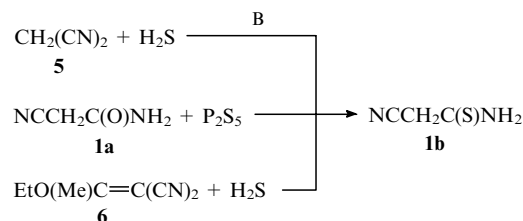
The present review aims to demonstrate the synthetic potential of cyanoacetamides in the synthesis of novel heterocyclic compounds. Primary attention is paid to the methods for preparation of the final products and much less to mechanistic aspects of the reactions surveyed. The structures of the feasible intermediates are considered only in the most synthetically important reactions.

II. Synthesis of cyanoacetamides, their thio- and selenocarbonyl analogues and aryl- and hetarylmethylidene derivatives

Cyanoacetamide (**1a**) can readily be obtained by several methods, viz., using the reactions of cyanoacetates (**2**) with ammonia,³⁵ of cyanoacetic acid (**3**) with NH_4OH ³⁶ and of chloroacetamide (**4**) with NaCN .³⁷



There are several methods for the preparation of cyanothioacetamide (**1b**), viz., treatment of an ethanolic solution of malononitrile with H_2S in the presence of triethylamine^{38–41} or triethanolamine,^{42,43} the reaction of cyanoacetamide (**1a**) with phosphorus pentasulfide in pyridine or ethyl acetate^{44–46} (the yield in the latter reaction does not exceed 36%), and the reaction of 1-ethoxyethylidenemalononitrile (**6**) with H_2S in ethanol.³⁹



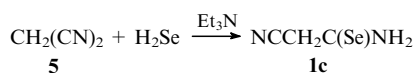
B = Et_3N , $(\text{HOCH}_2\text{CH}_2)_3\text{N}$.

Cyanoselenoacetamide (**1c**) was synthesised for the first time in 1985 by the reaction of malononitrile with H_2Se in diethyl ether in the presence of triethylamine at 5 °C under argon in 75% yield.⁴⁷

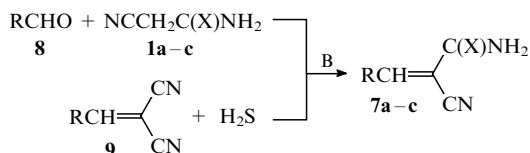
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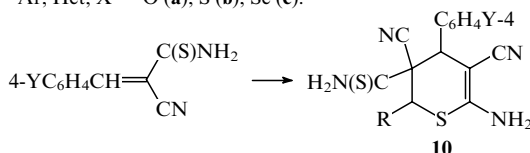
Uspekhi Khimii 68 (9) 817–844 (1999); translated by S V Chapyshev



Aryl- and hetarylmethylidene cyanoacetamides **7** are also promising reagents for the synthesis of functionally substituted heterocycles. These compounds are obtained by the reactions of aromatic or heteroaromatic aldehydes **8** with amides **1a–c** in the presence of organic bases, under argon in the case of cyanoselenoacetamide (**1c**).^{39, 44, 45, 48–56} Thioamides **7b** can also be prepared by the reactions of arylmethylidenemalononitriles **9** with H_2S .⁴⁸ In some cases, amides **7b** ($\text{R} = \text{Ph}$, 4- FC_6H_4 , 4- ClC_6H_4 , 4- BrC_6H_4 , 4- $\text{NO}_2\text{C}_6\text{H}_4$) readily undergo spontaneous [2+4]-cycloaddition to give 3,4-dihydro-2*H*-thiopyrans **10**.⁴⁸

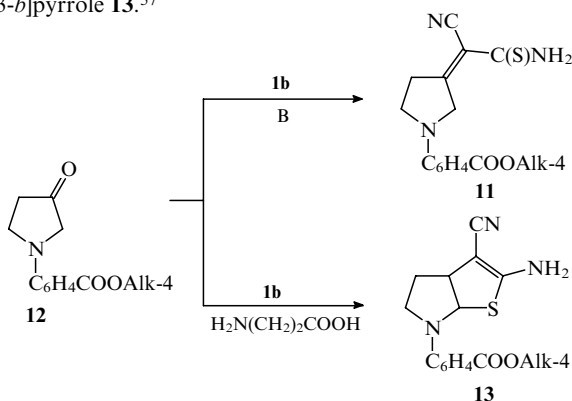


$\text{R} = \text{Ar}$, Het; $\text{X} = \text{O}$ (**a**), S (**b**), Se (**c**).

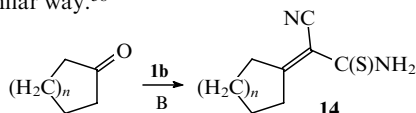


$\text{Y} = \text{H}$, F , Cl , Br , NO_2 .

1-[(4-Alkoxybenzylidene)pyrrolidin-3-ylidene]cyanothioacetamide (**11**) has been obtained by the reaction of pyrrolidone **12** with cyanothioacetamide (**1b**). The reaction of the same reactants in the presence of β -alanine with azeotropic distillation of water from the reaction mixture results in tetrahydrothieno[2,3-*b*]pyrrole **13**.⁵⁷

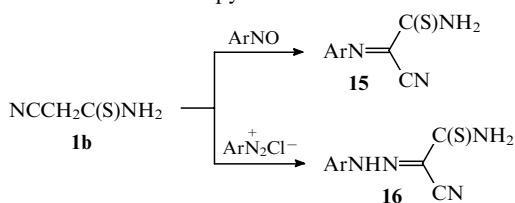


Cycloalkylidenecyanothioacetamides **14** were synthesised in a similar way.⁵⁸

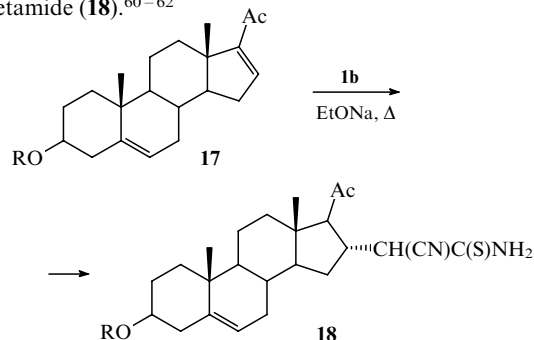


$n = 1, 2$.

Some other reactions involving the methylene group of cyanothioacetamide (**1b**) are known. Thus the condensation of this amide with nitroso-arenes affords the corresponding aryliminothioacetamides **15**⁵³ and the reaction with aryldiazonium salts affords compounds **16**.⁵⁹ The latter were used in the synthesis of thiazolidin-3-one and pyrimidine-2-thione derivatives.⁵⁹

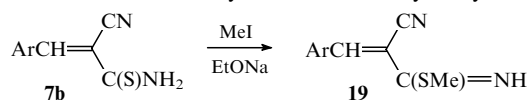


Cyanoacetamide **1b** adds unsaturated compounds. Thus its reaction with 3 β -acetoxy pregna-5,16-dien-20-one (**17**) in the presence of sodium ethoxide involves the double bond of the ring *D* yielding (3 β -hydroxy-20-oxopregn-5-en-16 α -yl)cyanothioacetamide (**18**).^{60–62}



$\text{R} = \text{H}$, Ac .

Arylmethylidenecyanothioacetamides **7b** are alkylated with methyl iodide to give the corresponding methyl thioimides **19**, which can be used in the synthesis of heterocyclic systems.^{63, 64}



III. The use of cyanoacetamides and their thio- and selenocarbonyl analogues in the synthesis of heterocyclic compounds

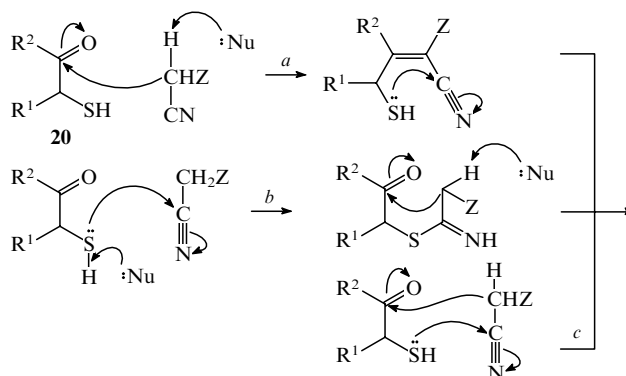
Owing to the presence of several highly reactive centres, first of all, the methylene and carbonyl or thio(seleno)carbonyl groups, cyanoacetamides have found wide use in the synthesis of diverse five- and six-membered heterocycles and their annulated analogues.

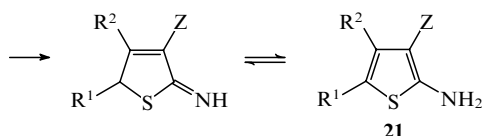
All reactions in this Section are systematised in accord with the size of the heterocycle, while each Subsection deals with a certain type of the reacting substrates.

1. Synthesis of five-membered heterocycles

a. Five-membered heterocycles with one heteroatom in the ring

Reactions of the α -mercapto carbonyl compounds **20** with nitriles that contain an active methylene group, including cyanoacetamide (**1a**), in the presence of bases at room temperature afford 2-aminothiophenes **21** in good yields (the Gewald reaction).^{65–74} The first stage of these reactions presumably involves the condensation of a nitrile with the carbonyl group of compounds **20** (the Knoevenagel-like reaction) and formation of 4-mercapto nitriles (path *a*) the structures of which are suitable for intramolecular cyclisation. However, two other possible mechanisms involving the initial nucleophilic attack on the cyano group by thiolate (path *b*) and the concerted cyclocondensation (path *c*) cannot also be excluded from consideration.





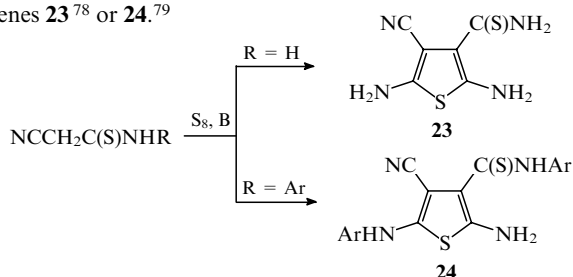
$R^1, R^2 = \text{H, Alk, Ar; } Z = \text{CN, CO}_2\text{R}^3, \text{CONH}_2, \text{COAr, 4-NO}_2\text{C}_6\text{H}_4\text{SO}_2\text{R}^4; R^3, R^4 = \text{H, Alk, Ar.}$

The use of dimeric 2,5-dihydroxy-1,4-dithianes ⁷³ instead of the α -mercapto carbonyl compounds **20** in the reactions with amides **1a,b** and other CH acids essentially simplifies the synthesis of substituted 2-aminothiophenes **21**.

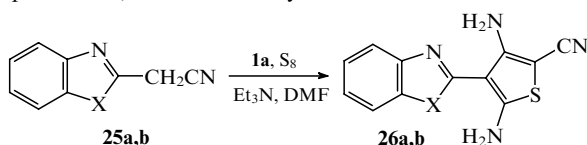
A yet more efficient version of the Gewald reaction consists in the use of a mixture of a carbonyl compound **22** (aldehyde, ketone or β -dicarbonyl compound) and sulfur in the presence of an organic base in ethanol or DMF instead of the α -mercapto carbonyl compounds **20**. This method results in higher yields of 2-aminothiophenes **21**.^{66, 68, 69, 73–77}



Treatment of cyanothioacetamide (**1b**) or its *N*-aryl derivatives with sulfur in the presence of bases affords 2,5-diaminothiophenes **23**⁷⁸ or **24**.⁷⁹

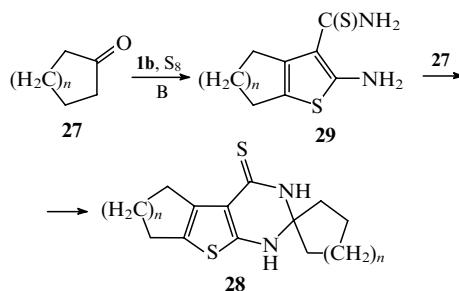


Heating of solutions of equimolar amounts of 2-cyanomethylbenzothiazole (**25a**) or 2-cyanomethyl-1*H*-benzimidazole (**25b**) and sulfur in dry DMF in the presence of a base affords 3,5-diamino-4-[benzothiazol(or imidazol)-2-yl]-2-cyanothiophenes **26a,b** in 61%–64% yields.⁸⁰



$X = \text{S (a), NH (b).}$

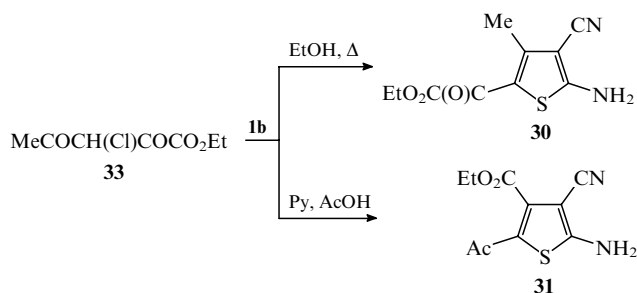
Treatment of a mixture of cyanothioacetamide (**1b**) and cyclic ketones **27** with sulfur in the presence of a base gives rise to thieno[2,3-*d*]pyrimidine-4-thiones **28**. Compounds **29** are assumed to be the intermediates of this reaction.⁷⁸



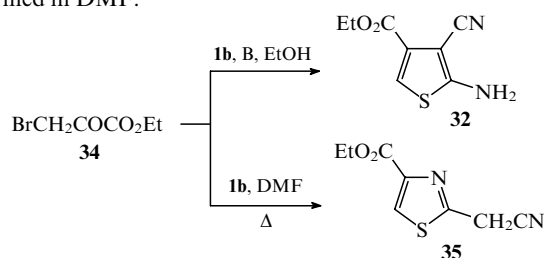
$n = 2, 3.$

A series of thiophene derivatives **30–32** has been obtained by the reactions of cyanothioacetamide (**1b**) with ethyl 3-chloro-2,4-dioxopentanoate (**33**)⁸¹ or ethyl bromopyruvate (**34**).⁸² In ethanol in the presence of a base, the reaction of the amide **1b** with compound **33** involves its acetyl group, whereas the reaction of the same compounds in a mixture of pyridine and acetic acid involves

the α -carbonyl group of compound **33** and results in ethyl 5-acetyl-2-amino-3-cyanothiophene-4-carboxylate (**31**).⁸¹

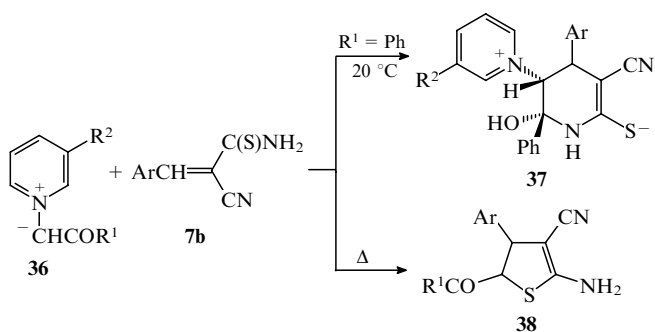


The course of the reaction of the amide **1b** with ethyl bromopyruvate (**34**) also depends on the solvent. Thus the reaction of these compounds in a mixture of pyridine and acetic acid results in ethyl 2-amino-3-cyanothiophene-4-carboxylate (**32**), whereas ethyl 2-cyanomethylthiazole-4-carboxylate (**35**) is formed in DMF.⁸¹



The use of pyridinium ylides in reactions with nitriles containing the activated methylene group has led to the creation, in recent years, of methods of regio- and stereoselective synthesis of partially hydrogenated five-membered heterocycles.^{83–91}

The course of the reactions of pyridinium ylides **36** (prepared *in situ* by treatment of the corresponding pyridinium salts with an equimolar amount of triethylamine) with aryl- or hetarylmethyldene cyanothioacetamides **7b** depends on the temperature. Thus the condensations of these compounds at 20 °C follow the $\text{Ad}_\text{N}\text{-E}_{1,6}$ mechanism to yield stereoselectively substituted 3,4-*trans*-1,2,3,4-tetrahydropyridines **37**, whereas the reactions of these compounds under reflux follow the $\text{Ad}_\text{N}\text{-E}_{1,5}$ mechanism and give rise to 2,3-dihydrothiophenes **38**.^{83–89}

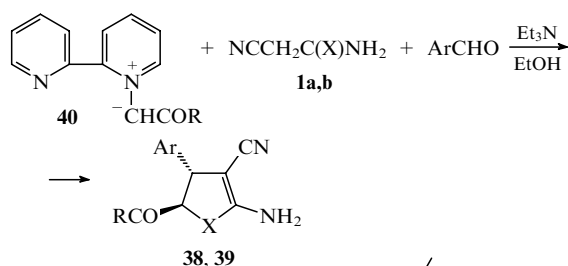


$\text{Ar} = 4\text{-FC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, \text{Naph-1-yl};$

$R^1 = \text{Ph, 1-adamantyl}; R^2 = \text{H, Br.}$

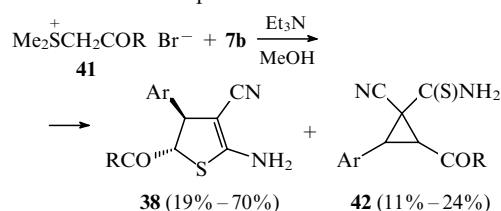
Compounds **38** were also obtained by a three-component condensation of pyridinium ylide **36** ($R^1 = 1\text{-adamantyl}$) with aromatic or heteroaromatic aldehydes and cyanothioacetamide (**1b**).^{83, 84, 87, 88}

A novel stereoselective method for the preparation of *trans*-dihydrothiophenes **38** and *trans*-dihydrofurans **39** has been developed based on the three-component condensation of ylides **40** with aldehydes and amides **1a,b** in ethanol in the presence of triethylamine.⁸⁹



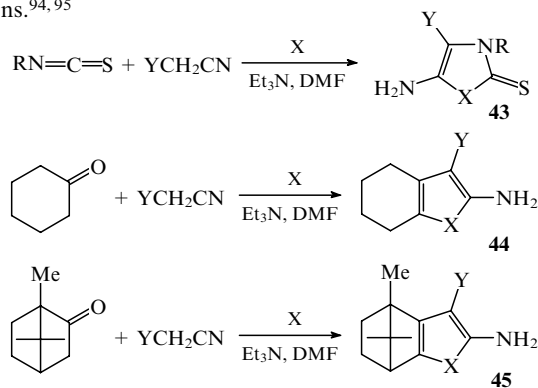
R = MeO, Ph; Ar = 2-MeOC₆H₄, 4-FC₆H₄, , ; X = S (**38**), O (**39**).

Functionally substituted *trans*-dihydrothiophenes **38** have also been obtained by the reactions of arylmethylidenecyanothioacetamides **7b** with stabilised sulfonium ylides generated *in situ* from bromides **41**. Cyclopropanethiocarboxamides **42** were found to be the minor products of these reactions.^{92,93}



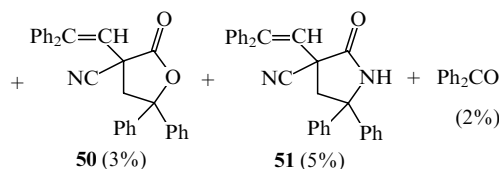
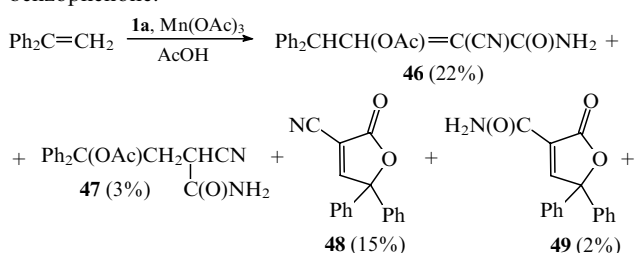
R = Ph, ; Ar = 2-MeC₆H₄, 2-NO₂C₆H₄, 4-MeOC₆H₄, , .

First publications on the use of the Gewald reaction in the synthesis of sulfur-, selenium- and tellurium-containing five-membered heterocycles have appeared recently.^{65–74} Compounds **43–45** were prepared in 60%–85% yields by treating mixtures of ethyl cyanoacetate (cyanoacetamide, malononitrile) and isothiocyanates, cyclohexanone or camphor with sulfur, selenium or tellurium. It has been found that ultrasound or microwave irradiation considerably accelerate these reactions.^{94,95}

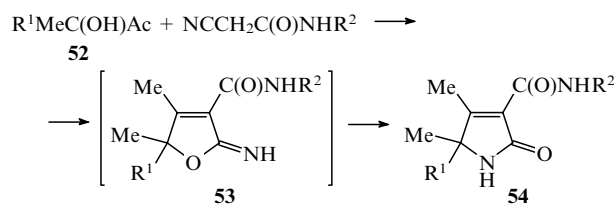


R = Ph, PhCO, CH₂=CHCH₂, Bu^tCO; X = S, Se, Te; Y = CO₂Et, CONH₂, CN.

The addition of cyanoacetamide (**1a**) to 1,1-diphenylethylene in acetic acid in the presence of Mn(OAc)₃ results in a complex mixture of amides **46** and **47**, lactones **48–50**, lactam **51** and benzophenone.⁹⁶

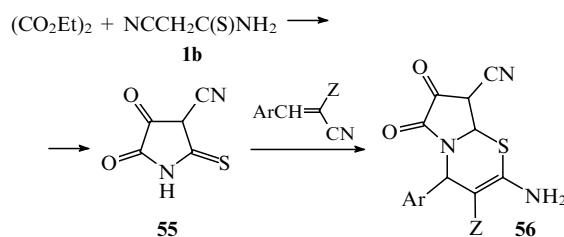


A new approach to the synthesis of substituted pyrrolinone derivatives has been developed using the Knoevenagel condensation of α -hydroxy ketones **52** with substituted cyanoacetamides aimed at comparing biological activities of oxygen- and nitrogen-containing five-membered heterocycles. These reactions occur *via* iminolactams **53**, which are readily converted into the corresponding pyrrolinones **54** under the reaction conditions.⁹⁷



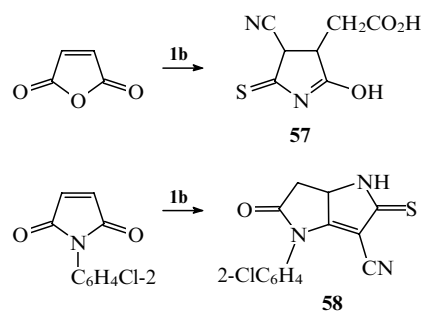
R¹ = Alk, CH₂=CHCH₂, Bn; R² = H, Alk, Bn, Het.

The condensation of cyanothioacetamide (**1b**) with diethyl oxalate results in 4-cyano-5-thioxopyrrolidine-2,3-dione (**55**). The latter reacts with arylmethylidene malonates yielding pyrrolidino[1,2-*b*]-1,3-thiazine-5,6-diones **56**.^{42,43,98}

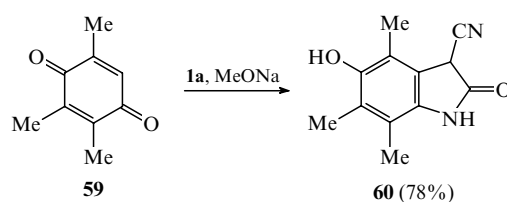


Z = CN, C(S)NH₂, CO₂Et.

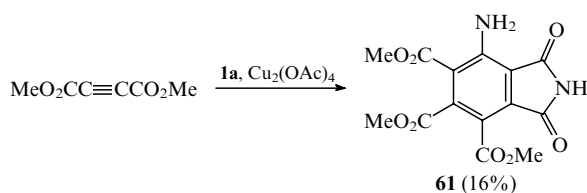
The reactions of amide **1b** with maleic anhydride or *N*-(2-chlorophenyl)maleimide afford pyrrolidine (**57**) or pyrrolo[3,2-*b*]pyrrole (**58**) derivatives.⁹⁹



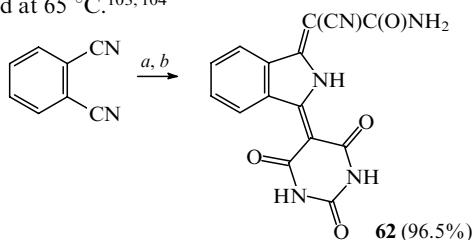
2,3,6-Trimethylbenzoquinone (**59**) reacts with cyanoacetamide (**1a**) in the presence of sodium methoxide yielding 5-hydroxy-4,6,7-trimethyl-3-cyanoindolin-2-one (**60**).^{100,101}



Polysubstituted phthalimide **61** has been obtained by condensation of methyl acetylenedicarboxylate with the amide **1a** in the presence of Cu₂(OAc)₄ in dioxane.¹⁰²

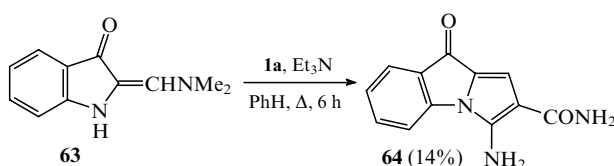


Cyanoacetamide (**1a**) has been used as the starting material in the synthesis of dye **62**. The cyclocondensation of phthalonitrile with the amide **1a** was carried out in methanol in the presence of NaOMe and then the reaction mixture was treated with barbituric acid at 65 °C.^{103, 104}



(a) **1a**, MeONa, MeOH; (b) $\text{H}_2\text{C}(\text{OC-NH})_2$, 65 °C.

The reaction of enamino ketone of the indoline series **63** with the amide **1a** (refluxing in benzene in the presence of triethylamine) gives rise to 3-amino-2-carbamoyl-9-oxopyrrolo[1,2-*a*]indole **64**.¹⁰⁵

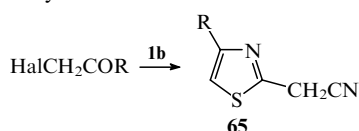


A series of pyrrolothiolates has been synthesised by reaction of the amide **1a** with sulfur in the presence of catalytic amount of diethylamine.¹⁰⁶

b. Five-membered heterocycles with two heteroatoms in the ring

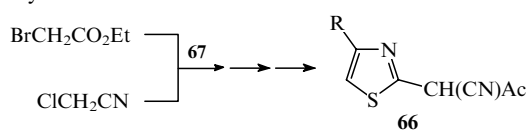
Cyanoacetamides and their chalcogen analogues have been successfully used in syntheses of five-membered heterocycles with two heteroatoms in the ring: thiazoles, isothiazoles, thiazolinones, oxazoles, pyrazoles, imidazoles, dithioles, *etc.*

Thus the condensation of cyanothioacetamide (**1b**) with α -halogeno carbonyl compounds involving their methylene group has been employed in the synthesis of 2-thiazolylacetonitriles **65** as well as thiazolylthiones and other five-membered heterocycles.^{34, 59, 80, 81, 107}



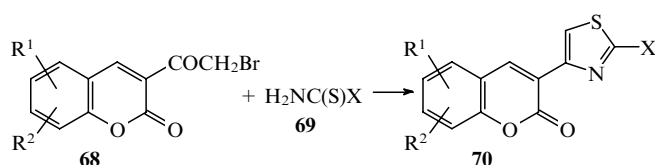
R = Alk, Ar, CO_2Et .

Thiazole derivatives **66** were synthesised by the reaction of 2-acetyl-2-cyanothioacetamide **67** (prepared by the acetylation of the amide **1b**) with ethyl bromoacetate or 1-chloroacetonitrile in good yields.¹⁰⁸



R = OH, NH_2 .

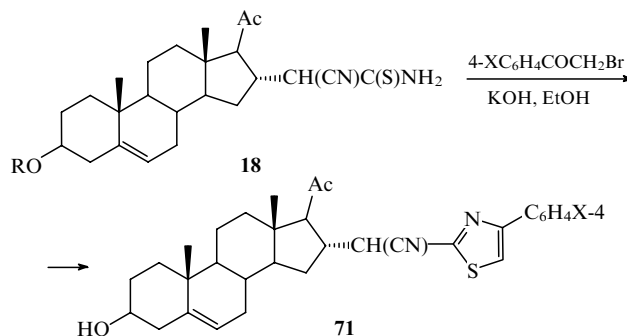
3-(Bromoacetyl)coumarins **68** react with activated thioamides **69** on heating in ethanol to give substituted thiazoles **70** in yields of up to 93%.¹⁰⁹



$\text{R}^1 = \text{R}^2 = \text{H}$; $\text{R}^1 - \text{R}^2 =$; $\text{R}^1 = 7\text{-NEt}_2$, $\text{R}^2 = \text{H}$;

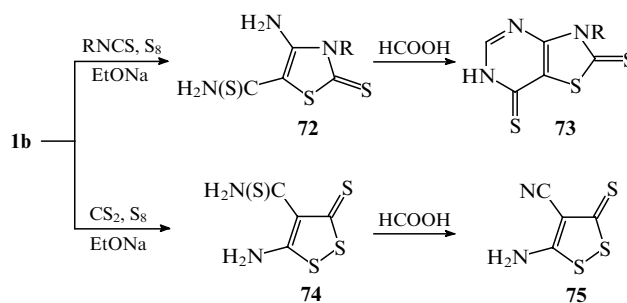
X = CH_2CN , NH_2 , NHNH_2 , $\text{C}(\text{S})\text{NMe}_2$.

The reaction of the pregnenolone derivative **18** containing the cyanothioacetamide fragment with phenacyl bromide was employed for the synthesis of thiazolyl-substituted steroids **71** (yields 85%–97%).^{60, 62, 110}



R = Alk; X = H, Cl, Br.

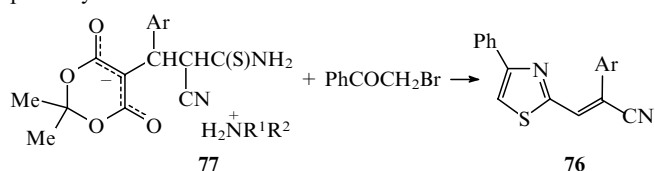
Cyanothioacetamide (**1b**) reacts with sulfur and isothiocyanates in the presence of bases yielding thiazoline-2-thione derivatives **72**. The latter are cyclised on treatment with formic acid to give thiazolo[4,5-*d*]pyrimidine-2,7-dithiones **73**.⁷⁸ Similar reaction of the amide **1b** with sulfur and hydrogen sulfide affords 1,2-dithiol-3-thione derivative **74**, which is converted into 5-amino-4-cyano-1,2-dithiol-3-thione (**75**) on treatment with formic acid rather than undergoes cyclisation.⁷⁸

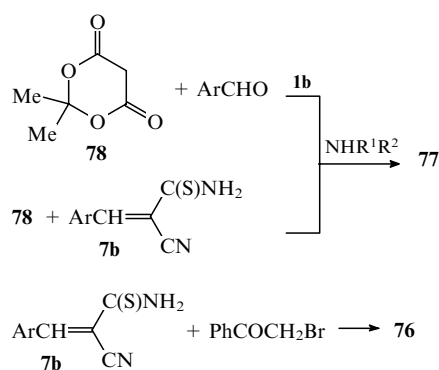


R = Me, Ph, $\text{CH}_2 = \text{CHCH}_2$.

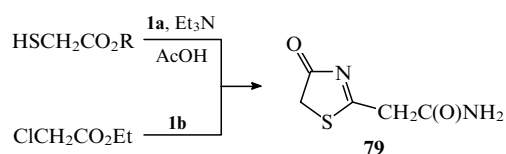
Reactions of the amide **1a** and its derivatives with isothiocyanates have also been employed in the synthesis of other substituted thiazoles.^{111, 112}

Thiazolyl-substituted acrylonitriles **76** can be prepared in two ways. The first one is the reaction of phenacyl bromide with salts **77**. The latter are obtained by the reaction of Meldrum's acid (**78**) with aromatic aldehydes and cyanothioacetamide (**1b**) or with arylmethylidenecyanothioacetamides **7b** (ethanol, 20–25 °C, equimolar amount of the secondary amine). The second method of preparation of acrylonitriles **76** is based on the reaction of phenacyl bromide with amides **7b**.^{113–117}



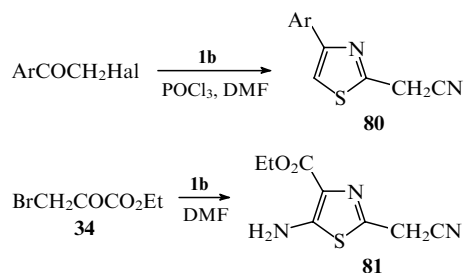


Thiazolinone **79** was obtained by the reaction of cyanoacetamide (**1a**) with mercaptoacetic acid or its ester.^{118,119} This compound can also be synthesised from cyanothioacetamide (**1b**) and ethyl chloroacetate.¹²⁰

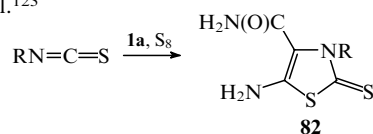


R = H, Alk.

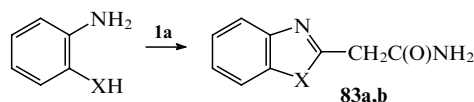
Thiazole derivatives **80** and **81** also have been synthesised using the amide (**1b**).^{81,82,109}



4-Thiazoline-2-thione derivatives **82** were obtained by the reaction of cyanoacetamide (**1a**) with isothiocyanates in the presence of elemental sulfur.¹²¹ The reaction of the same amide with 2-mercaptoaniline gives 2-carbamoylmethylbenzothiazole (**83a**).¹²² The latter is employed in light- and waterproof azo-dyes used in polycaprolactam manufacture. Benzoxazole **83b** is obtained in a similar way from the amide **1a** and 2-aminophenol.¹²³



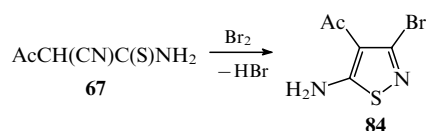
R = Ar, Alk.



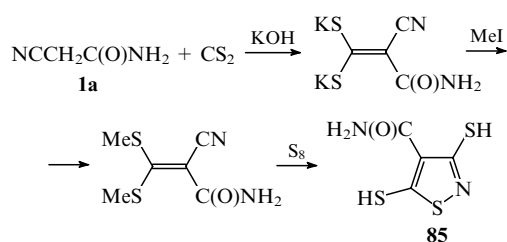
X = S (a), O (b).

Reactions of the amide **1a** with phenacyl benzoates in boiling xylene in the presence of BF_3 afford 2-aryl-4-phenyloxazoles in 75%–90% yields.¹²⁴

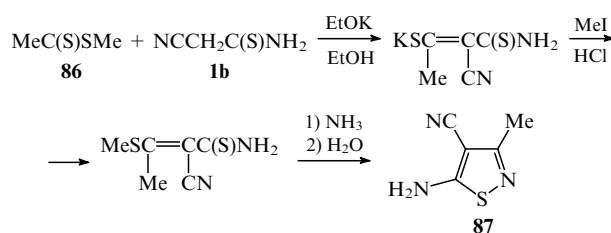
Isothiazole **84** has been obtained in good yield by bromination of acetyl(cyano)thioacetamide **67**.¹⁰⁸



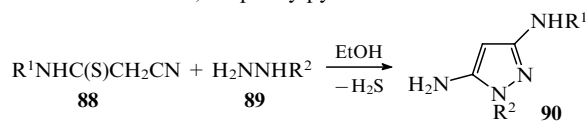
The condensation of the amide **1a** with CS_2 in the presence of KOH results in 3,5-dimercaptoisothiazole-4-carboxamide **85**.¹²⁵



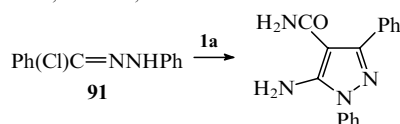
5-Amino-3-methyl-4-cyanoisothiazole (**87**) has been synthesised by the reaction of the amide **1b** with methyl dithioacetate (**86**).¹²⁶



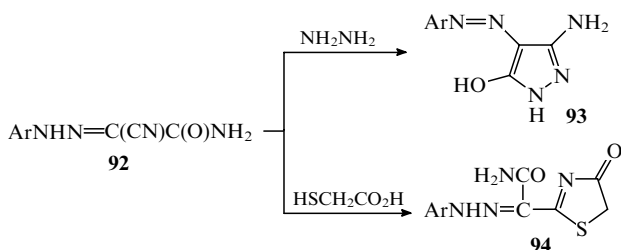
N-Substituted cyanothioacetamides **88** were prepared from ethyl cyanoacetates and aryl isothiocyanates,¹²⁷ their reactions with hydrazines **89** yielded 5-amino-3-arylaminopyrazoles **90**.¹²⁸ The analogous reaction of the amide **1a** with hydrazonoyl chloride **91** afforded 5-amino-1,3-diphenylpyrazole-4-carboxamide.¹²⁹



$\text{R}^1 = \text{Ar}; \text{R}^2 = \text{H}, \text{Ar}.$

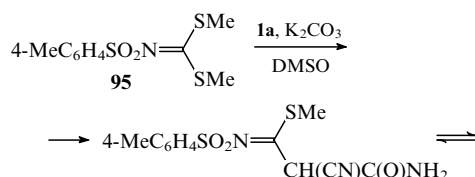


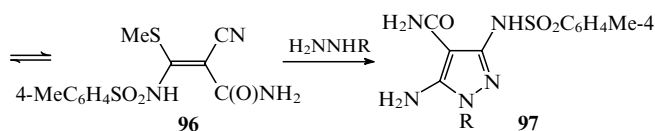
Cyanoacetamide derivatives **92** on heating with hydrazine give pyrazoles **93**, while their reactions with mercaptoacetic acid result in thiazolinones **94**.¹³⁰



Ar = Ph, 4-MeC₆H₄, 4-ClC₆H₄.

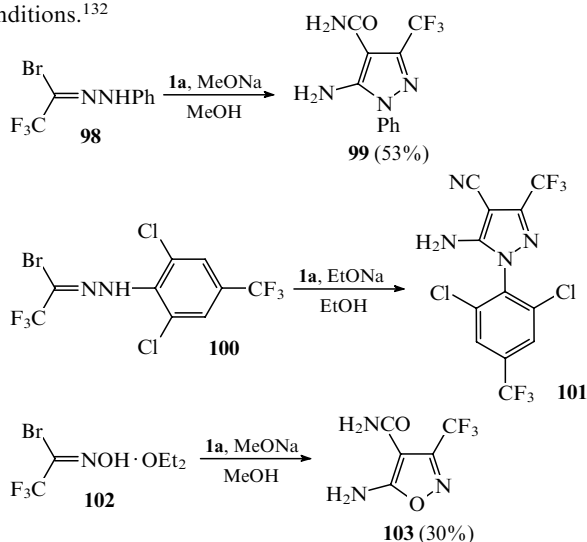
The reaction of N-[bis(methylthio)methylidene]toluene-4-sulfonamide (**95**) with the amide **1a** affords compound **96** in 94% yield. The latter gives pyrazoles **97** in yields of up to 98% on treatment with hydrazines.¹³¹



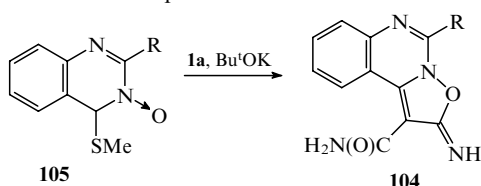


$\text{R} = \text{H}, \text{Ph}, 4\text{-ClC}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4$.

Phenylhydrazone **98** reacts with the amide **1a** in methanol in the presence of sodium methoxide yielding pyrazole **99**.¹³² An analogous reaction of hydrazone **100** with a bulky substituent affords pyrazole **101** in only 6% yield.¹³³ Isooxazole **103** is obtained from hydroximoyl bromide etherate under similar conditions.¹³²

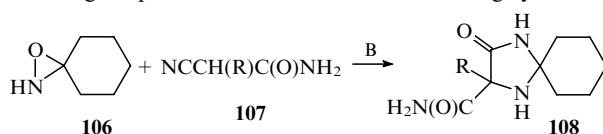


High yields of isoxazoloquinazolines **104** were obtained upon cyclocondensation of 4-methylthioquinazoline 3-oxides **105** with the amide **1a** in the presence of Bu^tOK .¹³⁴



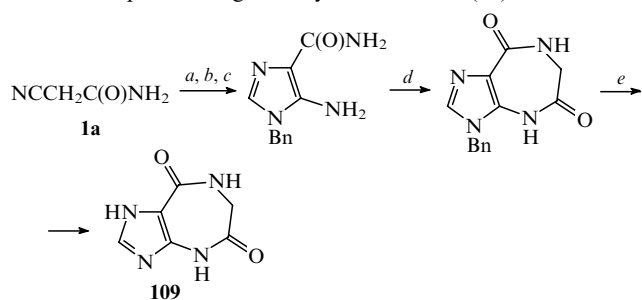
$\text{R} = \text{Ph}, 4\text{-MeC}_6\text{H}_4$.

Reactions of 1-oxa-2-azaspiro[2.5]octane (**106**) with cyanoamides **107** give spiroimidazoline derivatives **108** in high yields.¹³⁵



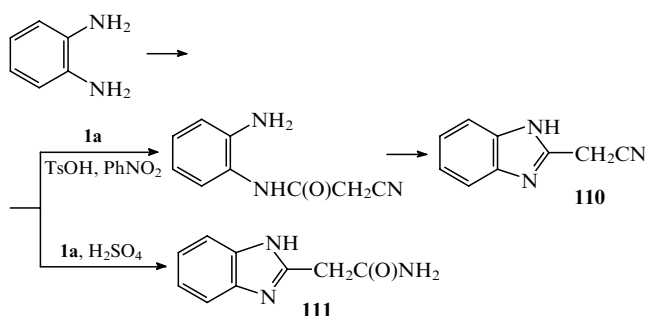
$\text{R} = \text{cyclo-C}_5\text{H}_9, \text{cyclo-C}_6\text{H}_{11}, \text{Me}(\text{CH}_2)_7, \text{PhCH}_2$.

A four-step synthesis of a xanthine analogue, viz., 5,6,7,8-tetrahydro-4*H*-imidazo[4,5-*c*]-1,4-diazepine-5,8-dione (**109**), has been developed starting from cyanoacetamide (**1a**).¹³⁶

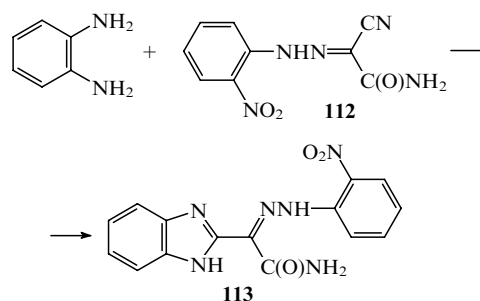


(a) HNO_2 ; (b) $[\text{H}]$; (c) $\text{CH}_2(\text{OEt})_2, \text{BnNH}_2$; (d) KOH ; (e) H_2/Pd .

2-Cyanomethylbenzimidazole (**110**) has been obtained by condensation of cyanoacetamide (**1a**) with *o*-phenylenediamine in good yield.¹³⁷ This reaction, carried out in the presence of concentrated sulfuric acid, was accompanied by hydrolysis of the cyano group resulting in 2-carbamoylmethylbenzimidazole **111**.^{138, 139}



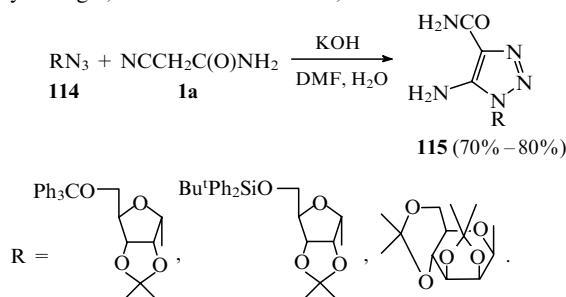
The reaction of *o*-phenylenediamine with substituted cyanoacetamide **112** under similar conditions gives rise to benzimidazole derivative **113**.¹⁴⁰



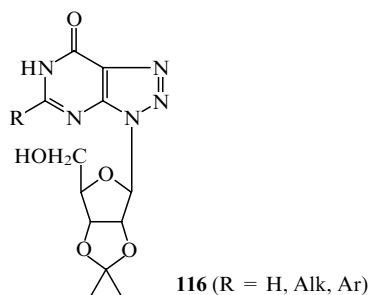
c. Five-membered heterocycles with three heteroatoms in the ring

The amide (**1a**) and thioamide (**1b**) are widely used in the synthesis of five-membered heterocycles with three heteroatoms in the ring, in particular, of 1,2,3-triazoles possessing a wide range of biological activities. Synthesis of substituted 1,2,3-triazoles by the reactions of cyanoacetamide (**1a**) with alkyl-, aryl- and hetarylazides can be mentioned as an example.^{141–145} It is noteworthy that the preparation of 1,2,3-triazole derivatives from compounds with an activated methylene group and phenyl azide was first reported by Dimroth in 1902.^{146, 147}

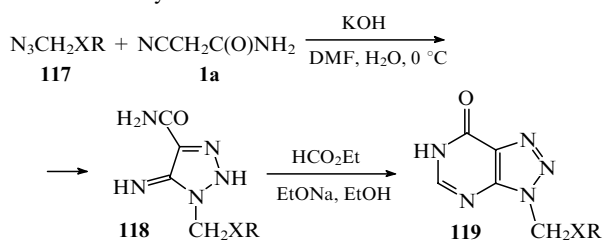
1-Azidoglycosides **114** react with the amide **1a** in aqueous DMF in the presence of KOH to give triazolonucleosides **115** in high yields. The reactions proceed with inversion of configuration yielding 1,2-*trans* adducts from 1,2-*cis* azides.¹⁴⁴



The synthesis of 2-substituted 9- β -D-ribofuranosyl-8-azahypoxanthines **116** from β -D-ribofuranosyl azide, sodium salt of the amide **1a** and carboxylic acid esters has also been described.¹⁴⁵

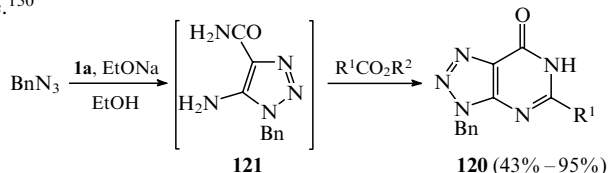


Synthesis of nucleosides with 1,2,3-triazoles and 8-azapurines as aglycones by reactions of azides **117** with the amide **1a** has been undertaken aimed at access to novel potential pharmaceutical preparations. In the presence of KOH in aqueous DMF at 0 °C, these reactions gave rise to 1,2,3-triazole derivatives **118**. The latter were readily converted into 8-azapurine derivatives **119** on treatment with ethyl formate.^{148, 149}



R = PhCH₂O(CH₂)₂, (PhCH₂OCH₂)₂CH; X = O, S.

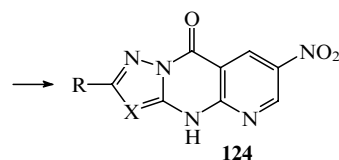
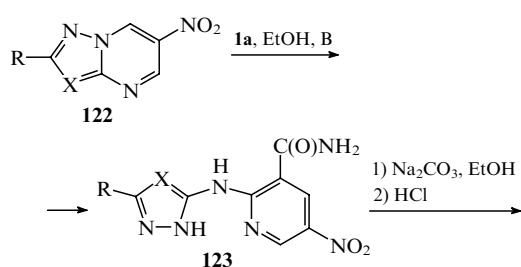
The reaction of benzyl azide with the amide **1a** in EtOH in the presence of NaOEt followed by treatment of the reaction mixture with carboxylic acid esters affords 3,5-disubstituted 7-hydroxy-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines **120**. 5-Amino-1-benzyl-1,2,3-triazole-5-carboxamide (**121**) has been postulated as an intermediate.¹⁵⁰



R¹ = H, Me, Et, Pr, CH₂OCH₂Me, CH(OCH₂Me)₂, (CH₂)₂CO₂H, CO₂Et, Ph, PhCO, CH₂NHCOPh; R² = Me, Et.

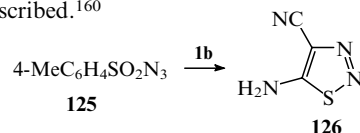
Many other 1,2,3-triazole derivatives possessing coccidiostatic, anticonvulsive, antiproliferative and other types of biological activities have been synthesised using the reactions of aromatic and aliphatic azides with the amide **1a**.^{151–157}

The reaction of 6-nitroazolo[1,5-*a*]pyrimidines **122** with the amide **1a** in refluxing ethanol involves transformation of the pyrimidine ring into the pyridine ring and affords substituted 2-azolyl-2-pyridylamines **123**. The latter are converted into 7-nitro-9-oxo-4,9-dihydroazolo[1,5-*a*]pyrido[2,3-*d*]pyrimidines **124** on subsequent treatment with sodium carbonate in ethanol and acidification with HCl.^{158, 159}

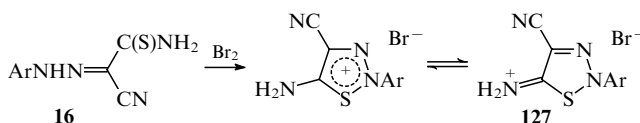


R = H, Me, SMe, CF₃, Cl, NH₂, NMe₂, Ph; X = N, CH, CNO₂.

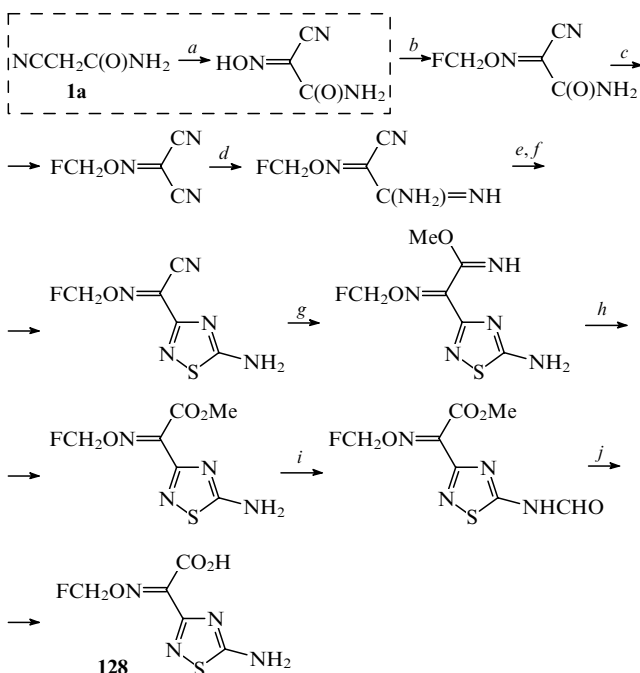
Synthesis of 5-amino-4-cyano-1,2,3-thiadiazole (**126**) by the reaction of tosyl azide **125** with cyanothioacetamide (**1b**) has been described.¹⁶⁰



Later,¹⁶¹ 1,2,3-thiadiazolium bromides **127** were obtained by bromination of arylhydrazonocyanothioacetamides **16**.



A group of Japanese scientists¹⁶² have developed a nine-step method of synthesis of a useful chemical modifier of cephalosporin antibiotics, viz., (Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(fluoromethoxy)imino]acetic acid (**128**), from cyanoacetamide (**1a**) according to the scheme shown below. The yield of the target product with respect to the initial cyanoacetamide was 17.6%.



(a) HNO₂ (81%); (b) BrCH₂F, Et₃N (75%); (c) POCl₃ (72%); (d) NH₄OH, NH₄Cl (84%); (e) Br₂; (f) KSCN, Et₃N (88%); (g) MeONa, MeOH (92%); (h) H₂SO₄, H₂O (84%); (i) HCO₂H, Ac₂O (84%); (j) NaOH, H₂O (84%).

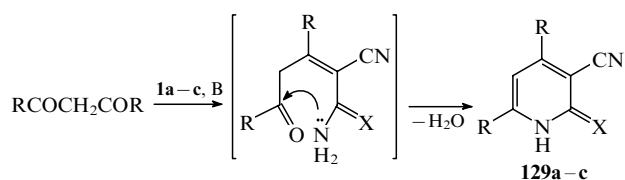
2. Synthesis of six-membered carbo- and heterocycles

Of six-membered heterocycles synthesised on the basis of cyanoacetamides, pyridin-2-one (-thione and -selenone) derivatives are of major interest (see, for example, reviews^{27, 28, 30–34, 74} and papers^{163–175}). Many of these compounds have been found to be highly effective cardiotonics^{176–251} (e.g., 'amrinone' and 'milrinone'^{242–251}), non-nucleoside inhibitors of HIV reverse transcriptase (potential pharmaceuticals for treatment of

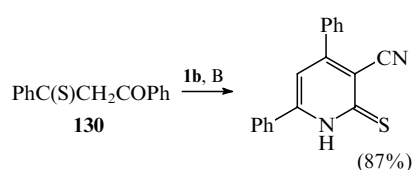
AIDS^{252–265}), tranquilisers,^{266–278} compounds with antiinflammatory, hypoglycemic, anticonvulsant, antiulcerous, fungicidal, bactericidal, pesticidal and many other types of biological activity.^{272–308} Pyridin-2-ones are also very useful starting materials in the design of novel calcium antagonists,^{309,310} CH antioxidants,^{311–315} folic acid analogues,³¹⁶ vitamin B₆,³¹⁷ and other biologically active compounds,^{311, 316–324} as well as models of redox coenzymes NAD and NADP.²⁸⁵ As an example, the use of substituted spiro[cyclopentane-piperidone] in the synthesis of ‘buspirone’, which is an antidepressant and an analgesic, and also prevents an affection to narcotics,²⁶⁹ can be mentioned. The only known natural alkaloid with the cyano group in a molecule is a representative of the class of pyridones (‘ricyan’, 3-cyano-4-methoxy-1-methylpyridin-2-one).³²⁵ Pyridin-2-one derivatives are employed as stabilisers of polymers and lacquers,³²⁶ as pigments and diazo-components in the synthesis of dyes,^{327–334} as acid–base indicators in titrimetric analysis;³³⁵ they possess liquid-crystalline³³⁶ and some other practically useful properties.

The simplest and most convenient methods for the preparation of functionally substituted pyridin-2(1*H*)-ones, -thiones and -selenones are based on the use of cyclisation reactions of carbonyl compounds and their enamines with compounds containing the activated methylene group, first of all, malononitrile and cyanoacetamides. This opens an indirect route to regioselective synthesis of functionally substituted pyridines. Direct functionalisation of the rather inert pyridine ring by electrophilic substitution reactions is quite difficult.

Condensations of symmetrical 1,3-dicarbonyl compounds with cyano(chalcogeno)acetamides **1a–c** occur smoothly in the presence of basic catalysts to give 3-cyanopyridin-2(1*H*)-ones, -thiones and selenones **129** in high yields.^{28, 85, 337–352} Similar reaction of monothiodibenzoylmethane (**130**) with cyanothioacetamide (**1b**) in ethanol in the presence of piperidine gives rise to 3-cyano-4,6-diphenylpyridine-2(1*H*)-thione.³⁵³

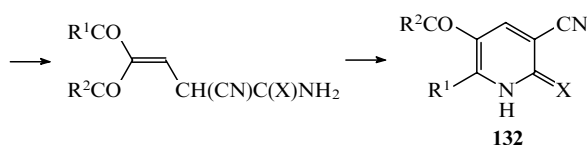
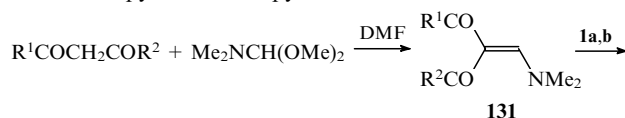


R = Alk, Ar, Het; X = O (a), S (b), Se (c).



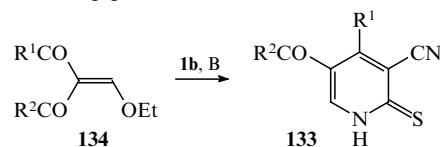
It is noteworthy that pyridin-2(1*H*)-ones **129a** were obtained by the above method as far back as the end of the past century, while the first thione analogue, *viz.*, 3-cyano-4,6-dimethylpyridine-2(1*H*)-thione, was synthesised by condensation of acetylacetone with the amide **1b** at the end of the 1950's,^{338,341} and the first selenone analogue was prepared in a similar way from the amide **1c** only in 1985.⁴⁷ Reactions of cyanothioacetamide (**1b**) occur under milder conditions and give higher yields of pyridines than with cyanoacetamide (**1a**). The reactions of cyanoselenoacetamide (**1c**) also occur under mild conditions, though an inert atmosphere is required in this case.

The reaction of 1,3-diketones with dimethylformamide dimethyl acetal affords β-enamino carbonyl compounds **131**, which are condensed with amides **1a,b** yielding functionally substituted pyridones and pyridinethiones **132**.^{232, 235, 354–356}



R¹ = Me, Et, CH₂CO₂Et; R² = Me, MeO, EtO; X = O, S.

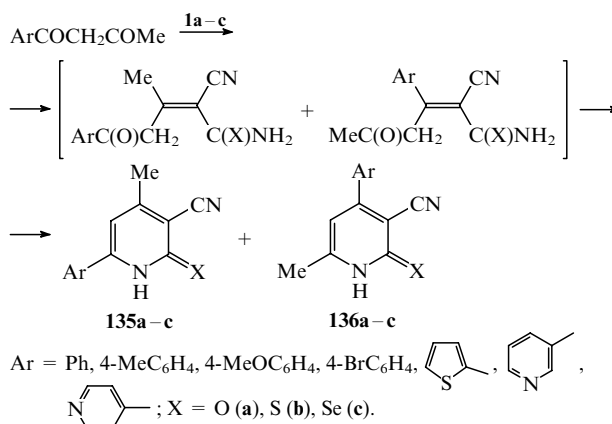
Synthesis of pyridinethiones **133** by the reaction of ethoxymethylidene diketones **134** with the amide **1b** in ethanol in the presence of piperidine has also been described.³⁵⁷



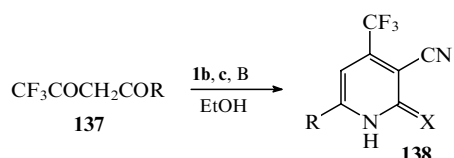
Condensations of unsymmetrical 1,3-dicarbonyl compounds with cyano(thio, seleno)acetamides **1a–c** leads to two isomeric pyridines with different substituents in positions 4 and 6, which allows one to elucidate the effect of the reactivities of the carbonyl groups on the regioselectivity of reactions. Thus it was shown^{85, 337, 347, 358} that the condensation of benzoylacetone with the amide **1b** gives both isomeric pyridinethiones **135b** and **136b** (Ar = Ph) in the ratio 2 : 1. Earlier, only the isomer **135b** was thought to be the reaction product.³⁴¹ However, the analogous reaction of benzoylacetone with cyanoselenoacetamide (**1c**) occurs with high regioselectivity to give only one isomer, *viz.*, 3-cyano-4-methyl-6-phenylpyridine-2(1*H*)-selenone (**135c**, Ar = Ph).^{358, 359}

Reactions of cyanothioacetamide (**1b**) with other unsymmetrical 1,3-diketones **137** (Ar = 4-MeC₆H₄, 4-MeOC₆H₄, 4-BrC₆H₄, 2-thienyl) also give rise to mixtures of the corresponding isomers **135b** and **136b**.^{360, 361}

Only the isomer **135a** (Ar = Ph) was earlier assumed^{362, 363} to be the reaction product of benzoylacetone with cyanoacetamide (**1a**) or ethyl cyanoacetate in the presence of ammonia or diethylamine. In the condensation of nicotinoylacetone with cyanoacetamide (**1a**), a mixture of isomers **135a** and **136a** (Ar = 3-pyridyl) in the ratio 3 : 2 is formed, while in the reaction of 4-pyridylcarbonylacetone, the isomer **136a** (Ar = 4-pyridyl) is the major product.¹⁶⁷

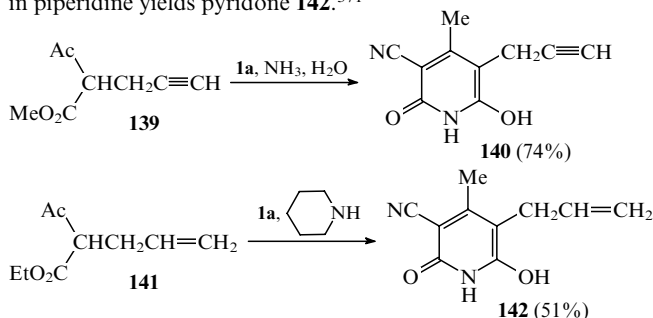


The regioselectivity of the reaction is the higher the stronger are the electron-withdrawing properties of a substituent at one of the carbonyl groups. Thus 1,3-diketones with the trifluoromethyl group **137** react with cyanoacetamides **1b,c** to give only 3-cyano-6-R-4-trifluoromethylpyridine-2(1*H*)-thiones and -selenones **138** in fairly high yields.^{345, 364–366} The change in the order of operations, *i.e.*, the preliminary generation of a carbanion from the thioamide **1b** by treating it with sodium ethoxide followed by the addition of trifluoroacetylacetone has led to the other isomer, *viz.*, 3-cyano-4-methyl-6-trifluoromethylpyridine-2(1*H*)-thione, in 94% yield.^{365, 367}

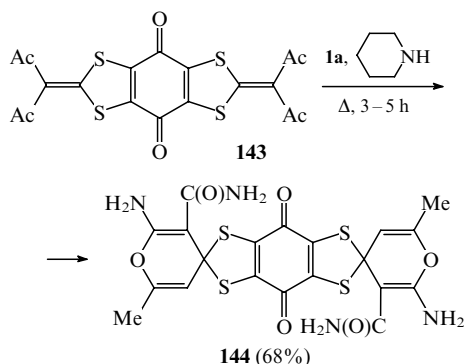


R = Alk, Ph, 4-MeC₆H₄, 4-MeOC₆H₄, 4-ClC₆H₄, ; X = S, Se.

Reactions of cyanoacetamide (**1a**) with 1,3-dicarbonyl compounds and their derivatives have successfully been employed in the synthesis of pyrimidines, pyrazines and other heterocycles.^{368–380} Thus the condensation of the amide (**1a**) with methyl 2-acetyl-4-ynoate (**139**) in concentrated aqueous ammonia solution gives rise to pyridone **140**. An analogous reaction of ethyl 2-acetyl-4-enoate (**141**) with the amide **1a** in piperidine yields pyridone **142**.³⁷¹

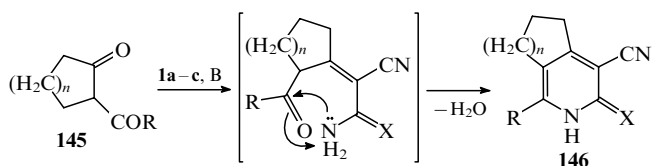


Substituted dispiro(dipyran[2,4':6,4']bisdithiolo[4,5-*b*:4',5'-*e*])-4,8-benzoquinone **144** was obtained by the reaction of 2,6-bis(diacetylmethylidene)bisdithiolo[4,5-*b*:4',5'-*e*]benzoquinone (**143**) with a twofold excess of the amide **1a** in ethanol in the presence of piperidine.³⁸⁰



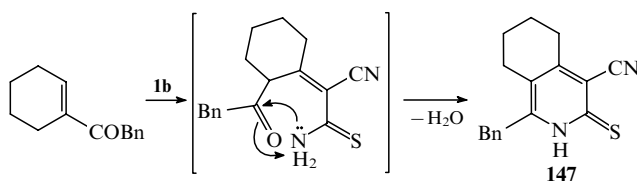
The kinetics of condensation of symmetrical and unsymmetrical 1,3-diketones (pentane-2,4-dione, 5-methylhexane-2,4-dione, 5,5-dimethylhexane-2,4-dione) with cyanoacetamide (**1a**) in the presence of piperidine as a catalyst under various reaction conditions has been studied. Judging from the rate constants and activation parameters as well as the structure of unsymmetrical 4,6-disubstituted 3-cyanopyridin-2(1*H*)-ones obtained, a plausible scheme for the reaction mechanism was suggested, which gives a rationale for the regioselectivity of the condensation and the positions of the substituents in the reaction products.³⁸¹

Cyclic 1,3-diketones have been successfully employed as substrates in the reactions with cyanoacetamides **1a-c**, and regioselective syntheses of bicyclic 3-cyanopyridin-2(1*H*)-ones, -thiones and -selenones **146** were proposed.^{85, 346, 382–394}

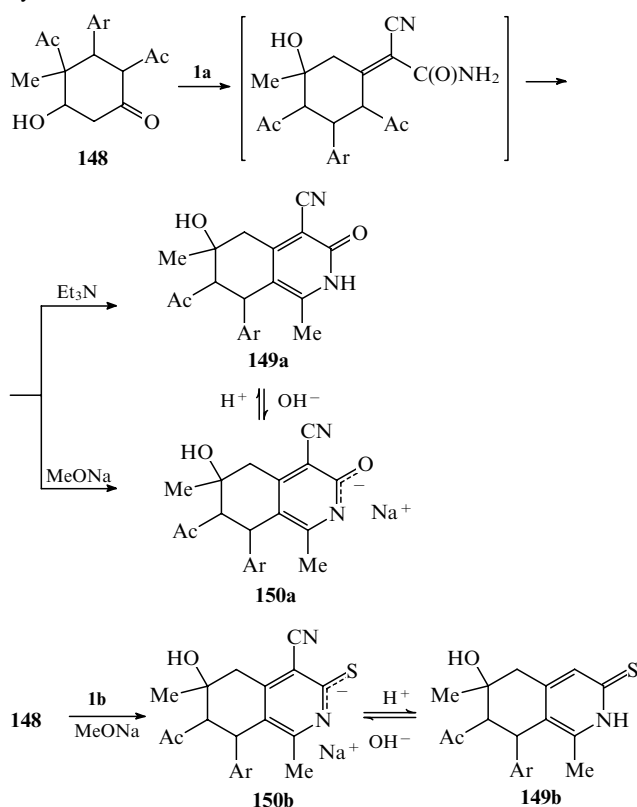


n = 1, 2; R = Alk, Ar; X = O, S, Se.

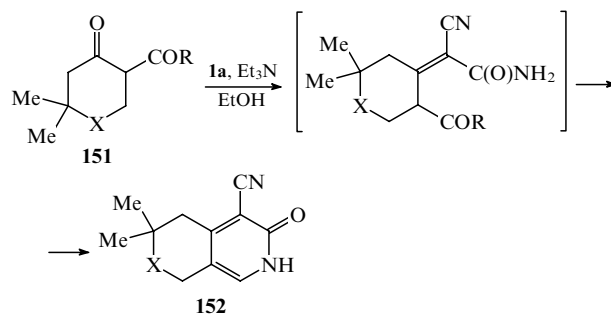
This approach has also been applied to the preparation of pyridone **147** having the skeleton of the alkaloid papaverine.³⁸⁶



7-Acetyl-8-aryl-4-cyano-1,6-dimethyl-6-hydroxy-5,6,7,8-tetrahydroisoquinolin-2(1*H*)-ones **149a**, -thiones **149b** and their sodium salts **150a,b** were obtained in high yields in reactions of the amides **1a,b** with 2,4-diacetyl-3-aryl-5-hydroxy-5-methylcyclohexanones **148**.³⁹⁴



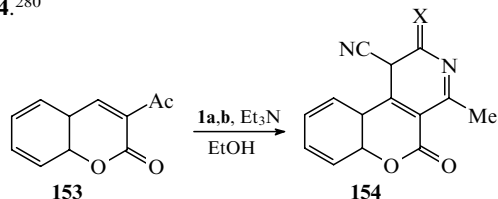
Of reactions of cyclic 1,3-diketones with cyanoacetamide (**1a**),^{277, 280, 395–399} the condensations of pyrans or thiopyrans **151** in ethanol in the presence of triethylamine can be noted as the method for preparation of 3-oxopyrano(thiopyrano)[3,4-*c*]pyridines **152**.^{277, 395, 396}



R = Alk, Ar; X = O, S.

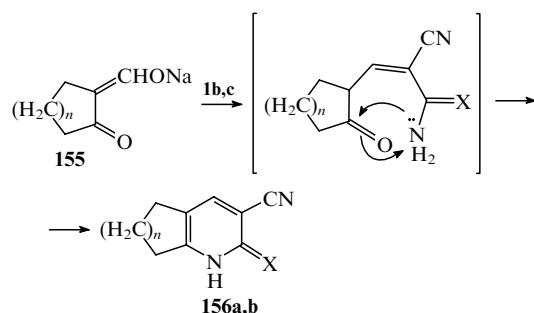
It is known that substituted coumarins and their annelated analogues exhibit bactericidal, spasmolytic and hypothermic activities. In order to develop methods of synthesis of substituted coumarins, which could be used in design of novel pharmaceuticals, it was necessary to study reactions of 3-acetylcoumarin

(**153**) with the amides **1a,b** in the presence of bases. This resulted in oxo- and thio-derivatives of benzopyrano[3,4-*c*]pyridines **154**.²⁸⁰



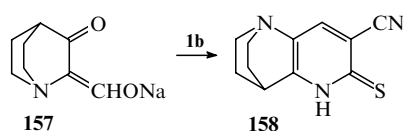
X = O (**a**), S (**b**).

Compared with cyclic 1,3-diketones, cyclic β -oxo aldehydes react with cyanoacetamides more selectively. Thus the condensations of sodium salts of 2-hydroxymethylidenecycloalkanones **155** with amides **1b,c** occur regioselectively to give only one of two possible isomers, viz., 5,6-annulated 3-cyanopyridine-2(1*H*)-thiones **156a** and -selenones **156b**.^{85, 387, 400–406}

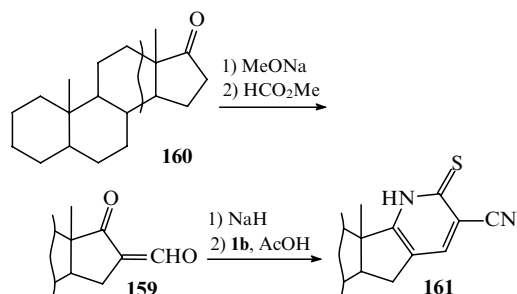


$n = 1, 2$; X = S (**a**), Se (**b**).

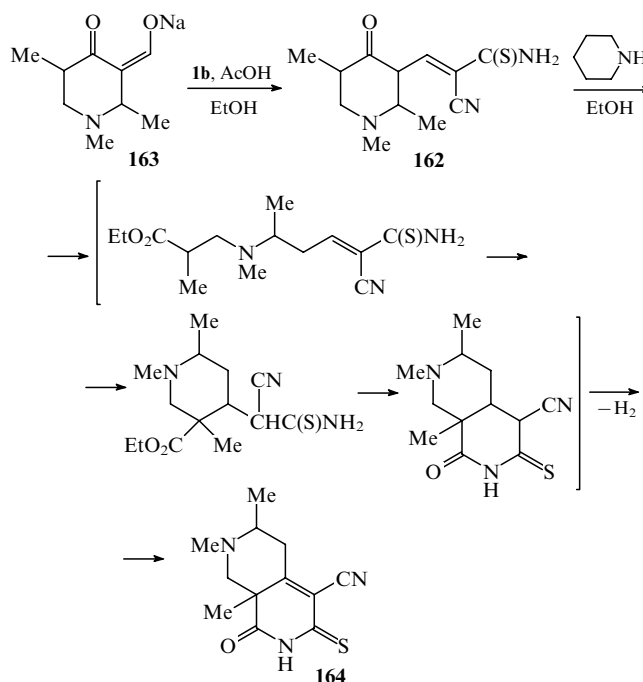
Yet another example of high regioselectivity is the reaction of sodium salt of 2-formylquinuclidone (**157**) with cyanothioacetamide (**1b**), which affords only bridged 3-cyano-1,5-naphthyridine-2(1*H*)-thione (**158**).⁴⁰⁷



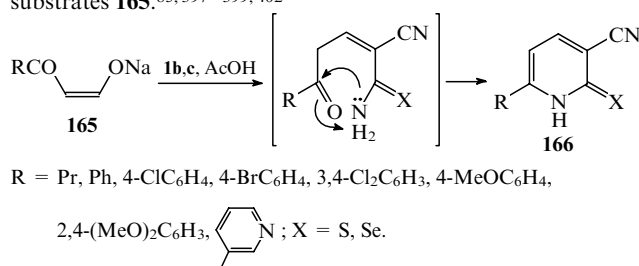
Cyanothioacetamide has been used in the synthesis of steroids annelated with the pyridine ring. Thus pyridinethione **161** was obtained in 80% yield by condensation of the amide **1b** with the sodium enolate of 16-formyl-5 α -androstan-17-one (**159**).^{60, 408} The latter has been prepared by formylation of 5 α -androstan-17-one (**160**) with methyl formate.



An example of recyclisation of (1,2,5-trimethyl-4-oxopiperidin-3-ylmethylidene)cyanothioacetamide (**162**), prepared from the sodium salt of 1,2,5-trimethyl-3-formylpiperidin-4-one (**163**) and the amide **1b**, into 4-cyano-6,7,8a-trimethyl-3-thioxo-1,2,3,5,6,7,8,8a-octahydro-2,7-naphthyridin-1-one (**164**) has been described.^{173, 409}



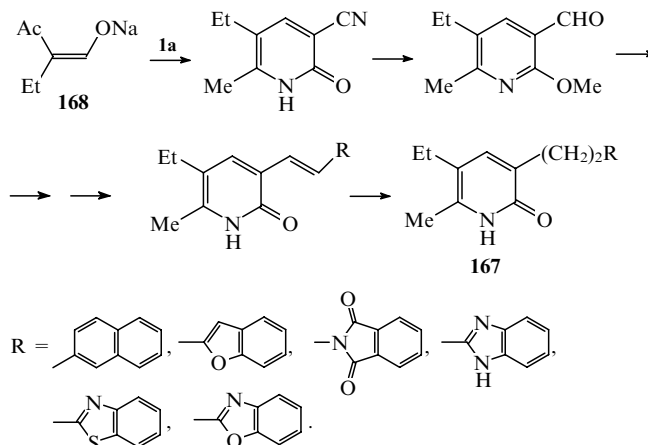
Similarly to cyclic β -oxo aldehydes, their acyclic analogues also react with high regioselectivity.^{38, 85, 174, 395, 410–422} Thus 6-substituted 3-cyanopyridine-2(1*H*)-thiones and -selenones (**166**) are formed in the reaction of amides **1b,c** with sodium enolates of β -oxo aldehydes (**165**). The regioselectivity of the reaction is independent of the nature of substituents (electron-donating or electron-withdrawing) in the benzene ring of the substrates **165**.^{85, 397–399, 402}

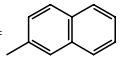
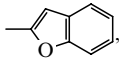
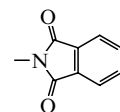
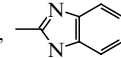
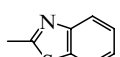
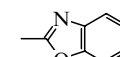


R = Pr, Ph, 4-ClC₆H₄, 4-BrC₆H₄, 3,4-Cl₂C₆H₃, 4-MeOC₆H₄,

2,4-(MeO)₂C₆H₃,  N; X = S, Se.

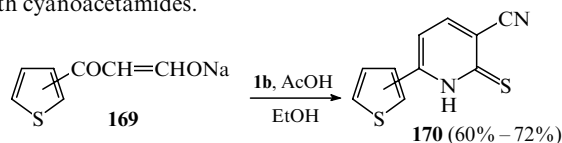
The key step in the synthesis of 2-pyridinone derivatives **167** possessing high anti-HIV activity^{253, 257} is the condensation of sodium enolate of 2-ethyl-3-oxobutane (**168**) with cyanoacetamide (**1a**) in the presence of piperidinium acetate.



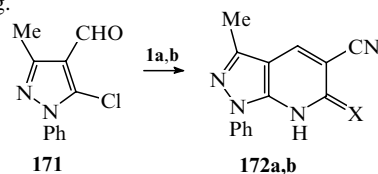
R = , , , , , .

The regioselective reaction of sodium enolates of 2- and 3-thenoylaldehydes **169** with cyanothioacetamide (**1b**) in ethanol in the presence of acetic acid, giving rise to the corresponding 3-cyano-6-thienylpyridine-2(1*H*)-thiones **170**,⁴²¹

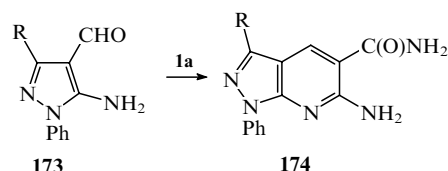
presents yet another example of successful synthesis of substituted pyridine-2-chalcogenones using condensations of oxo aldehydes with cyanoacetamides.



The condensations of cyanoacetamides with aliphatic, aromatic and heterocyclic aldehydes also lead to functionalised heterocycles.^{423–436} Among this type of the reactions, cyclocondensations of 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde (**171**) with amides **1a,b**, giving rise to pyrazolopyridines **172a,b**,⁴²⁶ and of 5-aminopyrazole-4-carboxaldehydes **173** with the amide **1a**, which makes possible the preparation of amino-substituted pyrazolo[3,4-*b*]pyridines **174**,⁴²⁹ are worth mentioning.

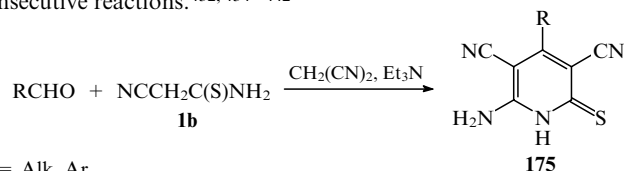


X = O (a), S (b).



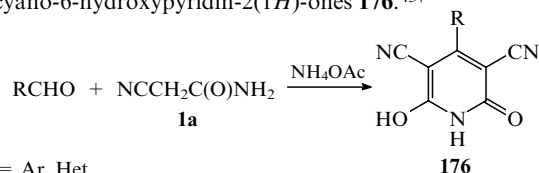
R = Me, Pr, Ph.

4-Substituted 6-amino-3,5-dicyanopyridine-2(1*H*)-thiones **175** are convenient building blocks in the synthesis of biologically active compounds. It is remarkable that they can be prepared from aliphatic or aromatic aldehydes, cyanothioacetamide (**1b**) and malononitrile in a one-pot preparative step including three consecutive reactions.^{432, 434–442}



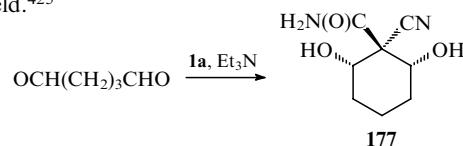
R = Alk, Ar.

Analogous reactions of aromatic and heterocyclic aldehydes with cyanoacetamide (**1a**) in the presence of ammonium acetate had earlier been employed for the synthesis of 4-substituted 3,5-dicyano-6-hydroxypyridin-2(1*H*)-ones **176**.⁴³⁷

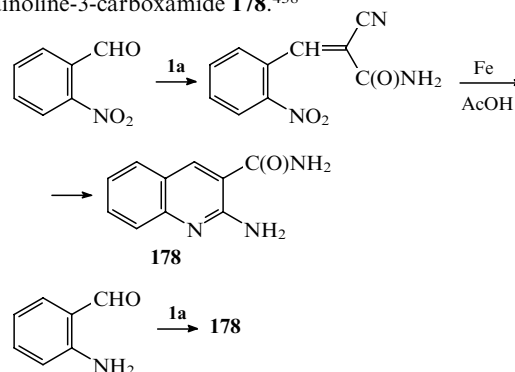


R = Ar, Het.

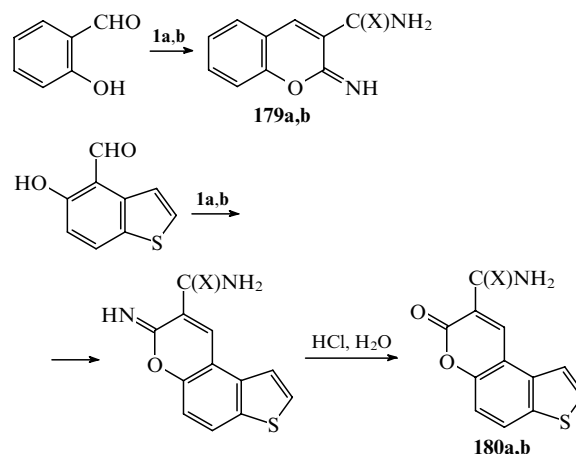
The cyclisation of glutaraldehyde with cyanoacetamide (**1a**) occurs in aqueous dioxane in the presence of triethylamine to give 1-cyano-2,6-dihydroxycyclohexane-1-carboxamide (**177**) in 75% yield.⁴²⁵



Reactions of the amide **1a** with 2-nitro- and 2-aminobenzaldehyde have been successfully used in the synthesis of 2-aminoquinoline-3-carboxamide **178**.⁴³⁸

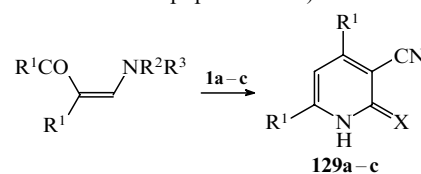


Analogous reactions of amides **1a,b** with hydroxybenzaldehyde and hydroxybenzo[*b*]thiophenecarbaldehyde have led to coumarin derivatives **179a,b** and **180a,b**.^{439–442}



X = O (a), S (b).

β-Enamino carbonyl compounds are widely used in the synthesis of various heterocyclic compounds. They are successfully employed for regioselective synthesis of 3-cyanopyridin-2(1*H*)-ones, -thiones and -selenones **129a–c** (see, for example, reviews^{28, 30, 85} and papers^{443–454}).

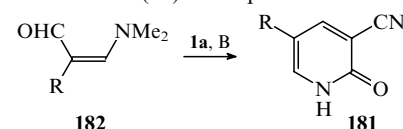


R¹ = Alk, Ar, Het; R², R³ = H, Ph;

R²–R³ = (CH₂)₅, (CH₂)₂O(CH₂)₂; X = O (a), S (b), Se (c).

It was found^{47, 85, 341–343, 349, 353, 387} that unlike the condensations of 1,3-dicarbonyl compounds, the reactions of the corresponding symmetrical β-enamines with cyanoacetamides occur under mild conditions (20–40 °C) and in the absence of basic catalysts to give selectively and in higher yields 4,6-disubstituted 3-cyanopyridin-2(1*H*)-ones, -thiones and -selenones **129a–c**.

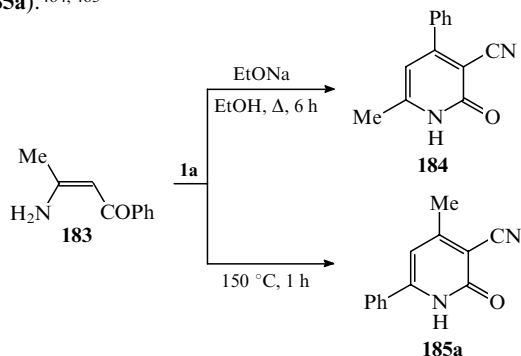
Synthesis of 5-substituted 3-cyanopyridin-2(1*H*)-ones **181** is based on the use of the reactions of β-enamino aldehydes **182** with cyanoacetamide (**1a**) in the presence of a base.^{272, 455–462}



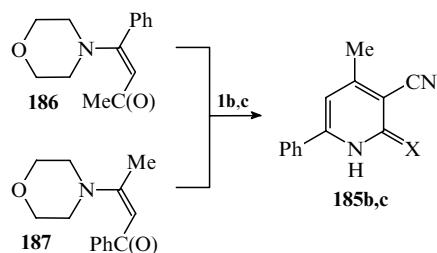
R = Ar, Het.

Condensations of β -enamines prepared from unsymmetrical 1,3-diketones with amides **1a–c** can afford isomeric 4,6-disubstituted 3-cyanopyridin-2(1*H*)-ones, -thiones and -selenones depending on whether the keto or the amino group of enamines is subjected to the initial nucleophilic attack by amides.^{85, 339, 345, 347, 358, 387, 446, 463–467} Varying the substituents in initial enamines and the reaction conditions, one may control the direction of these reactions leading to one particular isomer or to a mixture of both isomers.

Thus 2-amino-1-benzoylpropene (**183**) reacts with cyanoacetamide (**1a**) in the presence of sodium ethoxide to give 3-cyano-6-methyl-4-phenylpyridin-2(1*H*)-one (**184**),^{339, 464, 466, 467} while the condensation of these compounds at 150 °C for 1 h results in the isomeric 3-cyano-4-methyl-6-phenylpyridin-2(1*H*)-one (**185a**).^{464, 465}

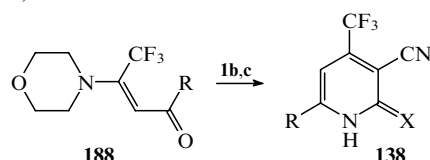


Only 3-cyanopyridine-2(1*H*)-thione **185b** and -selenone **185c** are obtained on brief refluxing of a mixture of β -enamino ketones **186** or **187** and amide **1b** or **1c** in ethanol in the presence of acetic acid.^{85, 347, 358, 446, 463}



X = S (**b**), Se (**c**).

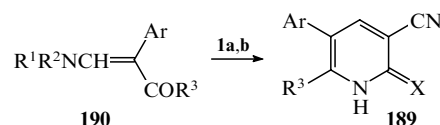
The stronger the electron-withdrawing properties of the substituent at the sp^2 hybridised carbon atom linked with the amino group, the higher the regioselectivity of the reaction. This is true even for those enamines which have the phenyl and 2-thienyl substituents at the carbonyl group. Thus condensations of trifluoromethyl-substituted enamino ketones **188** with amides **1b,c** in ethanol at 25–30 °C in the absence of a catalyst afford 3-cyano-6-phenyl- or -6-(2-thienyl)-4-trifluoromethylpyridine-2(1*H*)-thiones and -selenones **138**.^{85, 345}



R = Ph, ; X = S, Se.

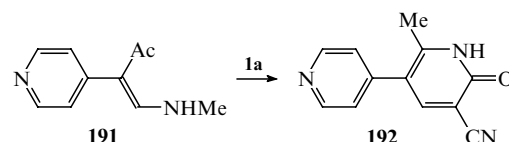
β -Enamino ketones can also be used for the preparation of 5,6-disubstituted 3-cyanopyridin-2(1*H*)-ones. Thus 6-alkyl-5-aryl-3-cyanopyridin-2(1*H*)-ones **189** possessing cardiotoxic activity have been obtained by condensation of enamino ketones **190** ($R^1 = R^2 = \text{Me}$) with cyanoacetamide (**1a**) in the presence of sodium methoxide.^{86, 87, 468–472} 3-Cyano-5-aryl-6-methylpy-

ridine-2(1*H*)-thiones **189** (X = S) were synthesised in a similar way from the enamino ketone **190** [$R^1 - R^2 = (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$].⁴⁷³

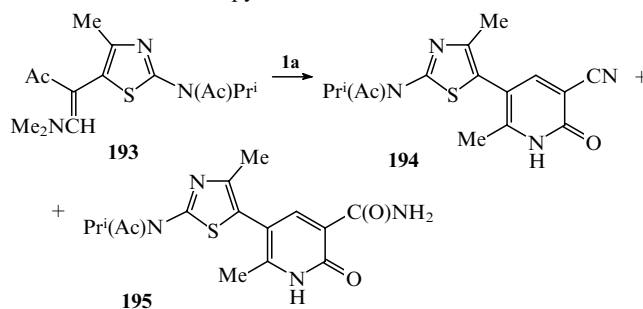


Ar = Ph, 4-MeSC₆H₄, 4-SO₂C₆H₄, 3,4-(MeO)₂C₆H₃; $R^1, R^2 = \text{Alk}$;
 $R^1 - R^2 = (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$; $R^3 = \text{Me}, \text{CH}(\text{OMe})_2, \text{cyclo-Alk}$; X = O, S.

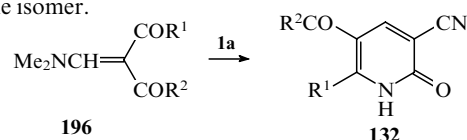
The well-known cardiotoxic preparation 'milrinone' (**192**) is obtained by the condensation of the enamine **191** with cyanoacetamide (**1a**) or malononitrile (**5**).⁴⁷⁴



The reaction of enamine **193** with the amide **1a** in isopropyl alcohol in the presence of sodium alkoxides is nonselective and results in a mixture of pyridones **194** and **195**.⁴⁷⁵

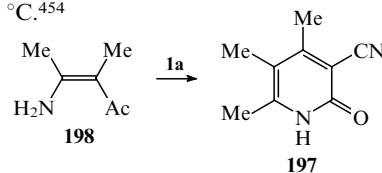


5,6-Disubstituted 3-cyanopyridin-2(1*H*)-ones **132** have been obtained by the reactions of 2-aminomethylidene derivatives of 1,3-dicarbonyl compounds **196** with the amide **1a** in the presence of sodium hydride in THF³⁶⁹ or sodium methoxide in DMF.⁴⁷⁶ Both symmetrical^{369, 476} and unsymmetrical^{477–479} β -diketones were used in these reactions. Compounds **196** with substituents $R^1 = \text{Bu}^n$, OEt and $R^2 = \text{Me}$ react regioselectively yielding only one isomer.

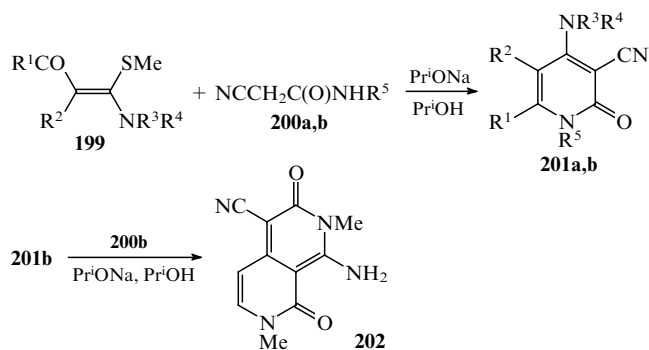


$R^1, R^2 = \text{Me}, \text{Pri}, \text{Bu}^t, \text{Bu}^n, \text{OEt}, \text{Ph}$.

3-Cyano-4,4,6-trimethylpyridin-2(1*H*)-one (**197**) has been obtained by the reaction of 4-amino-3-methylpent-3-en-2-one (**198**) with the amide **1a** at 150 °C for 30 min.⁴⁶⁵ This compound was also synthesised by the condensation of the enamine **198** with malononitrile (**5**) in THF in the presence of triethylamine at 20 °C.⁴⁵⁴

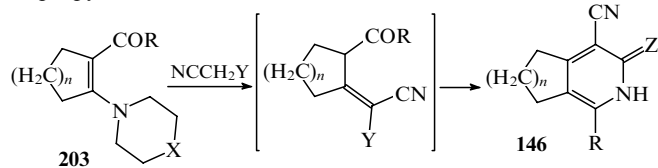


The condensations of β -enamino carbonyl compounds **199** with substituted cyanoacetamides **200a,b** occur with the elimination of methanethiol and result in 4-dialkylaminopyridones **201a,b** bearing the β -enamino amide fragment. Compound **201b** reacts with *N*-methylcyanoacetamide **200b** to give naphthyridine-dione **202**.⁴⁸⁰



$\text{R}^1 = \text{Me, Ph, 4-ClC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4$; $\text{R}^2 = \text{H}$;
 $\text{R}^3 = \text{Et, Ph, CH}_2\text{CH}(\text{OEt})_2, \text{Bn}$; $\text{R}^4 = \text{H}$;
 $\text{R}^3\text{--R}^4 = (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$; $\text{R}^5 = \text{H}$ (a), Me (b).

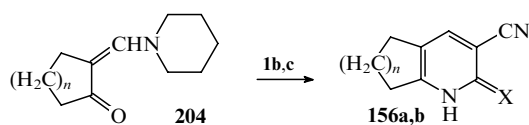
Synthesis of fused pyridinones, -thiones and selenones takes advantage of the high reactivity of cyclic β -enamino ketones with respect to cyanoacetamides **1a–c**.^{28, 30, 85, 346, 349, 382, 384–387, 446, 481, 482} Condensations of enamino ketones **203** with amides **1a–c** occur regioselectively to give in each case only one of two possible isomers in the absence of basic catalysts and afford the products in higher yields (on average, by 10%) than those obtained from 1,3-dicarbonyl compounds. Condensations of β -enamino ketones **203** bearing an aryl substituent instead of an alkyl one, demand more drastic reaction conditions. Thus 3-cyano-6-phenyltetrahydroisoquinolin-3-one **146** ($n = 4$, $\text{X} = \text{O}$, $\text{R} = \text{Ph}$) can be obtained on refluxing of the equimolar amounts of the starting compounds in isopropyl alcohol for 1.5 h.³⁸⁴



$n = 1, 2$; $\text{R} = \text{Alk, Ar}$; $\text{X} = \text{O, CH}_2$; $\text{Y} = \text{CN, C(Z)NH}_2$; $\text{Z} = \text{O, S, Se}$.

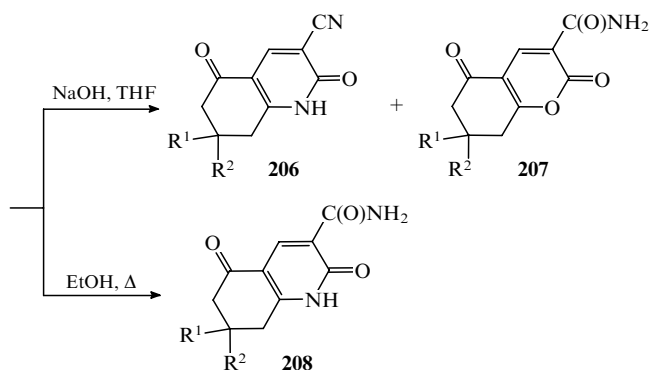
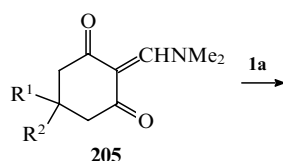
It has been noted^{369, 481} that condensations of enamines prepared from cyclic oxo aldehydes and secondary amines are more regioselective.

Hydrogenated 3-cyanoquinoline-2(1*H*)-thiones and -selenones **156a,b** were obtained by the condensation of 2-piperidinomethylidenecycloalkanones **204** with amides **1b,c** in ethanol in the presence of acetic acid in high yields.^{85, 352, 387, 402–404, 446}



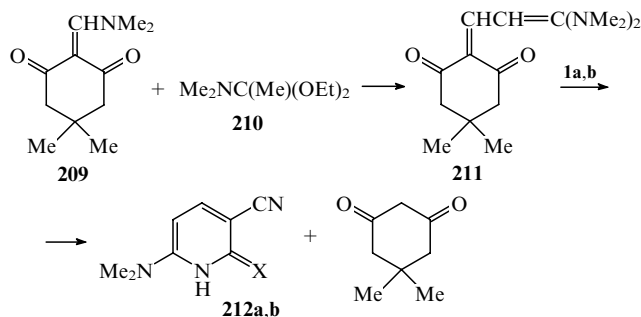
$n = 2, 3$; $\text{X} = \text{S}$ (a), Se (b).

The reaction of 2-dimethylaminomethylidenecyclohexanediones **205** with cyanoacetamide (**1a**) in THF in the presence of NaOH gives rise to a mixture of cyanopyridones **206** and carbamoylpyrones **207**. When enamines **205** are made to react with the amide **1a** in ethanol under reflux, only carbamoylpyridones **208** are obtained in high yields.³⁶⁹



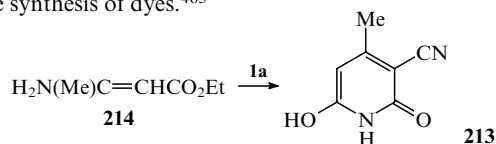
$\text{R}^1 = \text{H, Me}$; $\text{R}^2 = \text{H, Me, Ph}$.

The reaction of the enamine **209** prepared from dimedone with *N,N*-dimethylacetamide diethyl acetal (**210**) affords diaminodiene **211** in high yield. The latter reacts with amides **1a,b** with the elimination of dimedone to give 3-cyano-6-dimethylamino-pyridin-2(1*H*)-one (**212a**) or -thione **212b**, respectively.⁴⁴⁹

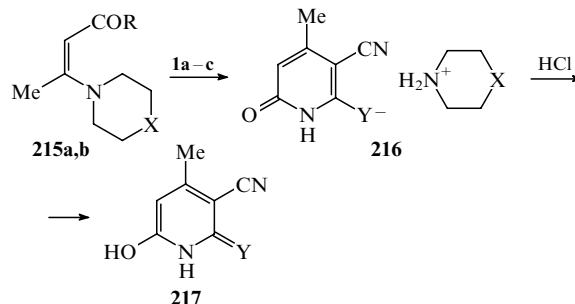


$\text{X} = \text{O}$ (a), S (b).

3-Cyanopyridin-2(1*H*)-ones, -thiones and -selenones can also be synthesised from β -enamino esters. Thus the condensation of the β -enamino ester **214** with the amide **1a** affords 3-cyano-6-hydroxy-4-methylpyridin-2(1*H*)-one (**213**), which is employed in the synthesis of dyes.⁴⁶⁵

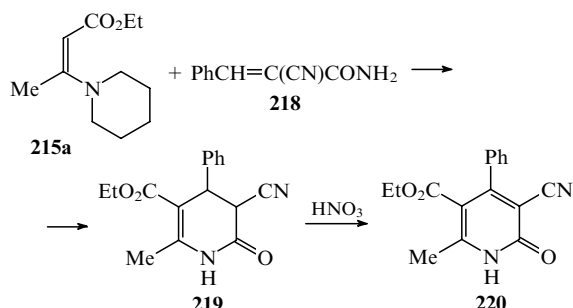


It was found^{447, 483, 484} that enamines **215a** and **215b** prepared from ethyl acetoacetate or acetoacetanilide are more reactive toward amides **1a–c** than ethyl acetoacetate itself. Thus the reactions of enamines **215a,b** with amides **1a–c** in ethanol at room temperature afford salts **216** in high yields. The latter are readily converted into the corresponding pyridinones, -thiones or -selenones **217** on treatment with HCl. The pyridone **217** ($\text{X} = \text{O}$) was also prepared by the reaction of the enamine **215a** ($\text{X} = \text{CH}_2$) with the amide **1a** in water followed by acidification of the reaction mixture.

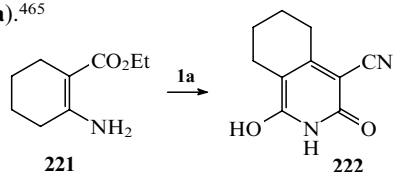


$\text{R} = \text{OEt}$ (**215a**), NHPh (**215b**); $\text{X} = \text{O, CH}_2$; $\text{Y} = \text{O, S, Se}$.

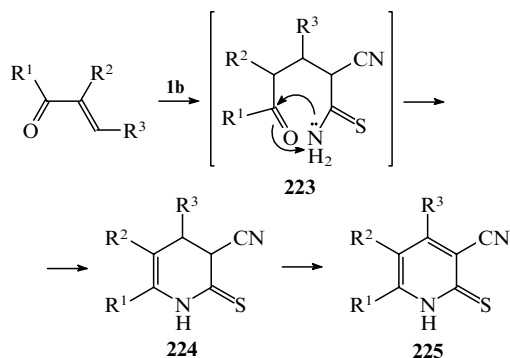
The β -enamino ester **215a** ($X = \text{CH}_2$) reacts with benzylidenecyanoacetamide **218** to give substituted 3,4-dihydropyridone **219**. The latter is transformed into ethyl 3-cyano-6-methyl-4-phenyl-1,2-dihydropyridine-5-carboxylate (**220**) on treatment with dilute nitric acid.⁴⁸⁵



Tetrahydroisoquinolinone **222** has been obtained by the condensation of β -enamino ester **221** with cyanoacetamide (**1a**).⁴⁶⁵



α,β -Unsaturated carbonyl compounds, owing to the substantial difference in reactivities of their nucleophilic centres, react with cyanothioacetamides yet more regioselectively than the corresponding enamino carbonyl compounds. In this case, the synthetic strategy consists in the condensation of unsaturated carbonyl compounds with cyanothioacetamide (**1b**) leading to 5-oxo thioamides **223**. The reason for regioselectivity is that Michael addition occurs preferentially, rather than the Knoevenagel condensation involving the carbonyl group. Further intramolecular cyclisation of the adducts **223** and dehydrogenation of pyridinethiones **224** result in 3-cyanopyridine-2(1*H*)-thiones **225** (see reviews^{28, 41} and papers^{486–500}).



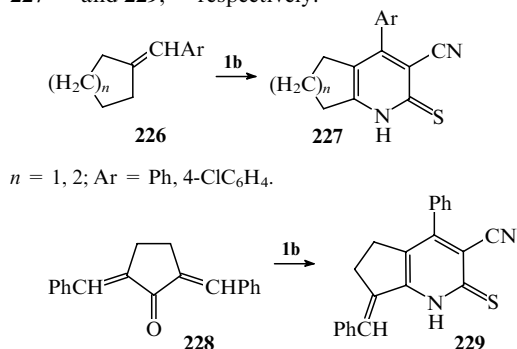
$R^1 = \text{H, Alk, Ph, Bn, } \text{pyridin-2-yl}$; $R^2 = \text{H}$; $R^3 = \text{Ph, 4-ClC}_6\text{H}_4$,
4-MeOC₆H₄, 4-NO₂C₆H₄, 4-MeNC₆H₄; $R^2-R^3 = (\text{CH}_2)_4$.

These reactions were initially used in the synthesis of 4,5-diaryl-3-cyanopyridine-2(1*H*)-thiones.^{343, 486, 488} Later, a series of 4,6-dihetaryl-pyridinethiones was obtained.^{352, 491, 492} α,β -Unsaturated carbonyl compounds were also employed in the synthesis of 4-aryl-6-methyl-^{347, 358} and 4,5,6-trisubstituted 3-cyanopyridine-2(1*H*)-thiones.^{41, 346, 385, 386, 487, 490} The direction of any particular reaction depends on the structure of the initial compounds, reaction conditions and catalyst. Thus reactions with the amide **1b** in boiling ethanol or methanol in the presence of sodium alkoxides result in the formation of substituted 3-cyanopyridine-2(1*H*)-thiones **225**.^{41, 343, 346, 347, 352, 358, 385, 386, 486, 487, 491, 492} However, if the sodium alkoxide catalyst is replaced by an equimolar amount of an organic base and the reaction is carried out at 20 °C, only tetrahydropyridines **224** are formed.^{489, 493–498} In this case, an

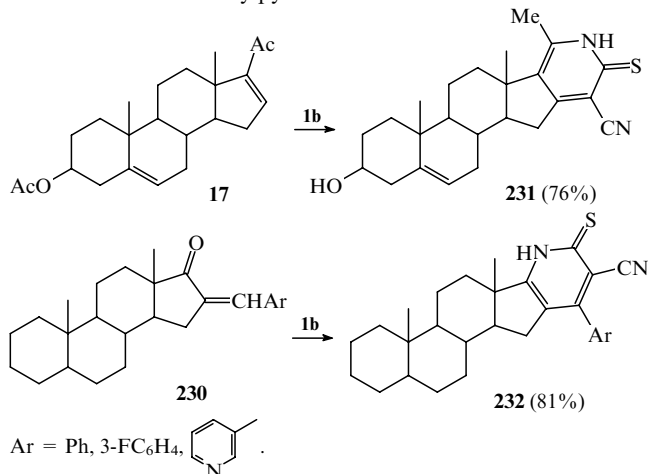
organic base acts not only as a catalyst but also as a stabiliser of the partially hydrogenated pyridinethiones, which can be isolated as stable salts. The latter are converted into pyridinethiones **225** on treatment with HCl and oxidation with atmospheric oxygen.

Although the condensations of α,β -unsaturated ketones with cyanothioacetamide (**1b**) afford the final products in somewhat lower yields compared to those obtained from 1,3-dicarbonyl compounds, this is counterbalanced by the selectivity of the reaction. Thus only the corresponding 3,4- or 4,4-bipyridines are formed from 1-(3- or 4-pyridyl)but-1-en-3-ones, respectively.¹⁶⁷

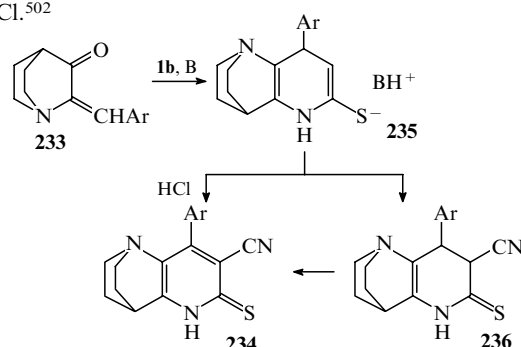
The reactions of 2-arylidene-cyclopentan(or -hexan)ones **226** and of 2,5-dibenzylidenecyclopentanone (**228**) with the amide **1b** give rise to 5,6-annulated 4-aryl-3-cyanopyridine-2(1*H*)-thiones **227**⁴⁹⁹ and **229**,⁵⁰¹ respectively.



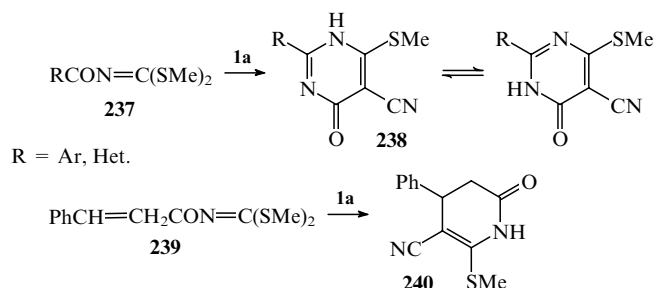
Pyridinethiones annulated with steroids were obtained using the reactions of the amide **1b** with α,β -unsaturated ketones **17** and **230**. The condensation of the amide **1b** with the ketone **17** is accompanied by hydrolysis of the acetoxy group and results in pyridinethione **231**. The reaction of the amide **1b** with arylidene-ketone **230** affords 4-arylpyridinethione **232**.^{60, 62}



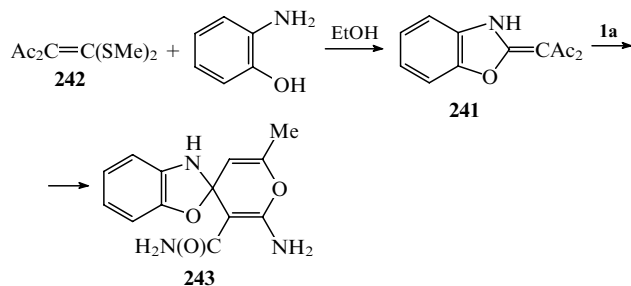
The condensations of 2-arylmethylidene-3-oxoquinuclidines **233** with the amide **1b** lead to the formation of stable salts **235**, which are converted into partially hydrogenated 4-aryl-3-cyano-1,5-naphthyridine-2(1*H*)-thiones **234** or **236** on treatment with HCl.⁵⁰²



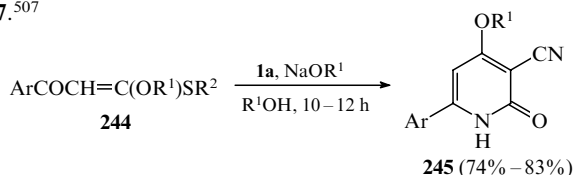
Reactions of cyanoacetamides with aroyl- and hetaroylimino dithioethers have been described.^{273, 503–506} Thus reactions of compounds **237** with cyanoacetamide (**1a**) in methanol in the presence of sodium methoxide afford 2-aryl(hetaryl)-5-cyano-6-methylthio-3,4-dihydropyrimidin-4-ones **238** in 40%–60% yields. However, a vinyllogue of compounds **237**, *viz.*, iminodithioether **239**, gives under similar conditions 5-cyano-6-methylthio-4-phenyl-3,4-dihydropyrimidin-2-one (**240**) in 70% yield.⁵⁰⁴



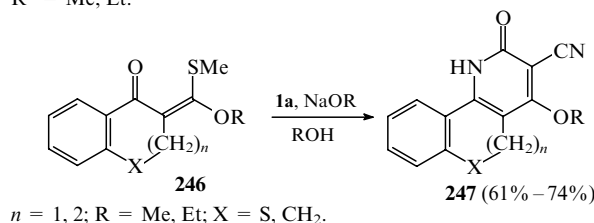
2-(Diacetylmethylidene)benzooxazole (**241**) prepared from dimethyl dithio acetal **242** and 2-aminophenol reacts with the amide **1a** in boiling methanol in the presence of piperidine to give spiro compound **243** in 58% yield.⁵⁰⁵



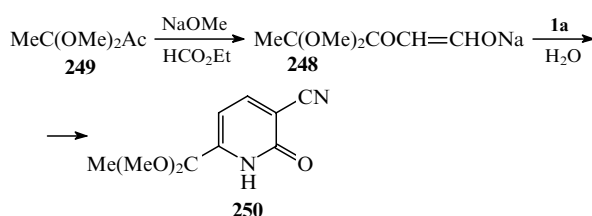
O,S-Acetals **244** react with the amide **1a** on heating in ethanol in the presence of sodium alkoxides yielding 4-alkoxy-3-cyanopyridin-2(1*H*)-ones **245**. Similar reactions of cyclic *O,S*-acetals **246** give rise to annelated 4-alkoxy-3-cyanopyridin-2(1*H*)-ones **247**.⁵⁰⁷



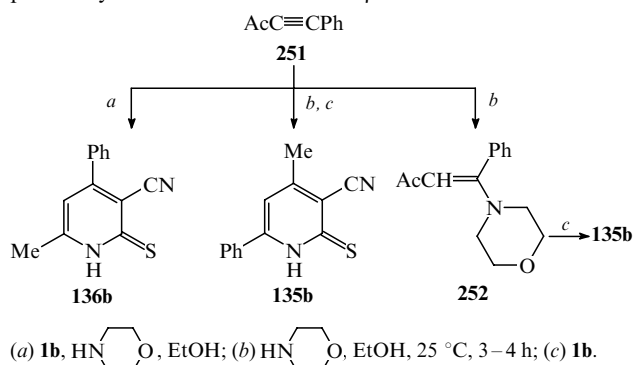
Ar = Ph, 4-MeOC₆H₄, 4-ClC₆H₄, , R¹ = Me, Et, Prⁿ; R² = Me, Et.



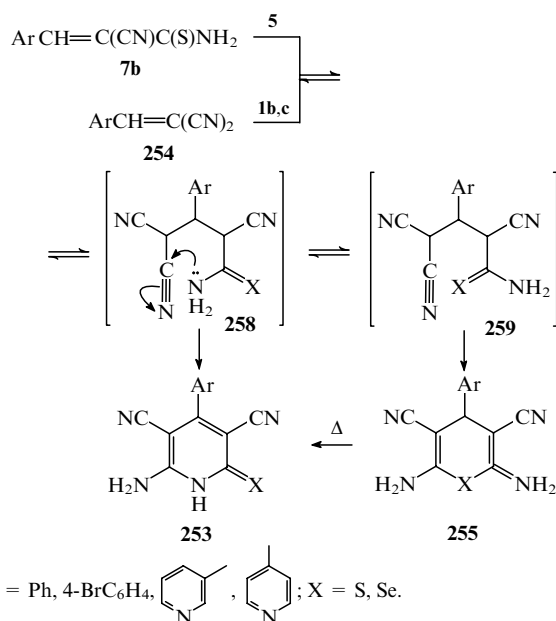
Salt **248** prepared by the reaction of diacetyl dimethyl ketal **249** with methyl formate in the presence of sodium methoxide reacts with the amide **1a** to give trimethyl orthopicolinate **250**.⁵⁰⁸

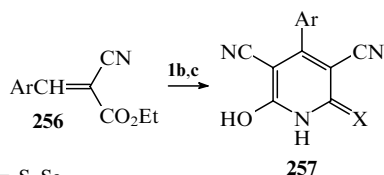


The use of α,β -ynones as substrates in the reactions with cyanoacetamides has been described.^{85, 347, 463, 509} 3-Cyano-6-methyl-4-phenylpyridine-2(1*H*)-thione (**136b**) was obtained on stirring a solution of acetylphenylacetylene (**251**) with cyanothioacetamide (**1b**) in ethanol in the presence of morpholine at 25 °C.^{85, 347, 463} However, the reaction of equimolar amounts of the ketone **251** with morpholine followed by the addition of the amide **1b** to the reaction mixture gave isomeric 3-cyano-4-methyl-6-phenylpyridine-2(1*H*)-thione **135b**. It was concluded⁸⁵ that the Michael addition of the amide **1b** to the ketone **251** is realised in the first reaction (path *a*) in which morpholine plays the role of a basic catalyst increasing the nucleophilicity of the methylene group in the amide **1b**. In the latter case (path *b*), β -enamino ketone **252** is initially formed, which then reacts with the amide **1b** in a selective manner to give the isomer **135b**. This mechanism was proved by isolation of intermediate β -enamino ketone **252**.⁸⁵



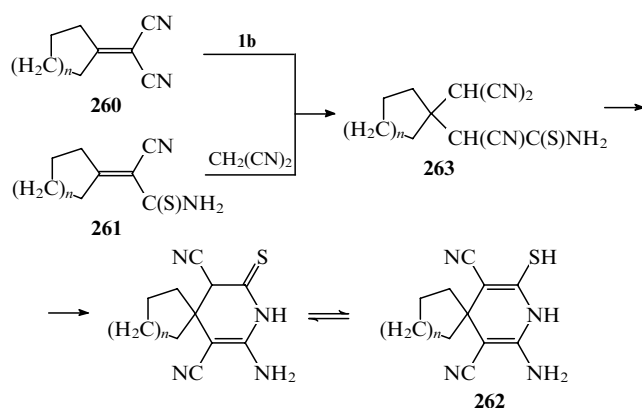
The use of α,β -unsaturated nitriles in reactions with amides **1b,c** for the preparation of 3-cyanopyridine-2(1*H*)-thiones and selenones is based on the formation of δ -oxothio- and δ -oxoselenoamide intermediates, which easily cyclise into a pyridine ring under the reaction conditions.^{49, 115, 353, 447, 498, 510–521} This is exemplified in the preparation of 6-amino-4-aryl(hetaryl)-3,5-dicyanopyridine-2(1*H*)-thiones and -selenones **253** by the reactions of arylmethylidenecyanothioacetamides **7b** with malononitrile (**5**) or of arylmethylidenemalononitriles **254** with thio- and selenoamides **1b,c**. Pyridinethiones and -selenones **253** can also be prepared by recyclisation of intermediate 2,6-diamino-4-aryl-3,5-dicyanothio(or -seleno)pyranones **255**. The latter were isolated in some cases.^{49, 510, 512, 515–518} 4-Aryl-3,5-dicyano-6-hydroxypyridine-2(1*H*)-thiones and -selenones **257** are synthesised by analogous reactions of arylmethylidenecyanoacetates **256** with amides **1b,c**.^{519–521}





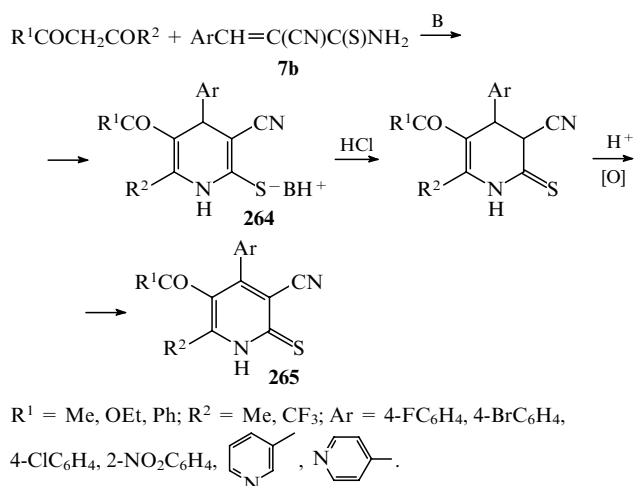
The ambident nature of the thioamide and selenoamide groups in intermediates **258** and **259** is believed to be the reason for the formation of pyridinechalcogenones **253** or thio(seleno)pyrans **255**, the outcome of the reactions depends on the reaction conditions. Thio(seleno)pyrans **255** are formed under kinetically controlled conditions, while pyridinechalcogenones **253** are formed under thermodynamic control. Such a dual chemical behaviour of intermediates **258** and **259** often prevents the unambiguous elucidation of the structure of the reaction products and often leads to misinterpretations. Thus the structure of 5-arylmethylidenepyridinethione has been erroneously attributed to the products of thermodynamically controlled reactions of arylmethylidenemalononitriles **254** with cyanothioacetamide **1b**.^{520, 521} This incorrect structure was then reproduced in reviews.^{34, 166} Another similar mistake has been made with respect to the product obtained in the reaction of (1-amino-2,2,2-trichloroethylidene)malononitrile with the amide **1b**;⁵²² this is not pyridinethione derivative **253** (X = S), but rather the thiopyran derivative **255**.⁵²³ Once again, no evidence in favour of earlier⁵²⁴ postulated formation of 3,4-dihydropyridinethiones has been found later.

One-step condensation of cycloalkylidenemalononitriles **260** with cyanothioacetamide (**1b**) or the corresponding cyanothioamides **261** with malononitrile proceeds *via* intermediates **263** and results in spirodihydropyridines **262**.⁵⁸

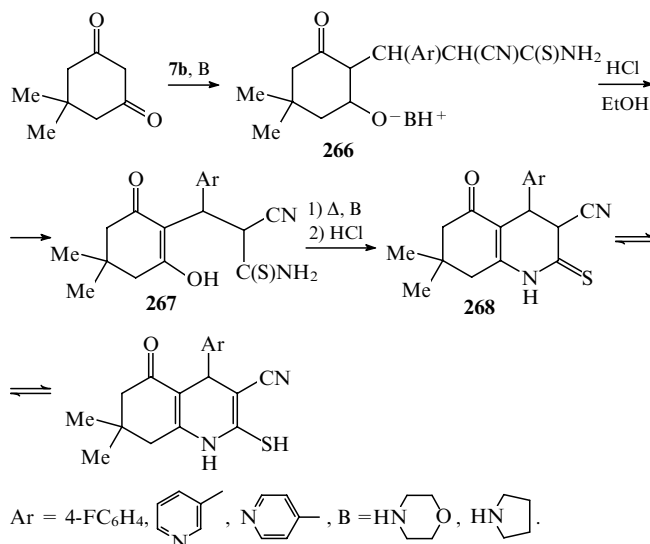


The reactions of arylmethylidenecyanothioacetamides **7b** with aldehydes, ketones, esters, amides and the corresponding enamines are also widely used in the synthesis of 4-aryl-3-cyanopyridine-2(1*H*)-thiones. Depending on the structure of the initial carbonyl compound and the reaction conditions, these reactions can stop in the stage of either hydrogenated pyridinethiones or their oxidised forms.^{49, 510–512, 525–530}

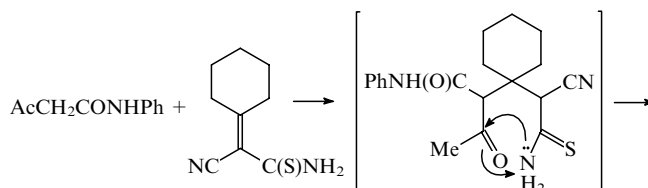
Unlike monocarbonyl compounds, acyclic 1,3-dicarbonyl compounds and β -amino carbonyl derivatives react with the amides **7b** in ethanol in the presence of an organic base (piperidine, morpholine, diethylamine, hexamethyleneimine) at 25 °C to give 1,4-dihydropyridine-2-thiolates **264**. The latter are converted into 3-cyano-3,4-dihydropyridine-2(1*H*)-thiones **265** upon treatment with 10% HCl.^{49, 113, 349, 352, 446, 488, 495, 510–512, 529, 531–538}

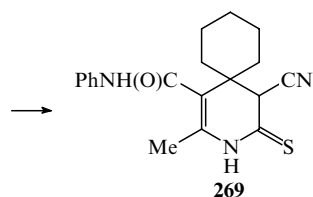


The reaction of the amide **7b** with a cyclic dicarbonyl compound such as dimedone allowed one to isolate the intermediate Michael adducts **266** as salts.^{113, 512} Acidification of the salts **266** affords compounds **267**. Heating of the latter in ethanol in the presence of a base followed by acidification results in 3,4-dihydropyridinethiones **268**.

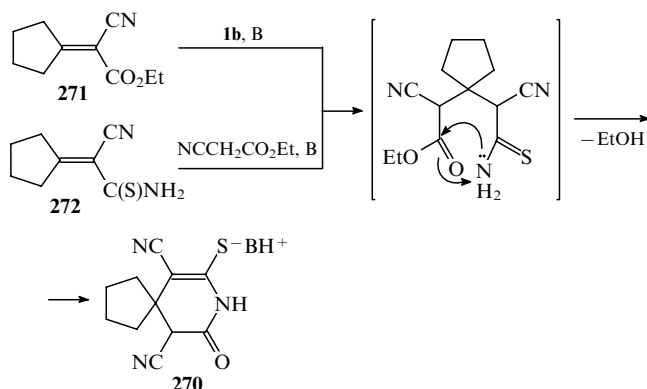


4-Aryl-5-arylcarbonyl-3-cyano-6-methylpyridine-2(1*H*)-thiones,⁵³⁹ stable 3-cyano-4-[2-furyl(thienyl)]-3,4-dihydropyridine-2(1*H*)-thiones,⁵⁴⁰ 3-cyano-4-(2-furyl)-6-methyl-5-phenylcarbonyl-1,4-dihydropyridine-2-thiolates and -selenolates⁵⁴ have been synthesised using the reactions of acetoacetanilides with the amides **7b**. This approach was also used for the preparation of 6'-methyl-5'-phenylcarbonyl-3',4'-dihydro-spiro[cyclohexane-1,4'-pyridine]-2'(1'*H*)-thione (**269**) from acetoacetanilide and cyclohexylidenecyanothioacetamide.⁵⁴¹

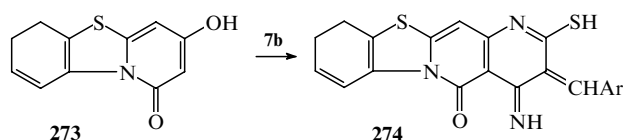




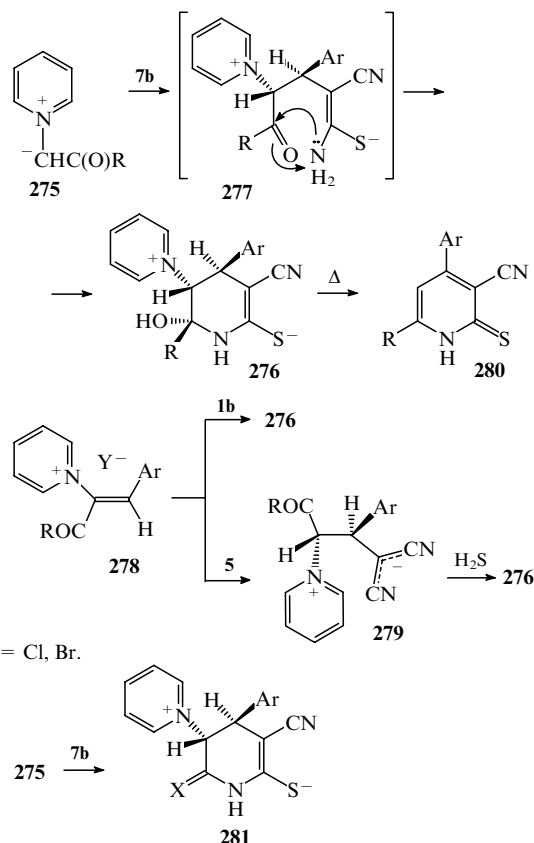
Synthesis of 3',5'-dicyano-6'-oxo-spiro[cyclopentane-1,4'-1',4',5',6'-tetrahydropyridine]-2'-thiolate **270** by the reaction of ethyl cyclopentylidenecyanoacetate (**271**) with cyanothioacetamide (**1b**) in the presence of *N*-methylmorpholine or by the reaction of cyclopentylidenecyanothioacetamide (**272**) with ethyl cyanoacetate under similar conditions is yet another example of the design of spiro-fused hydrogenated pyridine derivatives.⁵⁴²



All experimental results suggest that reactions of arylmethylidenecyanothioacetamides **7b** and their carbocyclic derivatives with 1,3-dicarbonyl compounds and their enamines always involve the stage of intermediate formation of Michael adducts such as 1,4-dihydropyridine-2-thiolates and 3,4-dihydropyridine-2(1*H*)-thiones. The only exception is the condensation of benzothiazolone **273** with the amides **7b**, which results in the formation of annelated system **274**.⁵⁴³



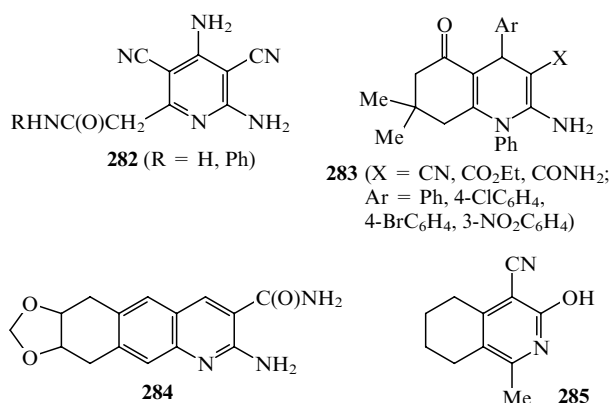
As to the stereochemical aspects of reactions of cyanoacetamides and their S- and Se-analogues, they remained unexplored until recently. Pyridinium ylides are very convenient model compounds for the study of regio- and stereoselectivity of formation of 3-cyanopyridine-2(1*H*)-thiones.^{58, 71, 83, 85–88, 288, 492, 544–559} It has been shown that condensations of arylmethylidenecyanothioacetamides **7b** with pyridinium ylides **275** generated *in situ* from the corresponding salts result in 3,4-*trans*-1,2,3,4-tetrahydropyridine-6-thiolates **276**. The high selectivity of these reactions is due to the stereoselective addition of the ylides **275** (X = S) to the amides **7b**. Subsequent cyclisation of adducts **277** into betaines **276** occurs with retention of the *trans*-arrangement of the hydrogen atoms.^{549, 554} Betaines **276** were obtained in high yields from pyridinium salts **278** and cyanothioacetamide (**1b**).⁵⁵¹ When malononitrile (**5**) was used in the reaction instead of amide **1b**, *trans*-adducts **279** were obtained from compounds (*E*)-**278**; these were isolated and examined. Treatment of the adducts **279** with H₂S afforded *trans*-tetrahydropyridines **276**. The latter gave 3-cyanopyridine-2(1*H*)-thiones **280** upon boiling in AcOH in the presence of ammonium acetate. The condensations of amides **7b** with pyridinium ylides **275** (X = O, S) give 2-oxo(thio)tetrahydropyridine-6-thiolates **281** in high yields.

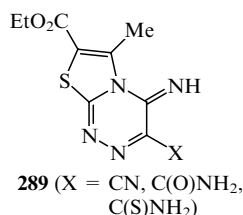
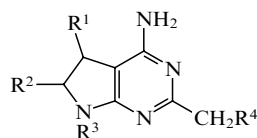
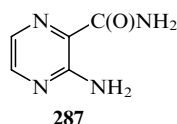
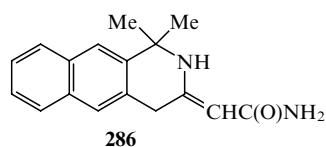


Y = Cl, Br.

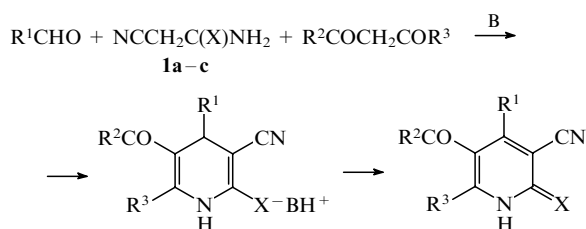
X = O, S.

A great number of other examples of the use of cyanoacetamides and their S- and Se-derivatives in the synthesis of functionalised 3-cyanopyridine-2(1*H*)-ones, -thiones and -selenones,^{560–604} 3-cyanopyridine-2-olates and -thiolates,^{605–609} pyrimidine-2-ones,^{610–616} tetrahydroquinoline-2-ones,^{617, 618} 5-cyano-3,4-diphenylpyridazine-6-one,⁶¹⁹ 2-aryl-5-cyano-4-methylthio-1,3-oxazine-6-ones⁶²⁰ and other heterocyclic compounds are also documented. Cyanoacetamides **1a, b** have found application in the synthesis of substituted pyridines **282**,⁶²¹ quinolines **178**,⁴³⁸ **283**,⁶²² **284**,^{623, 624} isoquinolines **285**,^{388, 389, 625} **286**,⁶²⁶ pyrazine **287**,⁶²⁷ dihydropyrrolopyrimidines **288**⁶²⁸ and triazines **289**.^{629, 630} Among other heterocyclic systems synthesised with the use of amides **1a–c** and their derivatives, thio- and selenopyrans,^{49, 510, 512, 515–518, 631, 632} coumarins and thiocoumarins,⁴³⁹ ^{442, 633, 634} and thiazines⁶³⁵ are worth mentioning. Apart from that, the preparation of carbocyclic systems of the cyclohexane series from cyanoacetamide (**1a**) has been described.^{425, 636}





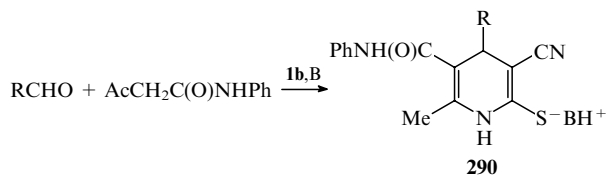
In the last decade, many derivatives of pyridin-2(1*H*)-ones, -thiones, -selenones and their salts have successfully been synthesised using a three-component condensation of cyanoacetamides or their derivatives with aliphatic, aromatic or heterocyclic aldehydes and 1,3-dicarbonyl compounds or their derivatives in the presence of an excess of organic base.^{495, 531, 532, 534, 535, 637–653}



$R^1 = \text{Alk, Ar, Het; } R^2 = \text{Alk, 2-MeC}_6\text{H}_4\text{NH; } R^3 = \text{Alk, NHPh;}$

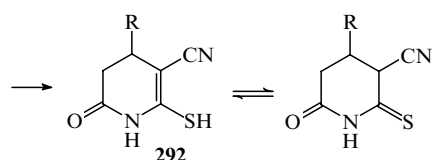
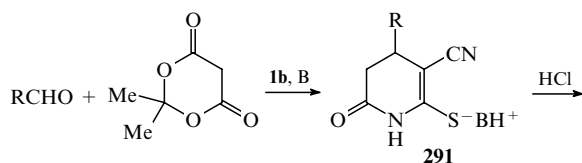
$X = \text{O, S, Se; } B = \text{HN} \begin{smallmatrix} \diagup \diagdown \\ \diagdown \diagup \end{smallmatrix} \text{O, MeN} \begin{smallmatrix} \diagup \diagdown \\ \diagdown \diagup \end{smallmatrix} \text{O, Et}_2\text{NH.}$

Synthesis of 4-(aryl or hetaryl)-3-cyano-6-methyl-5-phenylcarbamoyl-1,4-dihydropyridine-2-thiolates **290** from aromatic or heterocyclic aldehydes, amide **1b** and acetoacetanilide in the presence of an excess of *N*-methylmorpholine may be regarded as an illustration of such an approach.^{642–644}



$R = \text{Ph, 2-ClC}_6\text{H}_4, \text{2-MeC}_6\text{H}_4, \begin{smallmatrix} \diagup \diagdown \\ \diagdown \diagup \end{smallmatrix} \text{S, } \begin{smallmatrix} \diagup \diagdown \\ \diagdown \diagup \end{smallmatrix} \text{N; } B = \text{MeN} \begin{smallmatrix} \diagup \diagdown \\ \diagdown \diagup \end{smallmatrix} \text{O.}$

Cyclic diketones (cyclohexane-1,3-dione, dimedone, Meldrum's acid) were also used as 1,3-dicarbonyl components.^{645–647, 651} Thus 3-cyano-4-[aryl(or hetaryl)]-2-oxo-1,2,3,4-tetrahydropyridine-2-thiolates **291** have been obtained on refluxing an equimolar mixture of the corresponding aldehyde, the amide **1b** and Meldrum's acid in ethanol in the presence of *N*-methylmorpholine. Compounds **291** are converted into 5-amino-4-[aryl (or hetaryl)]-6-mercapto-3,4-dihydropyridin-2(1*H*)-ones **292** on acidification with 10% HCl to pH 5.⁶⁴⁶



$R = 4\text{-MeC}_6\text{H}_4, \begin{smallmatrix} \diagup \diagdown \\ \diagdown \diagup \end{smallmatrix}, \begin{smallmatrix} \diagup \diagdown \\ \diagdown \diagup \end{smallmatrix}, \begin{smallmatrix} \diagup \diagdown \\ \diagdown \diagup \end{smallmatrix}; B = \text{MeN} \begin{smallmatrix} \diagup \diagdown \\ \diagdown \diagup \end{smallmatrix} \text{O.}$

The use of pyridinium ylides **275** ($X = \text{O}$) in the three-component condensations allows one to perform a one-pot synthesis of 3-cyanopyridin-2(1*H*)-ones without preliminary synthesis of arylmethylidenecyanothioacetamides **7b**.^{58, 83, 85, 288, 492, 549, 550}

IV. Conclusion

The data considered here clearly demonstrate the high synthetic potential of cyanoacetamides and their thio- and selenocarbonyl analogues. Many biologically active heterocyclic compounds have been obtained based on these reagents. This suggests that cyanoacetamides and their arylmethylidene and hetarylmethylidene derivatives can be particularly promising starting materials in combinatorial synthesis of functionalised carbo- and heterocyclic compounds used in the design of novel highly effective pharmaceuticals with a broad range of action. The great interest of chemists in these reagents is confirmed by the fact that more than 490 papers of 653 cited in this review are dated to the last 10–15 years and more than 20% of them are patents.

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Synthesis and reactions of mixed halogenobuta-1,3-dienes

R V Kaberdin, V I Potkin, V A Zapol'skii

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Abstract. The published data on the methods for the preparation of mixed halogenobuta-1,3-dienes are generalised and systematised with a special emphasis on compounds of high practical value. Chemical transformations of mixed halogenodienes are considered and broad possibilities of the use of these compounds for the synthesis of various valuable, but difficultly accessible polyfunctional products are demonstrated. The bibliography includes 115 references.

I. Introduction

The first representative of halogenobutadienes, *viz.*, hexachlorobuta-1,3-diene, was obtained as early as 1876.¹ However, in the subsequent 50 years studies on the synthesis of halogenobutadienes were episodic and only in the early 1930s did they become purposeful and systematic. The development of preparation methods and the search for possible uses of this class of compounds in organic synthesis were stimulated by the discovery that mono- and dichlorobuta-1,3-dienes easily polymerise.

The first data on the synthesis of halogen derivatives of butadiene were generalised by Petrov in 1944.² Later studies devoted mainly to the synthesis and transformations of chloro and fluoro derivatives of butadiene were systematised in a fundamental Houben–Weyl monograph.³ Particularly intensive studies were carried out in the field of chloro derivatives of butadiene and their results were surveyed in reviews^{4–6} and monographs.^{7–9}

At present, there are numerous publications devoted to the synthesis of mixed halogenobutadienes (MHB) containing atoms of different halogens, *viz.*, fluorine, chlorine, bromine and iodine. Mixed halogenobutadienes possess a broad spectrum of useful properties: they are good dielectrics, refrigerants and heat-transfer agents; they are used as aerosols, lubricants and floatation agents and possess algicidal, bactericidal and fungicidal activities.^{10–15} A number of MHB manifest high antitumour activity.¹⁶ Chlorine–fluorine-containing butadienes are employed as monomers for the preparation of valuable polymers and copolymers resistant to heat, light, chemical corrosion, *etc.*^{13, 17, 18} And, finally, MHB

are promising semi-products in organic synthesis. For example, the preparation of polyfluoromethine compounds is based on MHB, which opens a way to the synthesis of novel polymethine dyes.¹⁹

It should be noted that the introduction of atoms of different halogens into the butadiene molecule leads to a considerable increase in the number of theoretically possible isomers. Thus consideration of structural and geometric isomers shows that dichlorobuta-1,3-diene has nine isomers,⁷ while for butadiene derivatives with two different halogen atoms the number of possible isomers increases tenfold. From a theoretical aspect, mixed halogenobutadienes, like other compounds with the butadiene system, are convenient subjects for studying the *s-cis*–*trans*-isomerism associated with the appearance of conformationally non-equivalent structures resulting from the hindered rotation of the vinyl fragments around the central C–C bond.^{20–22} They are also promising as model substrates for studying regularities of the processes of nucleophilic vinylic substitution (S_NVin). This review surveys the literature data on the chemistry of mixed halogenobuta-1,3-dienes published up to 1999. We presume that such a review will fill the gap in the relevant literature and will contribute to the further development of research into the chemistry of halogen derivatives of alkenes and alkadienes.

II. Synthesis of mixed halogenobuta-1,3-dienes

The basic methods for the preparation of MHB are:

(1) Elimination reactions (dehydrohalogenation and dehalogenation) of polyhalogenobutadienes and -butenes;

(2) halogenation and hydrohalogenation of acetylenic hydrocarbons of the C₄ series;

(1) thermal decomposition of accessible polyhalogenated compounds.

Other methods of the synthesis of individual representatives of MHB are also known.

1. Elimination reactions

Numerous chlorofluoro- and bromochlorobutadienes were obtained by dehydrohalogenation and dehalogenation of polyhalogenobutanes and -butenes).

Dehydrohalogenation of polyhalogenobutenes under the action of various dehydrohalogenation agents proceeds as the 1,4- or 3,4-elimination of a molecule of hydrogen halide depending on the position of the C=C bond. Another conventional way for the synthesis of MHB is dehalogenation of polyhalogenobutanes and -butenes, which is carried out under the action of metals, zinc in most cases.

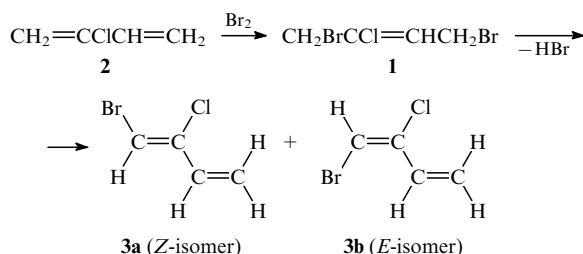
R V Kaberdin, V I Potkin, V A Zapol'skii Institute of Physical Organic Chemistry, National Academy of Sciences of Byelarus, ul. Surganova 13, 220072 Minsk, Byelarus. Fax (7-017) 284 16 79. Tel. (7-017) 284 16 00. E-mail: ifoch@ifoch.bas-net.by (R V Kaberdin, V A Zapol'skii). Tel. (7-017) 284 09 72. E-mail: potkin@ifoch.bas-net.by (V I Potkin)

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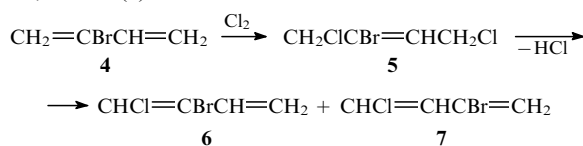
a. Dihalogenobutadienes

The simplest MHB containing two different halogen atoms can be obtained from trihalogenobut-1- and -2-enes. Thus the dehydrobromination of 1,4-dibromo-2-chlorobut-2-ene (**1**), which is the main product of chloroprene bromination (**2**), resulted in 1-bromo-2-chlorobuta-1,3-diene (**3**) in preparative yield.^{23,24} The diene **3** formed in this reaction is a mixture of geometric isomers with the predominance of the *Z*-isomer **3a**.²⁵

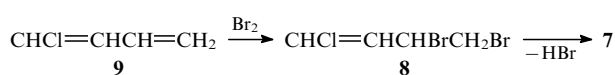


Papazyan *et al.*²⁶ have proposed performing the dehydrobromination of butene **1** in the presence of phase-transfer catalysts (PTC) that considerably simplified the process and made it more economical (the conditions for the synthesis of the diene **3**, its yield and the data related to all subsequent syntheses of MHB by the elimination reaction are presented in Table 1).

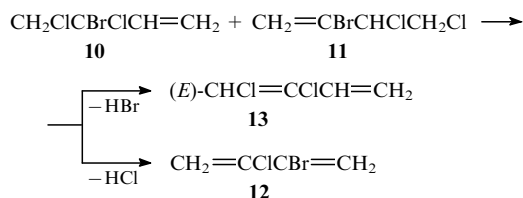
Chlorination of bromoprene (**4**) and subsequent dehydrochlorination of 2-bromo-1,4-dichlorobut-2-ene (**5**) leads to a mixture of *E*- and *Z*-isomers of 2- (**6**) and 3-bromo-1-chlorobuta-1,3-diene (**7**).^{27,28}



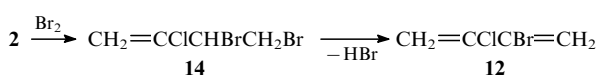
A more convenient synthesis of *E*- and *Z*-isomers of the diene **7** is based on the dehydrobromination of 3,4-dibromo-1-chlorobut-1-ene (**8**), which is the product of bromination of 1-chlorobuta-1,3-diene (**9**).²⁹



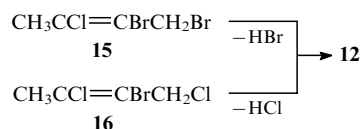
Dehydrohalogenation of the by-products of the chlorine addition to the diene **4**, *viz.*, a mixture of 3- (**10**) and 2-bromo-3,4-dichlorobut-1-enes (**11**), yielded a mixture of 2-bromo-3-chlorobuta-1,3-diene (**12**) and (*E*)-1,2-dichlorobuta-1,3-diene (**13**) (GLC).²⁷



The diene **12** was initially obtained by dehydrobromination of 3,4-dibromo-2-chlorobut-1-ene (**14**), which is a by-product of chloroprene **2** bromination.²⁴



The preparative synthesis of the diene **12** is based on the 1,4-elimination of hydrogen halide from 1,2-dibromo-3-chlorobut-2-ene (**15**) or 2-bromo-1,3-dichlorobut-2-ene (**16**) or a mixture of these butenes with an alkali (KOH or NaOH) in the presence of PTC.³⁰



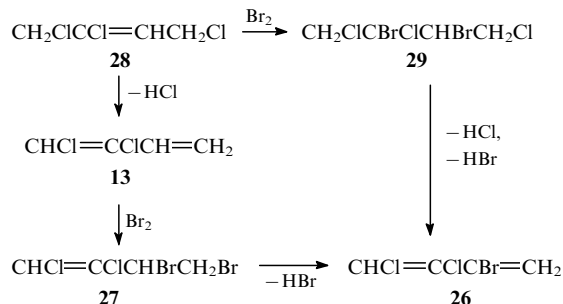
Of the disubstituted chlorofluorobutadienes, the following three compounds are known: 1-chloro-1-fluoro- (**17**), 1-chloro-2-fluoro- (**18**) and 3-chloro-2-fluoro-buta-1,3-dienes (**19**) (see Table 1).

The diene **17** was obtained as the result of dehydrochlorination of 4,4-dichloro-4-fluorobut-1-ene (**20**),^{31,32} whereas the diene (**18**) resulted from the dechlorination of 3,4,4-trichloro-3-fluorobut-1-ene (**21**).³³ The diene **19** is formed upon dehydrohalogenation of a liquid mixture of mono-, di- and trifluoro compounds which are the products of the reaction of 1,2,3,4-tetrachlorobutane with HF.³⁴ Yet another route to the diene **19** consists in the dehydrohalogenation of 2,4-dichloro-1,3-difluorobutane (**22**), which is the main product of ClF addition to butadiene (see Table 1).^{35,36}

b. Trihalogenobutadienes

The first representative of mixed trihalogenobutadienes, *viz.*, 3-bromo-1,1-dichlorobuta-1,3-diene (**23**), was initially prepared by the thermal dehydrochlorination of 3-bromo-1,1,4-tetrachlorobutane (**24**)³⁷ and later, of 2-bromo-4,4,4-trichlorobut-1-ene (**25**), which is the product of bromotrichloromethane addition to allene.³⁸ (see Table 1).

3-Bromo-1,2-dichlorobuta-1,3-diene (**26**) was obtained by a multistep synthesis the last stage of which was dehydrobromination of 3,4-dibromo-1,2-dichlorobut-1-ene (**27**), which is the main product of 1,2-dichlorobuta-1,3-diene (**13**) bromination. The latter is obtained by the dehydrochlorination of 1,2,4-trichlorobut-2-ene (**28**).³⁹ Papazyan *et al.*²⁶ simplified the synthesis of the diene **26** from the butene **28**. The target product **26** was obtained by direct bromination of the butene **28** and subsequent dehydrohalogenation of the adduct formed, *viz.*, 2,3-dibromo-1,2,4-trichlorobutane (**29**). The by-product of this reaction is 2-bromo-1,3-dichlorobuta-1,3-diene (**30**).



Two methods for the synthesis of 1-bromo-2,3-dichlorobuta-1,3-diene (**31**) are known. It is obtained by dehydrobromination of either 1,4-dibromo-2,3-dichlorobut-2-ene (**32**)³⁹ [the product of 2,3-dichlorobuta-1,3-diene (**33**) bromination]³⁹ or 1,2-dibromo-2,3,4-trichlorobutane (**34**) [the product of bromine addition to the accessible 2,3,4-trichlorobut-1-ene (**35**)].²⁶

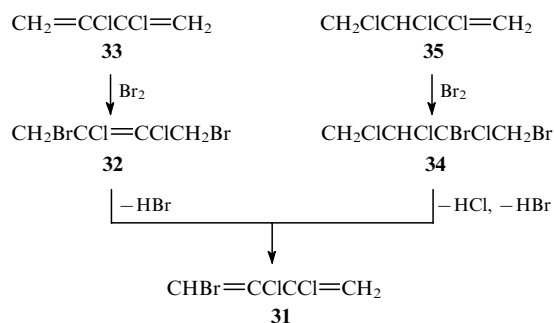


Table 1. Synthesis of mixed halogenobuta-1,3-dienes by the elimination from halogenobutanes and -butenes.

Starting compound	Elimination agent	Reaction conditions	Halogenobutadiene	Yield (%)	Ref.
CH ₂ BrCCl=CHCH ₂ Br (1)	KOH	EtOH	CHBr=CClCH=CH ₂ (3)	38	23, 24
CH ₂ BrCCl=CHCH ₂ Br (1)	KOH	96% EtOH, 0 °C, 14 h	(<i>Z</i>)-CHBr=CClCH=CH ₂ (3a), (<i>E</i>)-CHBr=CClCH=CH ₂ (3b)	31.5, 1.5	25
CH ₂ BrCCl=CHCH ₂ Br (1)	10% NaOH	water, 1% katamin AB,	CHBr=CClCH=CH ₂ (3)	72	26
CH ₂ ClCBr=CHCH ₂ Cl (5)	NaOH	EtOH, 40 °C, nitrosodiphenylamine	(<i>E</i>)-CHCl=CBrCH=CH ₂ (6a) + + (<i>Z</i>)-CHCl=CBrCH=CH ₂ (6b) + + CHCl=CHCBr=CH ₂ (7) (6a : 6b : 7 = 72:2:26)	—	27, 28
CHCl=CHCHBrCH ₂ Br (8) (<i>E</i> : <i>Z</i> = 3:1)	10% NaOH	water, katamin AB, 40 °C, 3 h	(<i>E</i>)- + (<i>Z</i>)-CHCl=CHCBr=CH ₂ (7) (<i>E</i> : <i>Z</i> = 82:18)	66.8	29
CH ₃ CCl=CBrCH ₂ Br (15)	NaOH	water, katamin AB	CH ₂ =CClCBr=CH ₂ (12)	60.2	30
CH ₃ CCl=CBrCH ₂ Cl (16)	NaOH	the same	CH ₂ =CClCBr=CH ₂ (12)	51.6	30
CH ₂ =CHCBrClCH ₂ Cl (10) + + CH ₂ =CBrCHClCH ₂ Cl (11) (10 : 11 = 1:4)	NaOH	EtOH, nitrosodiphenyl- amine, 46–48 °C	CH ₂ =CClCBr=CH ₂ (12) + + (<i>E</i>)-CHCl=CClCH=CH ₂ (13) (12 : 13 = 9:1)	—	27
CFCl ₂ CH ₂ CH=CH ₂ (20)	KOH	EtOH, boiling	CFCl=CHCH=CH ₂ (17)	53.5	31
CHCl ₂ CFCICH=CH ₂ (21)	Zn	the same	CHCl=CFCH=CH ₂ (18)	—	33
CH ₂ FCHClCHFCFCH ₂ Cl (22)	KOH	EtOH	CH ₂ =CClCF=CH ₂ (19)	—	35, 36
CCl ₃ CH ₂ CHBrCH ₂ Cl (24)	—	thermal dehydro- chlorination, 450 °C	CCl ₂ =CHCBr=CH ₂ (23)	45.0	37
CCl ₃ CH ₂ CBr=CH ₂ (25)	Et ₃ N	boiling, 2 h	CCl ₂ =CHCBr=CH ₂ (23)	~90	38
CHCl=CClCHBrCH ₂ Br (27)	KOH	MeOH, 20 °C	CHCl=CClCBr=CH ₂ (26)	65.0	39
CH ₂ ClCBrClCHBrCH ₂ Cl (29)	NaOH	80% EtOH, 40–50 °C	CHCl=CClCBr=CH ₂ (26) + + CHCl=CBrCCl=CH ₂ (30) (26 : 30 = 94.5:5.5)	80.0	26
CH ₂ BrCCl=CClCH ₂ Br (32)	KOH	MeOH, 20 °C	CHBr=CClCCl=CH ₂ (31)	54.0	39
CH ₂ ClCHClCBrClCH ₂ Br (34)	NaOH	EtOH	CHBr=CClCCl=CH ₂ (31)	47.0	26
CH ₂ BrCBrClCHBrCH ₂ Br (37)	NaOH	80% EtOH	CHBr=CClCBr=CH ₂ (38) + + CHBr=CBrCCl=CH ₂ (39) (38 : 39 = 93:7)	90.0	26
CH ₂ ClCBr=CBrCH ₂ Cl (41)	KOH	EtOH, 25 °C	CHCl=CBrCBr=CH ₂ (40)	58.0	42
CCl ₃ CH ₂ CBrFCH ₃ (46a)	Bu ₃ N	140 °C, 100 Torr	CCl ₂ =CHCF=CH ₂ (42)	—	43
CBr ₃ CH ₂ CBrFCH ₃ (46b)	Bu ₃ N	the same	CBr ₂ =CHCF=CH ₂ (43)	—	43
CBrF ₂ CCl ₂ CH=CH ₂ (48)	Zn	EtOH	CF ₂ =CClCH=CH ₂ (44)	—	16
CFCl=CFCH ₂ CH ₂ Br (50) (<i>E</i> : <i>Z</i> = 44:56)	KOH	EtOH (KOH:EtOH = = 1:1)	(<i>E</i>)- + (<i>Z</i>)-CFCl=CFCH=CH ₂ (45) (<i>E</i> : <i>Z</i> = 44:56)	80.0	47
CCl ₂ =CClCHBrCH ₂ Br (52)	NaOH	70% EtOH, 20–25 °C	CCl ₂ =CClCBr=CH ₂ (54) + + CCl ₂ =CClCH=CHBr (55) (54 : 55 = 10:1)	93.0	26
CHBrClCHBrCHClCHCl ₂ (57)	KOH	water, TEBA ^a	(<i>Z</i>)- + (<i>E</i>)-CBrCl=CHCH=CCl ₂ (56) (<i>Z</i> : <i>E</i> = 4:1)	60	49
CHBrClCHBrCH=CCl ₂ (58)	KOH	the same	CBrCl=CHCH=CCl ₂ (56)	91.0	50
CBrF ₂ CFCICCl=CH ₂ (59)	Zn	EtOH, boiling	CF ₂ =CFCCl=CH ₂ (61)	43.5	51
CBrF ₂ CFCIClCHClCHCl ₂ (60)	Zn	the same	CF ₂ =CFCH=CHCl (62)	—	51
CH ₂ =CBrCClFCBrF ₂ (64)	Zn	EtOH	CF ₂ =CFCBr=CH ₂ (63)	17.0	3
CCl ₂ =CHCBrClCHBrCl (65)	KOH	EtOH, 25 °C	(<i>Z</i>)- + (<i>E</i>)-CCl ₂ =CHCCl=CBrCl (66) (<i>Z</i> : <i>E</i> = 1:1)	68.0	53
CCl ₂ =CHCBrClCHBrCl (65)	20% NaOH	water, TEBA, ^a 40–45 °C, 4 h	(<i>Z</i>)- + (<i>E</i>)-CCl ₂ =CHCCl=CBrCl (66) (<i>Z</i> : <i>E</i> = 1:3)	85	54
CBr ₂ ClCHBrCH=CCl ₂ (67)	10% NaOH	water, TEBA, ^a 25 °C, 15 h	(<i>E</i>)- + (<i>Z</i>)-CBrCl=CBrCH=CCl ₂ (68) (<i>E</i> : <i>Z</i> = 7:3)	55.0	55
CBrCl ₂ CHBrCH=CBrCl (69)	10% NaOH	the same	(<i>E</i>)- + (<i>Z</i>)-CBrCl=CHCBr=CCl ₂ (70) (<i>E</i> : <i>Z</i> = 3:2)	49	55
CBrF ₂ CFCICCl=CHCl (71)	Zn	EtOH, boiling	CF ₂ =CFCCl=CHCl (73)	19.0	51
CFCl=CHCFCICF ₂ Cl (72)	Zn	Pr ⁿ OH or Pr ⁱ OH, boiling	CFCl=CHCF=CF ₂ (74)	64	56
CFCl ₂ CFCICFCICF ₂ Cl (76)	Zn	EtOH, boiling	CF ₂ =CFCF=CFCl (75)	47.7	10, 12
CFCl ₂ CFCICFCICF ₂ Cl (76) + + CFCl ₂ CFCICFCICF ₂ I (79)	Zn	EtOH	(<i>E</i>)- + (<i>Z</i>)-CF ₂ =CFCF=CFCl (75) (<i>E</i> : <i>Z</i> = 1:1)	73.0	57
CF ₂ ClCFCICCl ₂ CF ₂ Cl	Zn	EtOH	CF ₂ =CFCCl=CF ₂ (81)	—	10
CFCl ₂ CFCICFCICFCl ₂ (77)	Zn	BuOH, 85–95 °C	CFCl=CFCF=CFCl (82)	48.0	60, 61
CFCl ₂ CFCICFCICFCl ₂ (77)	Zn	dioxane, boiling	CFCl=CFCF=CFCl (82) (<i>E</i> , <i>E</i> : <i>E</i> , <i>Z</i> : <i>Z</i> , <i>Z</i> = 1:2.5:1.5)	82.5	62

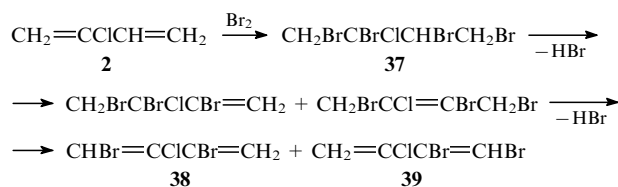
Table 1 (continued).

Starting compound	Elimination agent	Reaction conditions	Halogenobutadiene	Yield (%)	Ref.
CFCl ₂ CFCICFCICF ₂ I (79) + + CFCl ₂ CFCICF ₂ CFCII (89)	Zn	EtOH	CFCl=CFCF=CFCI (82), CF ₂ =CFCF=CFCI (75)	45 41	58
CF ₂ ClCCl ₂ CCl ₂ CF ₂ Cl (93)	Zn	EtOH	CF ₂ =CCICCl=CF ₂ (92)	—	10, 69
CBrCl ₂ CHBrCCl ₂ CHCl ₂ (98)	Et ₂ NH	water, 25 °C	CCl ₂ =CBrCCl=CCl ₂ (99), CBrCl=CBrCCl=CCl ₂ (100)	88.0 10.0	70
(<i>E</i>)-CBrCl=CClCHBrCBrCl ₂ (101)	KOH	20% KOH, TEBA ^a	(<i>E</i>)-CBrCl=CClCBr=CCl ₂ (102) (<i>E,E</i>)- + (<i>E,Z</i>)-CBrCl=CClCBr=CBrCl (103) (<i>E,E</i> : <i>E,Z</i> = 2:3)	60 16	71

^a Triethylbenzylammonium chloride.

1,1-Dibromo-3-chlorobuta-1,3-diene (**36**) is obtained as an insignificant admixture in the synthesis of 1,1,3-tribromobuta-1,3-diene.⁴⁰

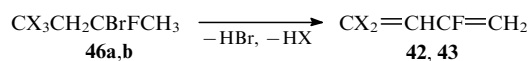
Upon dehydrobromination of 1,2,3,4-tetrabromo-2-chlorobutane (**37**) [the product of exhaustive bromination of chloroprene (**2**)], 1,3-dibromo-2-chlorobuta-1,3-diene (**38**) is mainly formed. In addition, a small amount of 1,2-dibromo-3-chlorobuta-1,3-diene (**39**) was detected by GLC.²⁶



2,3-Dibromo-1-chlorobuta-1,3-diene (**40**) was obtained by dehydrochlorination of 2,3-dibromo-1,4-dichlorobut-2-ene (**41**)⁴¹ (see Table 1).

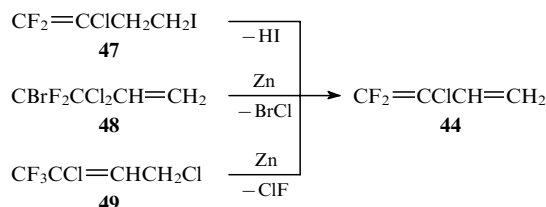
As regards the fluorine-containing trihalogeno derivatives of MHB, 1,1-dichloro-3-fluoro- (**42**), 1,1-dibromo-3-fluoro- (**43**), 2-chloro-1,1-difluoro- (**44**) and 1-chloro-1,2-difluorobuta-1,3-dienes (**45**) were obtained.

The synthesis of the dienes **42** and **43** is based on dehydrohalogenation of 3-bromo-3-fluoro-1,1,1-trihalogenobutanes (**46a,b**).⁴²

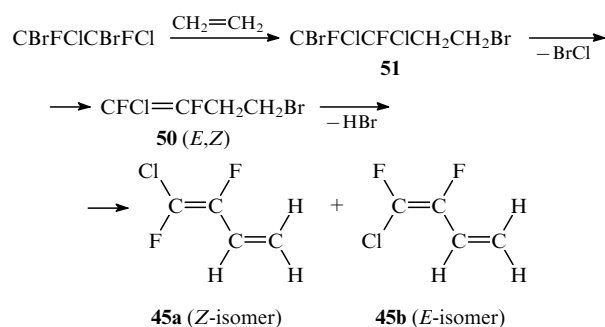


X = Cl (**42**, **46a**), Br (**43**, **46b**).

The butadiene **44** was first synthesised from 2-chloro-1,2-difluoro-4-iodobut-1-ene (**47**)⁴³ and later from 1-bromo-1,1-difluoro-2,2-dichloro-2-chlorobut-3-ene (**48**)¹⁶ and 2,4-dichloro-1,1,1-trifluorobut-2-ene (**49**).⁴⁴



The butadiene **45** is formed as a mixture of *E*- and *Z*-isomers upon dehydrobromination of the isomeric forms of 4-bromo-1-chloro-1,2-difluorobut-1-ene (**50**) obtained by dehalogenation of 1,4-dibromo-1,2-dichloro-1,2-difluorobutane (**51**), which is the product of telomerisation of CBrFCICBrFCl with ethylene under the action of benzoyl peroxide. It was shown that the starting butene **50** and the target diene **45** have the same ratio of isomers, *i.e.*, the elimination reaction occurs stereospecifically.⁴⁵

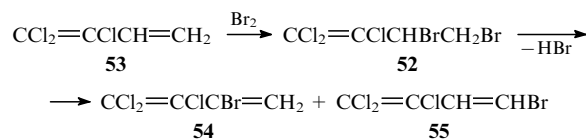


1,1,3-Trihalogenobutadienes are convenient subjects for the elucidation of characteristic features of conformational behaviour. The use of ¹H NMR and UV spectroscopy made it possible to establish that the bulky substituents (Cl, Br) in the 1,3 (or 2,4) positions of the diene chain destabilise the *s-trans*-form, which is characteristic of haloprenes and disubstituted butadienes, hence the 1,1,3-trihalogenobuta-1,3-dienes **23** and **36** exist in a skew conformation in the form of a single conformer.^{40, 46}

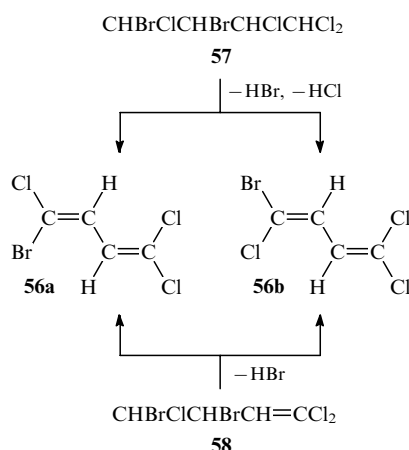
According to the ¹H NMR and IR spectroscopic data, the dienes **42** and **43** having a fluorine atom in the position 3 exist as a mixture of two conformers, *viz.*, the skew and *s-trans*-forms.^{42, 47}

c. Tetrahalogenobutadienes

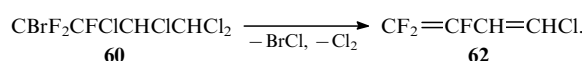
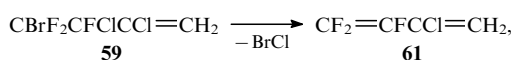
Several examples of the synthesis of tetrasubstituted MHB based on the elimination reaction are given below. Dehydrobromination of 3,4-dibromo-1,1,2-trichlorobut-1-ene (**52**), which is the product of bromine addition to the accessible 1,1,2-trichlorobuta-1,3-diene (**53**),⁴⁸ affords a mixture of 3- (**54**, the main product) and 4-bromo-1,1,2-trichlorobuta-1,3-dienes (**55**, the by-product).²⁶



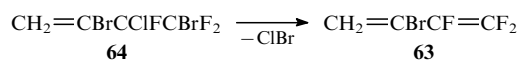
Two convenient methods have been developed for the synthesis of 1-bromo-1,4,4-trichlorobuta-1,3-diene (**56**). The first method consists in dehydrohalogenation of 1,2-dibromo-1,3,4,4-tetrachlorobutanes (**57**) in the presence of PTC. It was shown that the reaction product is a mixture of geometric isomers with the predominance of the *Z*-form.⁴⁹ The second method of the synthesis of the diene **56** is based on dehydrobromination of 3,4-dibromo-1,1,4-trichlorobut-1-ene (**58**) under the conditions of phase-transfer catalysis in the presence of triethylbenzylammonium chloride (TEBA).⁵⁰



Information about tetra(chloro, fluoro) MHB can be found only in the patent literature. Thus dehalogenation of 4-bromo-2,3-dichloro-3,4,4-trifluorobut-1-ene (**59**) and 1-bromo-2,3,4,4-tetrachloro-1,1,2-trifluorobutane (**60**) result in 3-chloro-1,1,2-trifluoro- (**61**) and 4-chloro-1,1,2-trifluorobuta-1,3-dienes (**62**), respectively.⁵¹

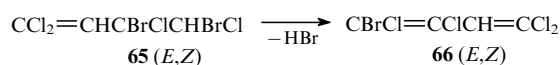


There is only one known representative of the bromine-containing tetrahalogenobutadienes, *viz.*, 3-bromo-1,1,2-trifluorobuta-1,3-diene (**63**), which was obtained in high yield by dehalogenation of 2,4-dibromo-3-chloro-3,4,4-trifluorobut-1-ene (**64**) (see Table 1).³

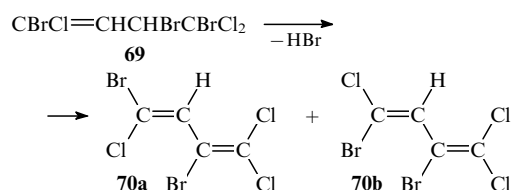
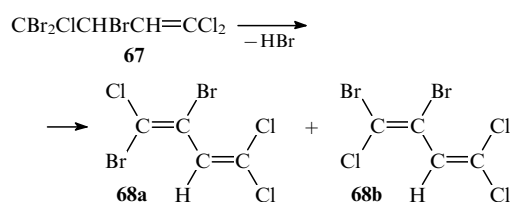


d. Pentahalogenobutadienes

Some pentasubstituted chlorobromo and chlorofluoro derivatives of butadiene can be obtained by an elimination reaction. Thus dehydrobromination of 3,4-dibromo-1,1,3,4-tetrachlorobut-1-ene (**65**) (the product of bromine addition to the *Z*- or *E*-isomers of 1,1,3,4-tetrachloro-1,3-butadiene) affords a mixture of geometric isomers of 1-bromo-1,2,4,4-tetrachlorobuta-1,3-diene (**66**), the yield of which depends to a considerable extent on the reaction conditions (see Table 1).^{52–54}



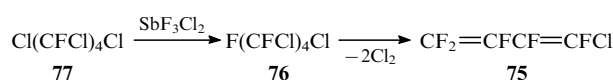
Dehydrobromination of 3,4,4-tribromo-1,1,4-trichlorobut-1-ene (**67**) in the presence of PTC leads to a mixture of *E*- and *Z*-isomers of 1,2-dibromo-1,4,4-trichlorobuta-1,3-diene (**68a,b**). Similarly, a mixture of *E*- and *Z*-isomers of 2,4-dibromo-1,1,4-trichlorobuta-1,3-diene (**70a,b**)⁵⁵ was obtained from 1,3,4-tribromo-1,4,4-trichlorobut-1-ene (**69**).



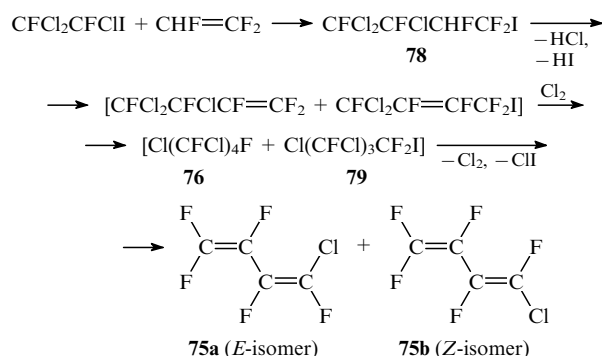
Dehalogenation of 4-bromo-1,2,3-trichloro-3,4,4-trifluoro- (**71**) and 1,3,4-trichloro-1,3,4,4-tetrafluorobut-1-ene (**72**) (see Table 1) yielded 3,4-dichloro-1,1,2-trifluorobuta-1,3-diene (**73**) and 4-chloro-1,1,2,4-tetrafluorobuta-1,3-diene (**74**),⁵⁶ respectively.

e. Hexahalogenobutadienes

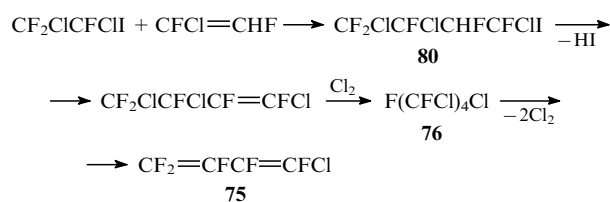
The synthesis of hexasubstituted MHB is documented; in particular, the methods for the preparation of some chlorine, fluorine-containing representatives are well developed. Thus 4-chloro-1,1,2,3,4-pentafluorobuta-1,3-diene (**75**) was first obtained by dehalogenation of 1,2,3,4,4-pentachloro-1,1,2,3,4-pentafluorobutane (**76**), which is the reaction product of 1,1,2,3,4,4-hexachloro-1,2,3,4-tetrafluorobutane (**77**) with a slight excess of SbF_3Cl_2 .^{10, 12}



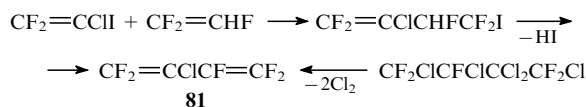
Later,^{57, 58} two new methods for the synthesis of the diene **75** have been proposed. The first method is based on the transformation of a 1 : 1 mixture of *erythro*- and *threo*-forms of 3,4,4-trichloro-1,1,2,3,4-pentafluoro-1-iodobutane (**78**), which is the product of free-radical addition of 1,2,2-trichloro-1,2-difluoro-1-iodoethane to trifluoroethylene (GLC). Dehydrohalogenation of this product and subsequent chlorination of intermediate polyhalogenobutenes yield a mixture of polyhalogenobutenes (**76** and **79**). Dehalogenation of these compounds gives high yield of the diene **75** as a mixture of *E*- and *Z*-isomers.⁵⁷



Another way to the synthesis of the diene **75** is based on the transformation of 1,3,4-trichloro-1,2,3,4,4-pentafluoro-1-iodobutane (**80**), which is the reaction product of 1,2-dichloro-1,2,2-trifluoro-1-iodoethane with 1-chloro-1,2-difluoroethylene.⁵⁸ Successive dehydroiodination, chlorination and dechlorination of polyhalogenobutane (**80**) yields the diene **75**.

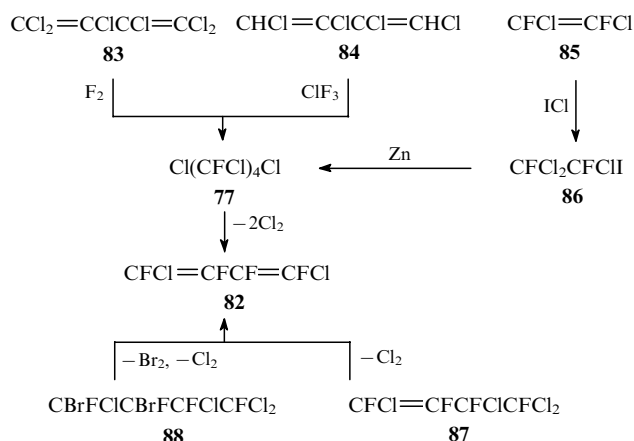


The synthesis of 3-chloro-1,1,2,4,4-pentafluorobuta-1,3-diene (**81**) is also based on elimination reactions.^{10, 43}



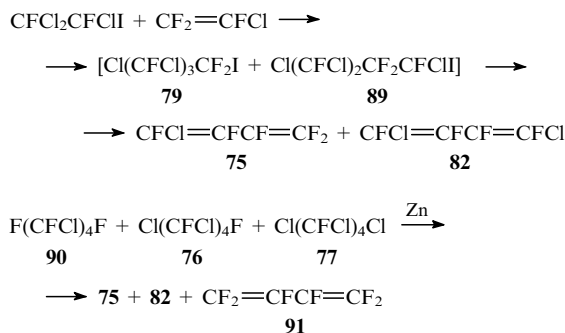
The synthesis of 1,4-dichloro-1,2,3,4-tetrafluorobuta-1,3-diene (**82**) has attracted much attention. The diene **82** was obtained for the first time by dechlorination of perhalogenobutane **77**,⁵⁹ which in turn was synthesised by fluorination of hexachlorobuta-1,3-diene (**83**),⁶⁰ the reaction of 1,2,3,4-tetrachlorobuta-1,3-diene (**84**) with ClF_3 (see Ref. 61) or chloriodination of 1,2-dichloro-1,2-difluoroethylene (**85**) with subsequent heating of the resulting 1,2,2-trichloro-1,2-difluoro-1-iodoethane (**86**) with acetic anhydride, dichloromethane and granulated zinc at 160 °C (Scheme 1).

Scheme 1

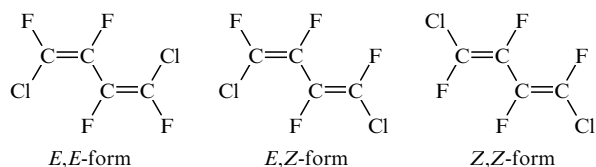


Yet another method for the synthesis of the diene **82** is based on dechlorination of 1,3,4,4-tetrachloro-1,2,3,4-tetrafluorobut-1-ene (**87**), which is the product of thermal dimerisation of the ethylene **85**.^{63,64} The diene **82** is formed in preparative yield upon treatment of 1,2-dibromo-1,3,4,4-tetrachloro-1,2,3,4-tetrafluorobutane (**88**), which is the product of bromine addition to the butene **87**,⁶⁴ with zinc in dioxane (Scheme 1).

And, finally, there are data on the synthesis of diene **82** based on transformations of a mixture of perhalogenobutanes.⁵⁸ Thus dehalogenation of a mixture of telomers $\text{Cl}(\text{CFCl})_3\text{CF}_2\text{I}$ (**79**) and $\text{Cl}(\text{CFCl})_2\text{CF}_2\text{CFCII}$ (**89**) or $\text{F}(\text{CFCl})_4\text{F}$ (**90**), $\text{Cl}(\text{CFCl})_4\text{F}$ (**76**) and $\text{Cl}(\text{CFCl})_4\text{Cl}$ (**77**) affords a 1 : 1 mixture of the dienes **75** and **82** (in the ratio 1 : 1) in the former case or a mixture of dienes **75**, **82** and hexafluorobuta-1,3-diene in the latter case.

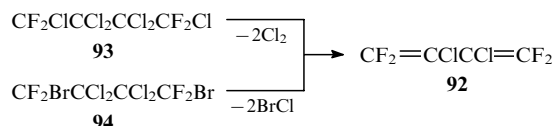


Theoretically, the diene **82** can exist in the form of three geometric isomers.

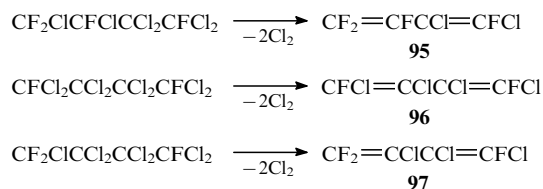


Indeed, as was shown by Kremlev *et al.*,⁶² the diene **82** is an equilibrium mixture of *E,E*-, *E,Z*- and *Z,Z*-isomers in the ratio of 1 : 2.5 : 1.5. The ^{19}F NMR (Ref. 65) and UV (Ref. 21) spectral data and the values of dipole moments⁶⁶ make it possible to conclude that the isomers are in the non-planar *s-cis*-conformation similarly to hexachloro- (**83**)⁶⁷ and hexafluorobutadienes (**91**).⁶⁸

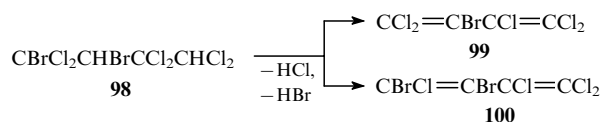
Two methods for the synthesis of 2,3-dichloro-1,1,4,4-tetrafluorobuta-1,3-diene (**92**) are known, *viz.*, dehalogenation of 1,2,2,3,3,4-hexachloro-1,1,4,4-tetrafluorobutane (**93**)¹⁰ and 1,4-dibromo-2,2,3,3-tetrachloro-1,1,4,4-tetrafluorobutane (**94**).^{60,69}



Some other difficultly accessible MHB, *viz.*, 3,4-dichloro-1,1,2,4-tetrafluoro- (**95**), 1,2,3,4-tetrachloro-1,4-difluoro- (**96**) and 2,3,4-trichloro-1,1,4-trifluorobuta-1,3-dienes (**97**), were obtained similarly.^{10,60}

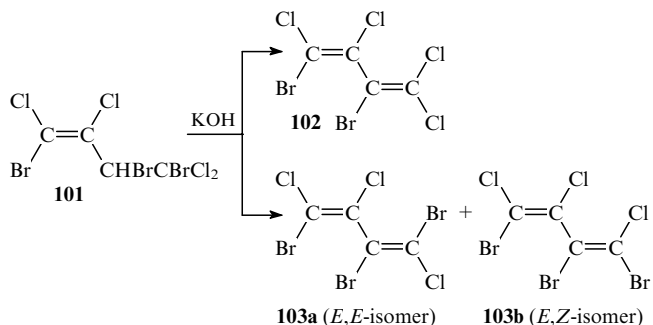


Bromine–chlorine-containing hexahalogenobutadienes were synthesised by an elimination reaction by the authors of this review. Thus dehydrohalogenation of 1,2-dibromo-1,1,3,3,4,4-hexachlorobutane (**98**) with aqueous-ethanolic solutions of alkalis yields two MHB, *viz.*, 2-bromo-1,1,3,4,4-pentachloro- (**99**) and 1,2-dibromo-1,3,4,4-tetrachlorobuta-1,3-diene (**100**), in the ratio of 2 : 1.



The use of an aqueous solution of diethylamine shifted the reaction towards the predominant formation of the diene **99**.⁷⁰

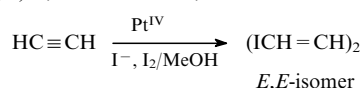
Dehydrohalogenation of (*E*)-1,3,4-tribromo-1,2,4,4-tetrachlorobut-1-ene (**101**) under the conditions of phase-transfer catalysis yielded (*E*)-1,3-dibromo-1,2,4,4-tetrachloro- (**102**) and 1,3,4-tribromo-1,2,4-trichlorobuta-1,3-dienes (**103**) as a mixture of two geometric isomers. Since the β -bromo- α,β -dichlorovinyl group of the butene (**101**) having the *E*-configuration is not directly involved in the reaction, the formation of the two isomeric forms of the diene **103** occurs due to the *E,Z*-isomerisation of the α,β -dibromo- β -chlorovinyl group in the molecule. Consequently, the diene **103** is a mixture of *E,E*- (**103a**) and *E,Z*-isomers (**103b**).⁷¹



2. Halogenation and hydrohalogenation of the acetylenic hydrocarbons of the C₄ series

Acetylenic hydrocarbons, mainly conjugated halogenobutenynes and dihalogenobutadiynes, have served as the starting compounds for the synthesis of the first representatives of MHB.² The syntheses based on acetylene derivatives have not found wide uses because of their poor accessibility and explosiveness. Nonetheless, nowadays procedures for the preparative synthesis of a number of di-, tri- and hexasubstituted MHB have been developed.

It is also noteworthy that a new catalytic reaction of acetylene dimerisation has been recently discovered. This is carried out in methanolic solution of NaI in the presence of Pt(IV); it is accompanied by the addition of an iodine molecule and results in (*E,E*)-1,4-diodobuta-1,3-diene.⁷²



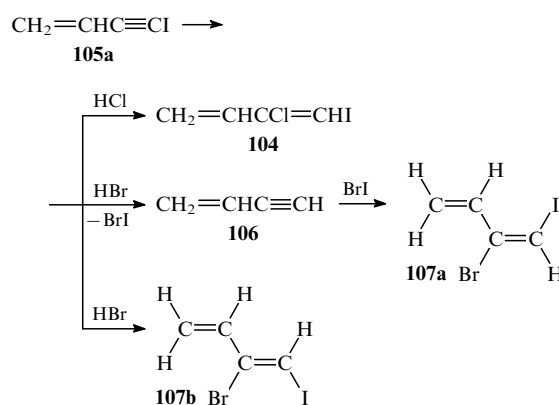
This reaction seems to be promising for the synthesis of certain MHB.

The currently used procedures for the synthesis of MHB by the addition of halogens and hydrogen halides to the carbon–carbon triple bond imply the use of the existing C₄ carbon chain.

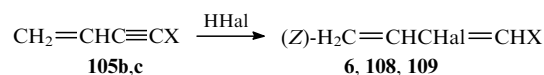
a. Dihalogenobutadienes

The first representative of the dihalogenobutadienes, *viz.*, 2-chloro-1-iodobuta-1,3-diene (**104**), was prepared by hydrochlorination of 4-iodobut-1-en-3-yne (**105a**) in the presence of catalysts CuCl + NH₄Cl.⁷³

In the reaction of this butenyne (**105a**) with HBr, the predominant direction is the reductive elimination of the iodine atom at the triple bond with the formation of vinylacetylene (**106**). Among the reaction products, a considerable amount of (*E*)-2-bromo-1-iodobuta-1,3-diene (**107a**) was also found as the addition product of BrI to the enyne (**106**). The yield of (*Z*)-2-bromo-1-iodobuta-1,3-diene (**107b**), which is the addition product of HBr to the initial butenyne **105a**, is insignificant.⁷⁴



The addition of hydrogen halides to the conjugated enynes with a halogen atom at the triple bond in the presence of copper(I) halides is widely used for the synthesis of MHB.⁷⁴ It was established that 4-halogenobut-1-en-3-yne (**105b,c**) add HBr and HI at the triple C≡C bond giving the corresponding dihalogenobutadienes. Thus hydrobromination of 4-chlorobut-1-en-3-yne **105b** proceeds stereospecifically with the formation of the *Z*-form of 2-bromo-1-chlorobuta-1,3-diene (**6b**) in high yield. The reaction of hydroiodination of chloro- (**105b**) and bromo-substituted (**105c**) enynes proceeds similarly and results in the formation of (*Z*)-1-chloro- and 1-bromo-2-iodobuta-1,3-dienes (**108** and **109**), respectively (Table 2).



6: X = Cl, Hal = Br; **108:** X = Cl, Hal = I; **109:** X = Br, Hal = I.

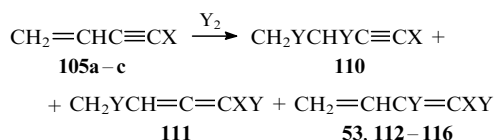
The addition of mixed halogens (CII and BrI) to the conjugated butenyne **106** was studied.^{74,75} It turned out that the 1,4-addition of halogens occurred predominantly. Only with the use of a large excess of enyne and in the presence of CuCl were the 1,2-addition products, *viz.*, the dienes **104** and **107** in the form of *E*-isomers, obtained.^{74,75}

Table 2. Synthesis of mixed halogenobutadienes based on acetylene derivatives.

Starting compound	Electrophilic agent (Hal ₂ or HHal)	Reaction conditions	Halogenosubstituted butadiene	Yield (%)	Ref.
CH ₂ =CHC≡CI (105a)	HCl	CuCl + NH ₄ Cl	CH ₂ =CHCCl=CHI (104)	—	73
CH ₂ =CHC≡CCI (105b)	HBr	CuBr	(<i>Z</i>)-CHCl=CBrCH=CH ₂ (6b)	95	74, 75
CH ₂ =CHC≡CCl (105b)	HI	CuI	(<i>Z</i>)-CHCl=CICH=CH ₂ (108)	45.2	74, 75
CH ₂ =CHC≡CBr (105c)	HI	CuI	(<i>Z</i>)-CHBr=CICH=CH ₂ (109)	70.8	74, 75
CH ₂ =CHC≡CI (105a)	HBr	CuBr	(<i>E</i>)- + (<i>Z</i>)-CHI=CBrCH=CH ₂ (107)	41.5	74, 75
CH ₂ =CHC≡CI (105a)	Cl ₂	−40 °C, CHCl ₃	CH ₂ =CHCCl=CCl (112)	9.7	74
CH ₂ =CHC≡CI (105a)	Br ₂	the same	CH ₂ =CHCBr=CBrI (113)	14.2	74
CH ₂ =CHC≡CCI (105b)	Br ₂	"	CH ₂ =CHCBr=CBrCl (114)	7.3	74
CH ₂ =CHC≡CBr (105c)	Cl ₂	"	CH ₂ =CHCCl=CBrCl (115)	8.5	74
CH ₂ ClC≡CCH ₂ Cl (117)	Br ₂ , 1,8-diazabicyclo-[5.4.0]undec-7-ene	CCl ₄	(<i>Z</i>)-CHCl=CBrCBr=CH ₂ (40)	91	76
CH ₂ ClC≡CCH ₂ Cl (117)	I ₂ , 1,8-diazabicyclo-[5.4.0]undec-7-ene	CH ₂ ClCH ₂ Cl	(<i>Z</i>)-CHCl=CICl=CH ₂ (118)	71	76
CH≡CC≡CH	CII	EtCl, −50 °C	CHI=CCICCl=CHI (119) (<i>Z,Z</i> + <i>Z,E</i> + <i>E,E</i>)	84.0	78
CHCl=CClC≡CH	CuBr ₂	MeOH, 1 h	CHCl=CClCBr=CBr ₂ (120)	50.0	79
CCl≡CC≡CCl (121a)	Br ₂	CCl ₄ , 25–60 °C	CBrCl=CBrCBr=CBrCl (122)	~98	11
CCl≡CC≡CCl (121a)	I ₂	CHCl ₃	CICl=CICl=CICl (123)	—	80, 81
CBr≡CC≡CBr (121b)	I ₂	CHCl ₃	CBrI=CICl=CBrI (125)	—	80, 81
CI≡CC≡CI (121c)	Br ₂	CHCl ₃	CBrI=CBrCBr=CBrI (126)	—	80, 81
CCl ₂ =CClC≡CCl (128)	Br ₂	CCl ₄	CCl ₂ =CClCBr=CBrCl (100)	84.0	42
CCl ₂ =CClC≡CBr	Br ₂	CCl ₄	CCl ₂ =CClCBr=CBr ₂ (130)	—	42
CCl ₂ =CClC≡CI	I ₂	dry ether	CCl ₂ =CClCI=CI ₂ (131)	—	42

b. Trihalogenobutadienes

An attempt to obtain mixed trihalogenobutadienes by the addition of halogens to the triple bond of enynes **105a–c** did not give satisfactory results.^{74,75} The reaction of chlorine and bromine with these enynes proceeded mainly as the addition of halogens to the double bond and the 1,4-addition of enynes with the formation of butynes **110** and allenes **111**, respectively. The addition of one mole of a halogen to the triple bond of enynes, which would lead to the corresponding trihalogenobuta-1,3-dienes, is less preferable, the yields of products **53**, **112–116** are low.^{74,75}

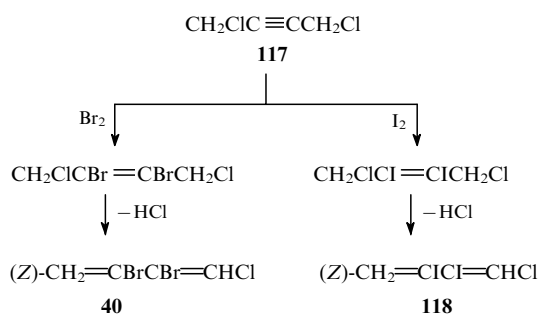


X = I; Y = Cl (**112**), Br (**113**);

X = Y = Cl (**53**); X = Cl, Y = Br (**114**);

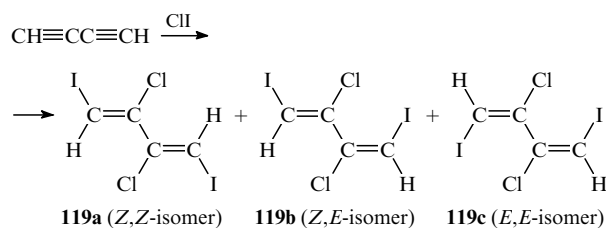
X = Br, Y = Cl (**115**); X = Y = Br (**116**).

The addition of bromine or iodine to 1,4-dichlorobut-2-yne (**117**) yielded the corresponding halogeno-substituted butenes, which gave (*Z*)-2,3-dibromo-1-chloro- (**40**) and (*Z*)-1-chloro-2,3-diiodobuta-1,3-dienes (**118**) upon catalytic 1,4-dehydrochlorination.^{76,77}



c. Tetra- and pentahalogenobutadienes

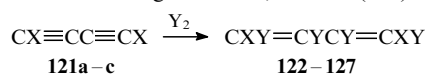
The synthesis of tetra- and pentasubstituted buta-1,3-dienes is demonstrated in separate examples. 2,3-Dichloro-1,4-diiodobuta-1,3-diene (**119**) was obtained as a mixture of *Z,Z*-, *Z,E*- and *E,E*-isomers by the reaction of diacetylene with chloriodine.⁷⁸



The reaction of copper(II) bromide with 1,2-dichlorobut-1-en-3-yne gives 1,1,2-tribromo-3,4-dichlorobuta-1,3-diene (**120**) (see Table 2).⁷⁹

d. Mixed perhalogenobutadienes

In 1930, difficultly accessible perhalogenobutadienes (**122–127**), including first representatives of MHB, were obtained by halogenation of dihalogenobuta-1,3-dienes (**121**).^{80,81}



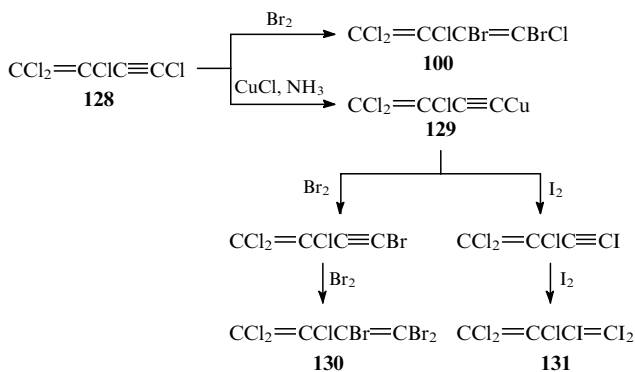
X = Cl (**a**), Br (**b**), I (**c**); Y = Br, I.

Compound	122	123	124	125	126	127
X	Cl	Cl	Br	Br	I	I
Y	Br	I	Br	I	Br	I

According to the patent data,¹¹ 1,4-dichloro-1,2,3,4-tetrabromobuta-1,3-diene (**122**) is formed in quantitative yield upon bromination of dichlorobuta-1,3-diene (**121a**).

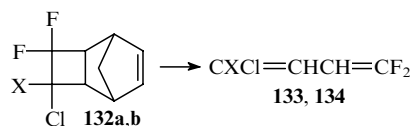
Synthesis of some mixed perhalogenobutadienes was carried out based on the accessible perchlorobutenyne (**128**).⁴² Thus direct bromination of the enyne **128** gave 1,3,4,4-tetrachloro-1,2-dibromobuta-1,3-diene (**100**) in high yield, whereas the synthesis of 1,1,2-tribromo- (**130**) and 3,4,4-trichloro-1,1,2-triiodobuta-1,3-dienes (**131**) was carried out using copper trichlorovinyl acetylide **129** (Scheme 2).⁴²

Scheme 2



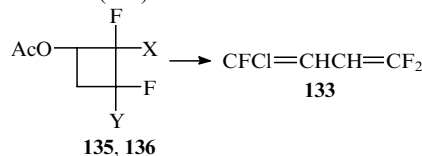
3. Synthesis of mixed halogenobutadienes by pyrolysis of polyhalogenated compounds

A number of preparative methods for obtaining MHB containing from four to six halogen atoms in the molecule are based on the pyrolysis of cyclic halogen-containing compounds. Thus the passage of 4-chloro-3,3,4-trifluoro- (**132a**) or 4,4-dichloro-3,3-difluoro-tricyclo[4.2.1.0^{2,5}]non-7-enes (**132b**) through a red-hot tube filled with rings of quartz glass yielded 4-chloro-1,1,4-trifluoro- (**133**) and 4,4-dichloro-1,1-difluorobuta-1,3-dienes (**134**), respectively.⁸²



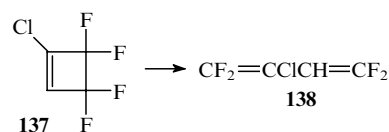
X = F (**132a**, **133**); X = Cl (**132b**, **134**).

A more convenient method for the preparation of the diene **133** is based on the pyrolysis of 1-acetoxy-2-chloro-2,3,3-trifluorocyclobutane (**135**) or 1-acetoxy-3-chloro-2,2,3-trifluorocyclobutane (**136**).⁸³



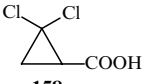
135: X = Cl, Y = F; **136**: X = F, Y = Cl.

Many MHB were obtained by the pyrolysis of the corresponding halogeno-substituted cyclobutenes. Thus the pyrolysis of 1-chloro-3,3,4,4-tetrafluorocyclobut-1-ene (**137**) gives 2-chloro-1,1,4,4-tetrafluorobuta-1,3-diene (**138**) in preparative yield (Table 3).^{13,83}



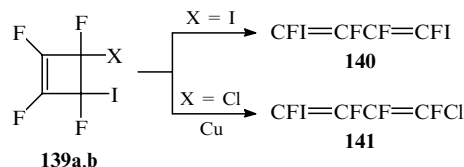
The main pyrolysis products of 1,2,3,4-tetrafluoro-3,4-diiodo- and 4-chloro-1,2,3,4-tetrafluoro-3-iodocyclobutenes (**139a,b**) are 1,2,3,4-tetrafluoro-1,4-diiodobuta-1,3-diene (**140**), formed as a

Table 3. Miscellaneous methods for the preparation of mixed halogenobutadienes.

Starting compound	Method of preparation ^a	Reaction conditions	Halogeno-substituted butadiene	Yield (%)	Ref.
132a (see ^b)	A	700 °C (1 Torr)	CFCI=CHCH=CF ₂ (133)	—	82
132b (see ^b)	A	700 °C (1 Torr)	CCl ₂ =CHCH=CF ₂ (134)	—	82
136 (see ^b)	A	700 °C (10 Torr)	CFCI=CHCH=CF ₂ (133)	56.0	83
137 (see ^b)	A	700 °C (1 Torr)	CF ₂ =CCICH=CF ₂ (138)	38.0	83
139a	A	580 °C (0.1 Torr)	CFI=CFCF=CFI (140) (<i>E,E</i> : <i>E,Z</i> : <i>Z,Z</i> = 21:16:8)	37.0	84
139b	A	Cu, 180–190 °C	CFI=CFCF=CFCl (141)	—	84
CFCl ₂ SO _n CH ₂ CH=CH ₂ (<i>n</i> = 1, 2)	A	heating	CFCI=CHCH=CH ₂ (17)	—	85
CHCl=CFCF ₂ CF ₂ COONa (142)	A	heating with a burner (1 Torr)	(<i>Z</i>)-CF ₂ =CFCF=CHCl (143)	82.0	86
CCl ₂ =CHCHO (145)	B	Ph ₃ P=CBr ₂ , CH ₂ Cl ₂ , 0 °C	CCl ₂ =CHCH=CBr ₂ (149)	76.0	88, 89
CCl ₂ =CClCHO (146)	B	the same	CCl ₂ =CCICH=CBr ₂ (150)	62.0	88, 89
CCl ₂ =CBrCHO (147)	B	"	CCl ₂ =CBrCH=CBr ₂ (151)	57.0	88, 89
Cl ₂ =CClCHO (148)	B	"	Cl ₂ =CCICH=CBr ₂ (152)	44.0	88, 89
CCl ₂ =CClCHO (146)	B	Ph ₃ P=CHCOOEt, Br ₂	(<i>Z</i>)-CHBr=CHCCl=CCl ₂ (55)	82.0	89
CCl ₂ =CBrCHO (147)	B	CCl ₂ =C=O, dry ether	CCl ₂ =CBrCH=CCl ₂ (154)	63.0	42
CBr ₂ =CClCHO (153)	B	the same	CBr ₂ =CCICH=CCl ₂ (155)	55.0	42
CHCl=CCICCl=CClLi	C	I ₂ , FeCl ₃ , ether, –110 °C	CHCl=CCICCl=CClI (157)	60.0	90
	C	SF ₄ , 140 °C	CF ₂ =CHCH=CCl ₂ (134)	—	91
CFCl=CFI	C	Cu, 145 °C	CFCI=CFCF=CFCl (82) (<i>E,E</i> : <i>E,Z</i> : <i>Z,Z</i> = 19:51:30)	49.0	92, 93

^a A is pyrolysis; B is synthesis of MHB from polyhalogenoacroleins; C is other methods. ^b The starting compounds were obtained by the [2 + 2]-cycloaddition reaction.

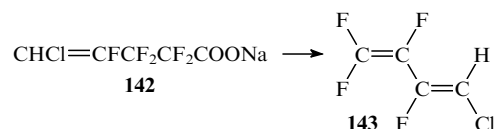
mixture of *E,E*-, *E,Z*- and *Z,Z*-isomers, and 4-chloro-1,2,3,4-tetrafluoro-1-iodobuta-1,3-diene (**141**), respectively.⁸⁴



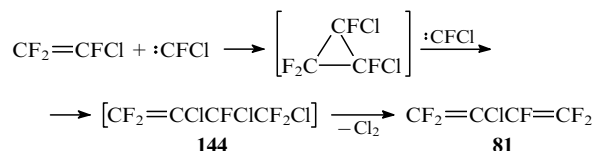
X = I (**139a**), Cl (**139b**).

Mixed halogenobutadienes are also formed by the pyrolysis of some aliphatic compounds. Thus heating of sulfoxide CFCl₂SOCH₂CH=CH₂ or sulfone CFCl₂SO₂CH₂CH=CH₂ yielded 1-chloro-1-fluorobuta-1,3-diene as one of the reaction products (**17**).⁸⁵

Decarboxylation of sodium 5-chloro-2,2,3,3,4-pentafluoropent-4-enoate (**142**) *in vacuo* gives high yield of (*Z*)-4-chloro-1,1,2,3-tetrafluorobuta-1,3-diene (**143**).⁸⁶

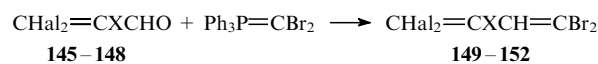


The butadiene **81** is present among the pyrolysis products of chlorofluoroethylene. Presumably, this results from thermal dechlorination of butene **144**, which appears in the reaction due to the addition of chlorofluorocarbene to the initial chlorotrifluoroethylene.



4. Synthesis of mixed halogenobutadienes based on polyhalogenoacroleins

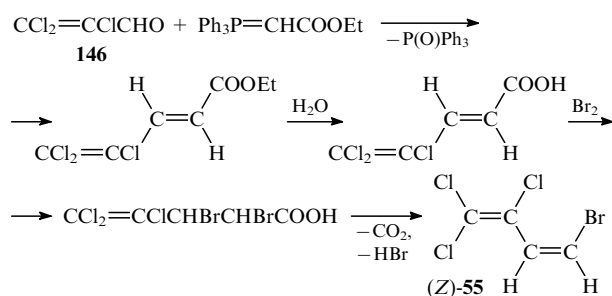
An original way of the preparation of some bromine, chlorine-containing MHB is based on the reaction of polyhalogenoacroleins **145–148** with dibromomethylenetriphenylphosphorane.^{88, 89}



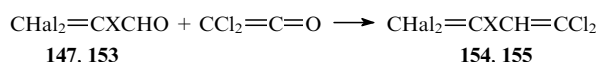
Hal = Cl: X = H (**145**, **149**), Cl (**146**, **150**), Br (**147**, **151**);
Hal = I: X = Cl (**148**, **152**).

The first representative of MHB containing three different halogen atoms, *viz.*, 4,4-dibromo-2-chloro-1,1-diiodobuta-1,3-diene (**152**) was obtained in 1970 by the reaction of α -chloro- β,β -diiodoacrolein (**148**) with Ph₃P=CBr₂.^{88, 89}

A method of preparation of (*Z*)-4-bromo-1,1,2-trichlorobuta-1,3-diene (**55**) from the acrolein **146** and phosphorylide Ph₃P=CHCOOEt has been developed.⁸⁹

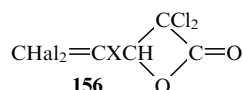


Yet another method of the synthesis of MHB is based on the reaction of halogenoacroleins with dichloro ketene. Starting from the acrolein **147** and β,β -dibromo- α -chloroacrolein (**153**), 2-bromo-1,1,4,4-tetrachloro- (**154**) and 1,1-dibromo-2,4,4-trichloro-buta-1,3-dienes (**155**) were obtained, respectively.⁴²



147, 154: Hal = Cl, X = Br; **153, 155:** Hal = Br, X = Cl.

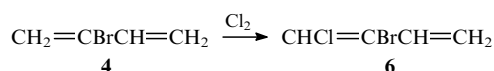
This reaction is supposed to proceed through the initial formation of a lactone **156**, which is easily decarboxylated with the formation of the target products **154** and **155**.



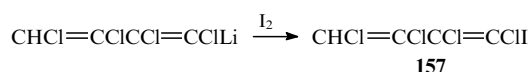
The yields of the dienes **55**, **149–152**, **154**, **155** and conditions of their synthesis are listed in Table 3.

5. Miscellaneous reactions for the preparation of mixed halogenobutadienes

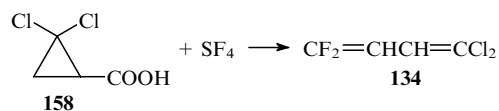
It was shown²⁸ that chlorination of bromoprene (**4**) yields, along with different addition products, also 2-bromo-1-chlorobuta-1,3-diene (**6**) as a mixture of *Z*- and *E*-isomers.



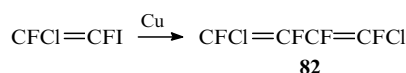
The reaction of lithium 1,2,3,4-tetrachlorobuta-1,3-dien-1-ide with iodine yielded 1,2,3,4-tetrachlorobuta-1-iodo-1,3-diene (**157**).⁹⁰



The synthesis of 1,1-dichloro-4,4-difluorobuta-1,3-diene (**134**) in low yield by the reaction of sulfur tetrafluoride with 2,2-dichlorocyclopropanecarboxylic acid (**158**) has been reported.⁹¹



A convenient method for the preparation of 1,4-dichloro-1,2,3,4-tetrafluorobuta-1,3-diene (**82**) is the reductive dimerisation of a mixture of *Z*- and *E*-isomers of 2-chloro-1,2-difluoro-1-iodoethylene in the presence of a copper powder.^{92,93} The diene **82** is formed as a mixture of *E,E*-, *E,Z*- and *Z,Z*-isomers in approximately the same ratio as reported elsewhere⁶² (see Table 3).



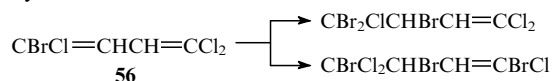
Unfortunately, the attempt to extend this reaction for the synthesis of other MHB has been unsuccessful because of inaccessibility of iodine-containing halogenoethylenes.

III. Chemical properties of mixed halogenobuta-1,3-dienes

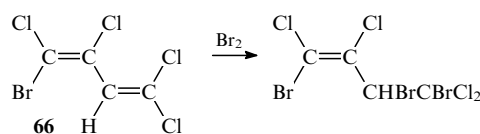
1. Addition reactions. Halogenation of mixed halogenobutadienes

Despite the fact that MHB possess electrophilic properties, they add, like other diene compounds with conjugated double bonds, halogens to both the terminal positions of the diene system (1,4-addition) and to one of the double bonds (1,2- or 3,4-addition). The direction of this reaction is determined to a considerable extent by the nature of MHB and the halogenation agent; experimental conditions are also highly important. The 1,4-addition is characteristic of the dienes having a small number of bulky substituents (Cl, Br or I) and low asymmetry. In the MHB with a high extent of substitution with bulky substituents, the π,π -conjugation is disturbed so that these dienes react as alkenes. Sometimes, an exhaustive halogenation takes place at both C=C bonds and results in the formation of polyhalogenobutanes.

It was shown that the bromination of a mixture of *E*- and *Z*-isomers of 1-bromo-1,4,4-trichlorobutadienes (**56**) (*E*:*Z* ratio = 1 : 4) occurs at the 1,2- and 3,4-positions and results in a mixture of two products, viz., 3,4,4-tribromo-1,1,4-trichloro- and 1,3,4-tribromo-1,4,4-trichlorobut-1-enes in the ratio 70 : 30 with a total yield of 76 %.^{55,94}

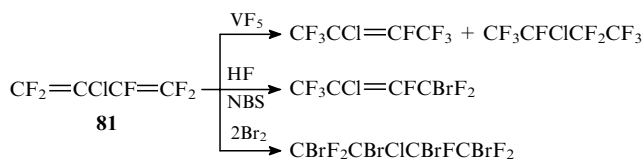


Bromination of the *E*-isomer of the diene **66** (45–50 °C, illumination with an incandescent 60 W lamp, 8 h) occurs exclusively at the β,β -dichlorovinyl group and results in (*E*)-1,3,4-tribromo-1,2,4,4-tetrachlorobut-1-ene in a yield of 93%.⁷¹

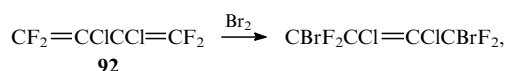


Monochloropentafluoro- and dichlorotetrafluorobuta-1,3-dienes (their structure has not been unequivocally established) add one molecule of bromine with the formation of the corresponding butenes of the general formulae $\text{C}_4\text{ClBr}_2\text{F}_5$ and $\text{C}_4\text{Cl}_2\text{Br}_2\text{F}_4$ at 20–150 °C.⁶¹

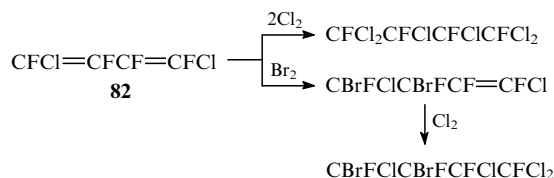
The diene **81** adds two molecules of bromine at 50 °C and gives 1,2,3,4-tetrabromo-3-chloro-1,1,2,4,4-pentafluorobutane, the structure of which was confirmed by the results of chromatomass spectrometry.⁸⁷ According to Petrov *et al.*,⁹⁵ the chlorination and bromination of the diene **81** occur exclusively as the 1,4-addition and lead to the corresponding but-2-enes. Thus treatment of the diene **81** with a mixture of *N*-bromosuccinimide (NBS) and HF in THF yielded a mixture of *E*- and *Z*-isomers of 3-chloro-1-bromo-1,1,2,4,4,4-hexafluorobut-2-ene (*E*:*Z* = 5 : 1) in a total yield of 82 %. Fluorination of the diene **81** with VF_5 from –20 to –30 °C occurs predominantly as the 1,4-addition and results in 2-chloroheptafluorobut-2-ene as a mixture of *Z*- and *E*-isomers (yields, 20% and 36%, respectively). A small amount (8%) of 2-chlorononafluorobutane is formed as the product of exhaustive fluorination.⁹⁶



According to the patent literature,⁹⁷ the diene **92** reacts with bromine (illumination with a 100 W lamp) to give 1,4-dibromo-2,3-dichloro-1,1,4,4-tetrafluorobut-2-ene (1,4-addition),



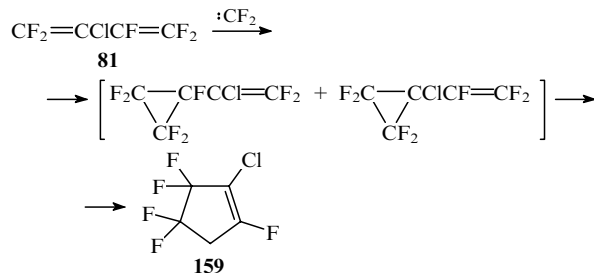
whereas with the diene **82** 1,2-addition occurs, which results in 3,4-dibromo-1,4-dichloro-1,2,3,4-tetrafluorobut-1-ene. Its chlorination gives 1,2-dibromo-1,3,4,4-tetrachloro-1,2,3,4-tetrafluorobutane.⁶⁴ Chlorination of the diene **82** affords 1,1,2,3,4,4-hexachloro-1,2,3,4-tetrafluorobutane.⁶⁴



2. Cycloaddition reactions

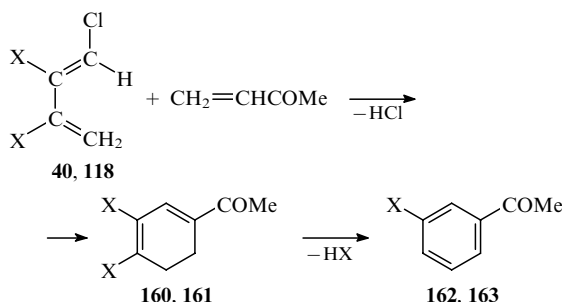
a. Reaction of mixed halogenobutadienes with difluorocarbene

The addition of carbenes to MHB was studied only for the reaction of difluorocarbene with the diene **81**. Petrov *et al.*⁹⁸ used hexafluoropropylene oxide as the source of difluorocarbene. Heating of an excess of the epoxide with the diene **81** in an autoclave gave the halogeno-substituted cyclopentene **159** in high yield. The cyclopentene **159** is one of the pyrolysis products of chlorotrifluoroethylene.⁸⁷ According to Petrov *et al.*,⁹⁸ the difluorocarbene formed in the course of pyrolysis adds to the diene **81** to give polyhalogenovinylcyclopropanes, whose intramolecular rearrangement yields the cyclopentene **159**.⁸⁷



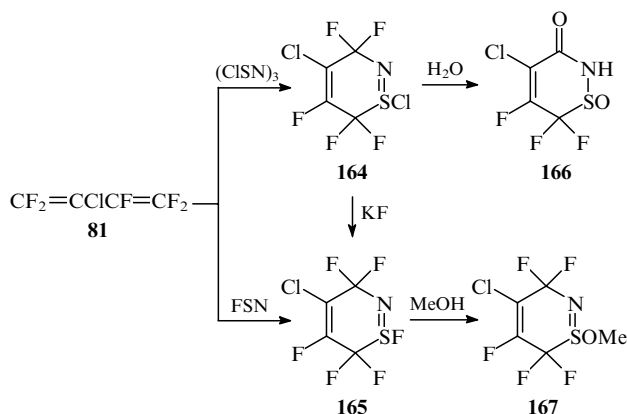
b. Diels–Alder syntheses involving mixed halogenobutadienes

Chloro-substituted buta-1,3-dienes (mostly, mono- and dichloro-derivatives) are convenient subjects for studying the Diels–Alder reaction and preparation of practically valuable compounds.⁷ Some MHB were also studied in the [4 + 2]-cycloaddition. Thus upon prolonged boiling of an excess of the dienes **40** and **118** with methyl vinyl ketone in the presence of Na₂CO₃, the corresponding 1-acetyl-3,4-dihalogenocyclohexa-1,3-dienes **160** (X = Br) and **161** (X = I) were obtained. Upon treatment of the cyclohexadienes **160** and **161** with 1,8-diazabicyclo[5.4.0]undec-7-ene, they are readily aromatised into the corresponding halogenoacetophenones **162** and **163**.^{77, 99}



The [4 + 2]-cycloaddition of (ClSN)₃ and FSN to the butadiene **81** yielded the difficultly accessible and highly reactive 6-membered heterocycles **164** and **165**, respectively, which are the derivatives of 1,2-thiazines (Scheme 3). Treatment of the 1,2-thiazine **164** with water yields the 1,2-thiazin-3-one-1-oxide **166**. The reaction of methanol with the 1,2-thiazine **165** results in the

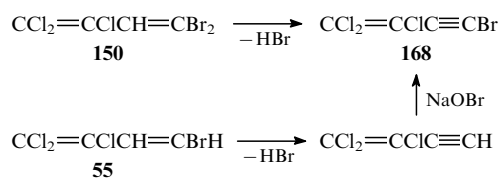
Scheme 3



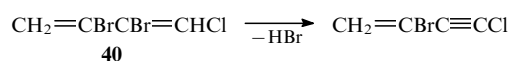
substitution of the methoxy group for the sulfur-bound fluorine atom by the methoxy group with the formation of the product **167**. Thiazine **164** is easily fluorinated with KF and gives a high yield of the thiazine **165**.¹⁰⁰

3. Elimination reactions

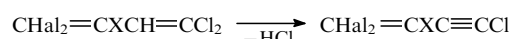
As has been shown above (see Section II.2), butenyne is widely used in the synthesis of MHB. In turn, the accessible MHB can be used in the synthesis of some highly reactive halogen-containing butenyne. Thus the preparation of 4-bromo-1,1,2-trichlorobut-1-en-3-yne (**168**) has been developed based on dehydrobromination of the dienes **55** and **150**. The synthesis of the butenyne **168** (yield 60 %) from the diene **55** (Z-isomer) includes two stages: the elimination of HBr under the action of the methanolic solution of potassium carbonate and the substitution of bromine for a hydrogen atom in the 1,1,2-trichlorobut-1-en-3-yne obtained under the action of sodium hypobromite. The second method of the synthesis of the butenyne **168** consists in the dehydrobromination of the diene **150**. It was established that the yield of the target product depends to a considerable extent on the nature of the dehydrohalogenation agent. When the methanolic solution of potassium carbonate is used, the yield of butenyne **168** is 57.5 %; this amounts to 70% with the use of benzyltrimethylammonium hydroxide (Triton B).^{89, 101, 102}



It was shown that the dehydrobromination of the diene **40** under the action of finely ground KOH at 100 °C results in 2-bromo-4-chlorobut-1-en-3-yne in 51 % yield.⁴²



Dehydrochlorination of some pentahalogenosubstituted MHB yielded the previously inaccessible tetrahalogenobutenynes.



Hal = Cl, X = Br; Hal = Br, X = Cl.

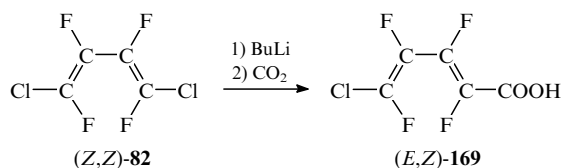
4. Substitution reactions

a. Interaction of mixed halogenobutadienes with organometallic compounds

Organolithium and -magnesium reagents found rather limited uses in the chemistry of MHB. The pronounced 'affinity' of these compounds to halogens, on the one hand, and the presence of a large number of halogen atoms in the MHB molecules, on the

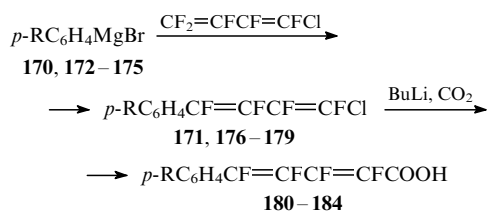
other hand, largely prevent selective nucleophilic substitution in these substrates, though such reactions are known (see below). The metal-halogen exchange is more characteristic of MHB. Thus starting from 1,2,3,4-tetrachlorobuta-1,3-diene **84** and butyllithium, mono- and dilithium derivatives were obtained, based on which a number of fine syntheses were carried out.^{103, 104}

Syntheses involving MHB were studied in the example of 1,4-dichloro-1,2,3,4-tetrafluoro-1,3-butadiene (**82**).⁶² Treatment of an isomeric mixture of the diene **82** (*E,E*:*E,Z*:*Z,Z* = 1:2.5:1.5) with butyllithium and then with CO₂ gave (*E,Z*)-5-chloro-2,3,4,5-tetrafluoropenta-2,4-dienoic acid (**169**) in 25% yield. Comparison of the ratio of isomeric forms of this diene and the yield of the acid shows that it is the *Z,Z*-isomer of the diene **82** that reacts. This reaction proceeds through the stage of exchange of an *exo*-chlorine atom for lithium (according to Kremlev *et al.*,⁶² the starting diene exists in a non-planar *s-cis*-conformation).



The reaction of organomagnesium compounds with MHB occurs in a different way. The reaction of 1-chloroperfluorobuta-1,3-diene (**75**) (*E*:*Z* = 1:1) with phenylmagnesium bromide (**170**) includes the nucleophilic substitution of the phenyl radical for the terminal fluorine atom of the trifluorovinyl fragment, which results in the formation of 4-chloro-1,2,3,4-tetrafluoro-1-phenylbuta-1,3-diene (**171**) as a mixture of *E,E*-, *E,Z*- and *Z,Z*-isomers in the ratio 2:1:2 and in a total yield of 77%.⁵⁷

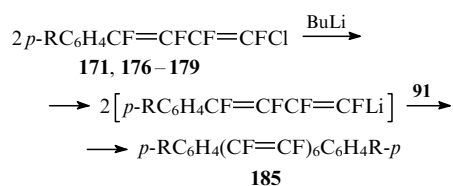
Various *para*-substituted arylmagnesium bromides (**172**–**175**) were used in this reaction, and this extended appreciably the synthetic possibilities of this method.¹⁰⁵ It was shown that the resulting 1-aryl-4-chloro-1,2,3,4-tetrafluorobuta-1,3-dienes (**176**–**179**) (yields of 40%–49%) represent mixtures of *E,E*-, *E,Z*- and *Z,Z*-isomers in the ratio 1:1:1 (NMR data). The crystalline *E,E*-isomer of compound **176** was isolated in individual form. Metallation of products **171**, **176**–**179** with butyllithium and subsequent carbonisation yielded a series of (*E,E*)-5-aryl-2,3,4,5-tetrafluoropenta-2,4-dienoic acids (**180**–**184**).



R = H (**170**, **171**, **180**), Me₂N (**172**, **176**, **181**), MeO (**173**, **177**, **182**), Me (**174**, **178**, **183**), CF₃ (**175**, **179**, **184**).

¹⁹F NMR studies of the electronic effect of substituents and determination of the acidity have shown that the 1,2,3,4-tetrafluorobuta-1,3-diene system is involved in the transfer of the electronic influence from a substituent in the aromatic ring to the corresponding reaction centre, *viz.*, the carboxyl group or a fluorine atom.¹⁰⁵

Compounds **171**, **176**–**179** served as the basis for the synthesis of symmetrical α,ω -diarylperfluoropolyenes (**185**).¹⁹



Compounds of the type **185** with the (CF=CF)_{*n*} groups are good conductors of the conjugation effect because the fluorine atoms do not create any steric hindrance to its transfer. This opens up a broad perspective for the synthesis of a novel type of polymethine dyes with a totally or partially fluorinated chain.^{19, 105}

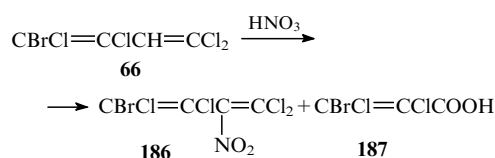
b. Nitration reactions

Of all the principal methods for the preparation of nitrobutadienes, the leading part belongs to the nitration of dienes with nitric acid or nitration mixtures.

Nitro- and especially polychloronitrobutadienes are widely employed in organic synthesis.¹⁰⁶ For example, pentachloro-2-nitrobuta-1,3-diene, which was obtained by the reaction of pentachloro-2*H*-buta-1,3-diene with nitric acid, proved to be a versatile starting material for numerous syntheses of compounds belonging to different classes.^{107–109}

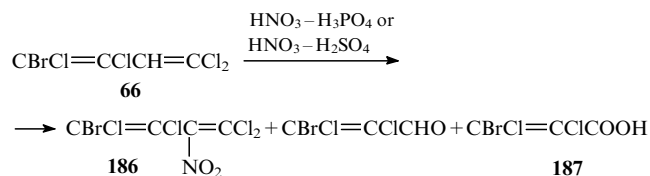
The first representative of nitroderivatives of MHB [4-bromo-1,1,3,4-tetrachloro-2-nitrobuta-1,3-diene (**186**)] was obtained by the reaction of 60% nitric acid with a 1:1 mixture of *Z*- and *E*-isomers of 1-bromo-1,2,4,4-tetrachlorobuta-1,3-diene **66** at 80–85 °C. The nitrodiene **186** is a mixture of two isomers (GLC).

Along with the nitration of the initial diene **66** at the β,β -dichlorovinyl group, competitive oxidative destruction takes place, which leads to the formation of 3-bromo-2,3-dichloroacrylic acid (**187**) as a by-product.¹¹⁰

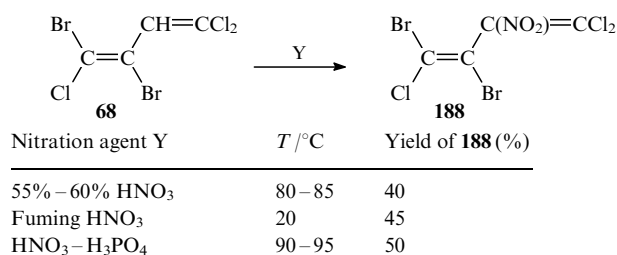


Recently,⁵⁴ the nitration of the diene **66** with nitrating mixtures HNO₃–H₃PO₄ and HNO₃–H₂SO₄ has been studied over a broad range of concentrations and temperatures. It was found that the optimum conditions for the nitration process are as follows: the temperature 95–100 °C, the ratio of the components of the nitration mixture HNO₃:H₃PO₄ (or HNO₃:H₂SO₄) equal to 10:1 and the ratio of diene:nitration mixture equal to 1:3 or 1:4. Under these conditions, the reaction is completed in 23 h; the yield of the nitrodiene **186** reaches 56% upon nitration with the HNO₃–H₂SO₄ mixture and 58% upon nitration with the HNO₃–H₃PO₄ mixture.

The nitration of the diene **66** (as a mixture of *Z*- and *E*-forms in the ratio 1:3) yields an isomeric mixture of the nitrodiene **186** in virtually the same ratio. Among by-products of this reaction, β -bromo- α,β -dichloroacrolein (yield 8%) and 3-bromo-2,3-dichloroacrylic acid (**187**) were detected.

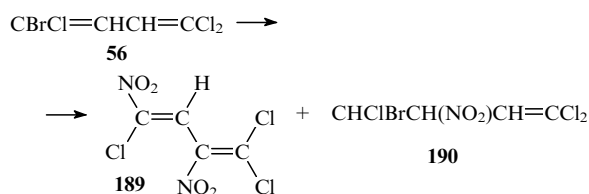


The nitration of other pentasubstituted MHB, *viz.*, 1,2-dibromo-1,4,4-trichloro- (**68**) and 1,3-dibromo-1,4,4-trichlorobuta-1,3-dienes (**70**) with nitric acid or nitration mixtures occurs similarly. Thus nitration of the *E*-isomer of the diene **68** with the 55%–60% nitric acid, fuming nitric acid or a nitration mixture HNO₃–H₃PO₄ yielded (*E*)-3,4-dibromo-1,1,4-trichloro-2-nitrobuta-1,3-diene (**188**).



The nitration of the diene **70** with the above-cited reagents under similar conditions gives 1,3-dibromo-1,4,4-trichloro-2-nitrobuta-1,3-diene in yields of 35%, 43% and 48%, respectively.

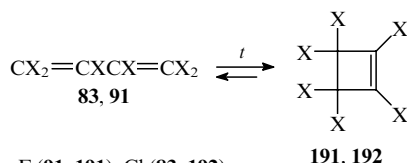
1-Bromo-1,4,4-trichlorobuta-1,3-diene (**56**) reacts differently with nitric acid and with nitration mixtures. In this case, the nitration proceeds in the two directions: (1) substitution of a hydrogen atom in the β,β -dichlorovinyl group and (2) substitution of a bromine atom in the β,β -bromochlorovinyl group resulting in the formation of 1,1,4-trichloro-1,3-dinitrobuta-1,3-diene (**189**). Another reaction product is 4-bromo-1,1,4-trichloro-3-nitrobut-1-ene (**190**). Under the optimum conditions [the nitration mixture HNO₃–H₃PO₄ (10 : 1), 90–95 °C, 2 h], the yields of 1,4-dinitrobuta-1,3-diene **189** and nitrobutene **190** are 18% and 40%, respectively.⁴⁹



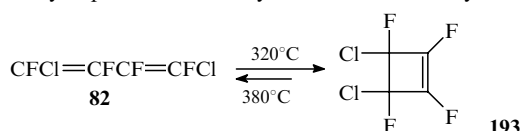
According to the IR spectroscopy and the X-ray diffraction analysis, the diene **189** is the *Z*-isomer and has a virtually planar *s-trans*-configuration.^{111, 112}

5. Isomerisation reactions

It was shown above (see Section II.3) that the accessible polyhalogenocyclobutenes are convenient starting compounds for the synthesis of some MHB. As early as 1949, the thermal cyclisation of hexafluorobuta-1,3-diene (**91**) at 150–180 °C was carried out and resulted in hexafluorocyclobutene (**191**) and a mixture of dimers C₈F₁₂ and trimers C₁₂F₁₈.¹¹³ Later, these transformations were also performed for hexachlorobuta-1,3-diene (**83**), and hexachlorocyclobutene (**192**) was isolated by distillation.⁷ The isomerisation of halogenobutadienes into the corresponding cyclobutenes is a reversible reaction.

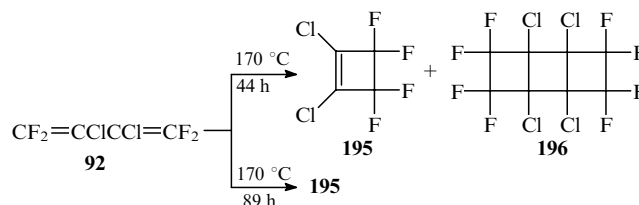


The isomerisation of MHB was studied in the example of 1,4-dichloro-1,2,3,4-tetrafluorobuta-1,3-diene (**82**) and 2,3-dichloro-1,1,4,4-tetrafluorobuta-1,3-diene (**92**). It was shown that heating of the diene **82** at 250 °C in a sealed glass tube results in 3,4-dichlorotetrafluorocyclobutene (**193**) in 56% yield. Upon heating of this diene in a platinum crucible over activated carbon to 320 °C, the yield of the butene **193** reaches 74%. The reverse process (transformation of cyclobutene into diene) occurs at 380 °C at a lower rate, therefore, the content of butadiene in the thermolysis products of the cyclobutene **193** is only 14%.⁶⁴



Heating of a mixture of *E,E*-, *E,Z*- and *Z,Z*-isomers of the diene **82** in a nickel tube at 330 °C yielded three products, viz, 3,4-dichloro- (**193**), 1,4-dichloro- (**194**) and 1,2-dichlorotetrafluorocyclobutenes (**195**). Presumably, the cyclobutenes **194** and **195** are formed due to the double bond migration catalysed by the fluoride ion.¹¹⁴

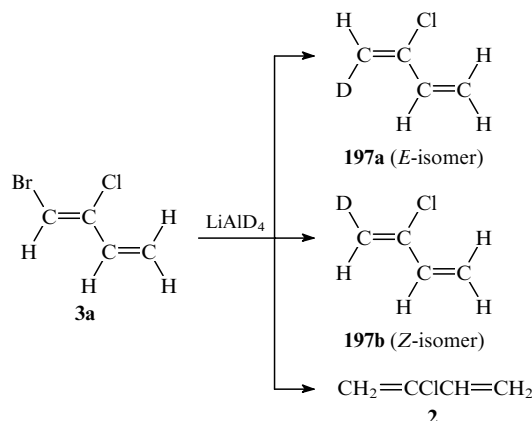
The diene **92** undergoes only partial transformation when heated in a sealed steel tube at 170 °C for 44 h. The unreacted diene **92** was recovered, 1,2-dichlorotetrafluorocyclobutene (**195**) and a small amount of unsaturated dimers and a dimer **196**⁹⁷ were isolated from the reaction mixture. The total conversion of the diene **92** into the cyclobutene **195** occurs after 89 h.⁹⁷



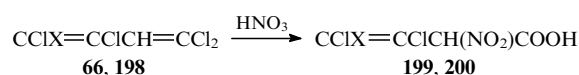
It was supposed⁶⁴ that the reaction diene $\rightleftharpoons$ cyclobutene is a general characteristic of the polyhalogenobutadienes.

6. Miscellaneous reactions

The reduction of MHB was studied only in the example of (*Z*)-1-bromo-2-chlorobuta-1,3-diene (**3**). It was shown that the reduction of *Z*-diene (**3a**) with LiAlD₄ in diethyl ether occurs with high stereoselectivity and leads to the formation of a mixture of (*E*)- (**197a**), (*Z*)-2-chloro-1-deuteriobuta-1,3-diene (**197b**) and 2-chlorobutadiene (**2**) in the ratio 94.2 : 2.2 : 3.6, respectively.²⁵



In example of the reaction of pentachloro-2*H*-buta-1,3-diene (**198**) with fuming nitric acid it was shown that the reaction product is 3,4,4-trichloro-2-nitrobut-3-enoic acid (**199**), i.e., the β,β -dichlorovinyl group of the diene **198** is involved in the reaction and an earlier transformation into the CH(NO₂)COOH group occurs.¹¹⁵ An analogous reaction giving 4-bromo-3,4-dichloro-2-nitrobut-3-enoic acid (**200**) in high yield also occurs upon interaction of fuming nitric acid with 1-bromo-1,2,4,4-tetrachlorobuta-1,3-diene (**66**).¹¹⁰

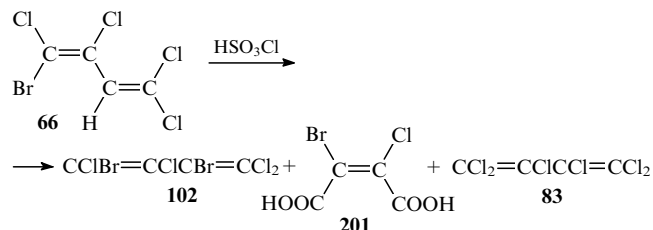


X = Cl (**198**, **199**), Br (**66**, **200**).

The reaction of the *E*-isomer of the diene **66** with chlorosulfonic acid proceeds in an unusual manner. Under the optimum conditions (70–80 °C, the diene : acid ratio equal to 1 : 2; 5 h), the reaction gives (*E*)-1,3-dibromo-1,2,4,4-tetrachlorobuta-1,3-diene **102** in 31% yield as the main product.

In addition, bromochloromaleic acid **201** (yield 6%) and hexachlorobuta-1,3-diene **83** (yield ~ 2%) were also found among the reaction products. Dienes **102** and **83** are apparently

formed upon halogenation of the starting compound **66** with chlorine and bromine, which appear in the reaction mixture upon destruction and resinification of the substances involved. Acid **201** is the hydrolysis product of the diene **102**.



When the diene **66** is used in the reaction in the form of *E*- and *Z*-isomers (1 : 1), the diene **102** is also formed as a mixture of two isomers in the ratio 1 : 1.⁷¹

IV. Conclusion

Analysis of the published data shows that constant attention is paid to the synthesis of mixed halogenobuta-1,3-dienes. Nowadays, there are rather well developed methods for the synthesis of hexasubstituted chloro-, fluoro- and chlorobromobutadienes, while the methods for the synthesis of MHB containing from 2 to 5 atoms of halogens are somewhat less developed.

Most of the methods for the preparation of MHB are based on the elimination reactions of accessible polyhalogenobutenes and -butanes, *i.e.* they rely on the use and transformations of the existing C_4 carbon chain. At present, novel methods have been proposed for the synthesis of MHB under the conditions of phase-transfer catalysis, which makes their preparation simpler and more efficient.

Virtually all of the synthesised MHB contain two kinds of the halogen atoms. At present, there is a convenient procedure for the synthesis of only one MHB representative containing three kinds of the halogen atoms. Unfortunately, until now no MHB have been prepared with four different halogen atoms (F, Cl, Br, I) which could be used as convenient models for studying regularities of competitive processes of nucleophilic vinylic substitution ($\text{S}_\text{N}\text{Vin}$) of different halogen atoms.

Transformations of MHB are represented in the relevant literature to a lesser extent; nonetheless, the available data show that MHB possess broad possibilities for the development of new methods for the synthesis of polyfunctional compounds which are difficultly accessible or totally inaccessible by other ways.

We hope that a stimulus for the further development of studies in this field will be the fact that many MHB possess a broad spectrum of useful properties.

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Aryl (meth)acrylates and polymers based on them

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Abstract. Data on the synthesis, polymerisation and copolymerisation of aryl (meth)acrylates are generalised and systematised. Chemical and photochemical properties of the polymers and copolymers are considered. Basic directions of practical application of poly[aryl (meth)acrylates] and copolymers are demonstrated. The bibliography includes 449 references.

I. Introduction

Aryl (meth)acrylates $\text{H}_2\text{C}=\text{C}(\text{R})\text{CO}_2\text{Ar}$ (hereinafter $\text{R} = \text{H}, \text{Me}$) occupy a special place in the series of (meth)acrylates due, first of all, to the diversity of functional groups which may be introduced into the aromatic ring of these monomers and the derived polymers. Specificity of physical properties of poly[aryl (meth)acrylates] is determined by the enhanced rigidity of the polymeric chains (because of the presence of aromatic rings). Aryl (meth)acrylates are easily copolymerised with most of the known monomers, which opens broad prospects for their application.

Until recently, the results of numerous studies on the synthesis and properties of aryl (meth)acrylates have not been generalised. The present review is intended to fill this gap.

II. Methods for the synthesis of aryl (meth)acrylates

Earlier methods for the synthesis of aryl (meth)acrylates were rather complicated and were not of a general character. Thus phenyl acrylate (PA) was prepared by direct esterification of phenol with acrylic acid in the presence of trifluoroacetic anhydride¹ and also by the Reppe reaction, *i.e.*, by the reaction of acetylene and carbon monoxide with phenol.² Phenyl³ and naphthyl acrylates⁴ were obtained by pyrolysis of 2-acetoxypromates $\text{MeCH}_2(\text{OAc})\text{CO}_2\text{Ar}$. The systematic studies of the methods for the preparation of aryl acrylates were initiated by Magagnini and Pizzirani⁵ who investigated the reactions of

acryloyl chloride with phenols. In addition to PA, these authors described acrylates of isomeric cresols, chlorophenols, thymol, hydroxybiphenyl and 4-methoxyphenol. It should be noted that the reactions were carried out under conditions precluding the addition of hydrogen chloride to the double bond. In earlier attempts of the synthesis of acrylates by this method, this addition took place; therefore, β -chloropropionates were the major products. Conducting of these reactions in the presence of triethylamine allowed a considerable increase in the yields of methacrylates of substituted phenols. This method was successfully used to prepare isomeric phenol di(meth)acrylates,⁶ 2-biphenyl acrylate⁷ and 4-biphenyl (meth)acrylate⁸ and mono- and di(meth)acrylates of substituted 2,2'-methylenebisphenols.⁹

Aryl (meth)acrylates are usually synthesised by the reaction of phenols with (meth)acryloyl chloride in the presence of hydrogen chloride acceptors. This process may be carried out in inert solvents in the presence of Na_2CO_3 ,¹⁰ in pyridine,¹¹ in ethanolic solution of KOH ¹² or triethylamine.⁷ It is also convenient to use the Schotten–Baumann reaction, which involves the acylation of phenolates with (meth)acryloyl chloride in aqueous solutions at reduced temperature in the presence of an excess of alkali.¹³ This reaction occurs efficiently at the interface of the aqueous and organic phases.¹⁴ Monomers based on halogenated 2,2-di(4-hydroxyphenyl)propanes¹⁵ and hydroxyphenyl derivatives of 2*H*-benzotriazole¹⁶ were prepared in this manner.

The methods described above have allowed the preparation of numerous alkyl- (see Refs 4, 6, 13, 17, 18), halogeno- (see Refs 4, 6, 11, 14) and nitro-substituted^{4,10,19} phenyl (meth)acrylates (PMA). At the same duration and temperature of the reaction, the yields of esters decreased in the following order: *meta*-isomer > *para*-isomer > *ortho*-isomer > disubstituted phenol.¹⁰ Optimum conditions were found for the preparation of 2,6-dimethylphenyl acrylate, 2,4,6-trichloro-, 2,4,6-tribromo-, 2,4,6-trimethyl-, 2,6-diisopropyl- and 2,6-di(*tert*-butyl)-phenyl methacrylates, 2,4,5-trichlorophenyl acrylate²¹ and methacrylate.²²

PMA with substituents in the aromatic ring containing the aldehyde and ketone,²³ carboxy,^{24,25} benzyl,²⁶ tetracyanocyclobutyl²⁷ and dioxolane²⁸ groups have been described. Special mention should be made of (meth)acrylates of hydroxyphenylacetic²⁹ and hydroxybenzoic^{24,25} acids as well as of surfactant salts³⁰ of the general formula $\text{CH}_2=\text{CMeC}(\text{O})\text{OC}_6\text{H}_4(\text{CH}_2)_n\text{X}$ [$n = 3, 7$; $\text{X} = \text{CO}_2\text{Na}, \text{N}^+(\text{C}_n\text{H}_{2n+1})_3\text{Z}^-$; $\text{Z} = \text{Cl}, \text{Br}, \text{I}, \text{MeSO}_4$].

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4-(Meth)acryloyloxybenzoic acids form liquid-crystalline polymers upon polymerisation and give birth to a large number of mesomorphic monomers and polymers.³¹ Of all monomers of this type, the best studied are the esters of the general formula $\text{CH}_2=\text{C}(\text{R}')\text{C}(\text{O})\text{OYCR}''$ ($\text{R}' = \text{H},^{32} \text{Me},^{33} \text{OR}''$; $\text{R}'' = \text{Me},^{32-35} \text{Pr},^{34} \text{Bu}^n,^{32-34,36} \text{n-C}_6\text{H}_{13},^{37}$ and $\text{Alk}(\text{C}_8-\text{C}_{16})^{36}$ (hereinafter $\text{Y} = 1,4\text{-C}_6\text{H}_4$). Monomers with more complex structures have been also described, *e.g.*, methacrylates with the mesogenic side groups $\text{YC}(\text{O})\text{OYOC}(\text{O})\text{YOR}'$ ($\text{R}' = \text{H}, \text{Alk}$);³⁸ or thermotropic bisacrylates $\text{R}'\text{XR}'$ ($\text{X} = (\text{CH}_2)_n$; $n = 6-10, 12$; $\text{R}' = \text{CH}_2=\text{CHC}(\text{O})\text{O}.$ $\text{YC}(\text{O})\text{OYCR}''$).³⁹ It should be noted that mesomorphic monomers are also found among aryl (meth)acrylates with a different character of substitution. These are acrylates and methacrylates of hydroxybiphenyl with alkyl⁴⁰ and alkoxy^{41,42} substituents or the CN group⁴³ at the position 4'. It is noteworthy that poly(4,4'-biphenylene diacrylate) does not possess liquid-crystalline properties.⁴⁴

The group of mesomorphic monomers also includes easily polymerisable acrylates of azomethines derived from 4-hydroxybenzaldehyde. Polymers with Schiff's bases as the pendent groups can be obtained by polymer-analogous transformations from polyacryloyl chloride and the corresponding hydroxybenzylideneaniline.⁴⁵ A large group of this type of monomers of the general formula $\text{CH}_2=\text{C}(\text{R}')\text{C}(\text{O})\text{OYCH}=\text{NX}$ [$\text{X} = \text{Alk}(\text{C}_1-\text{C}_4), \text{C}_6\text{H}_4\text{Z}$; $\text{Z} = \text{OH}, \text{OMe}, \text{OEt}, \text{NMe}_2, \text{NEt}_2, \text{NHPh}, \text{naphthyl}, \text{pyridyl}$] has been proposed⁴⁶ for the preparation of non-aqueous dispersions of polymers used in polygraphy.

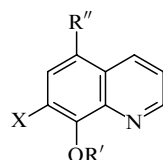
4-(4-Acryloyloxybenzylideneamino)phenyl acrylate⁴⁴ and *N*-(4-cyanobenzylidene)-4-acryloyloxyaniline are azomethines based on 4-aminophenol.⁴⁷ Mesomorphic monomers (as well as the derived polymers) are rarely found among methacryloylazomethines.⁴⁸

(Meth)acrylates of hydroxyazobenzenes⁴⁹⁻⁵¹ and hydroxyazoxybenzenes⁵² were used to prepare liquid-crystalline polymers. Azo-monomers possess, as a rule, alkyl, alkoxy or aryl substituents in the *para*-position relative to the azo group. The respective polymers are lyotropic or thermotropic liquid crystals, which undergo reversible changes under the action of UV radiation.⁵³ Liquid-crystalline polymers based on 4,4'-(bisacryloyloxy)azoxybenzene⁴⁴ are also obtained by the reaction of 4-hydroxyazobenzene with poly(acryloyl chloride).⁵⁴ Comb-like polymers with liquid-crystalline properties were obtained by polymerisation of hydroquinone mono(meth)acrylates esterified at the second OH group with 4-*n*-alkoxybenzoic acids.⁵⁵⁻⁵⁸

The results of studies on liquid-crystalline polymers derived from aryl (meth)acrylates have been described rather comprehensively in monographs.^{59,60}

Syntheses of (meth)acrylates of derivatives of condensed aromatic systems (naphthalene, anthracene, phenanthrene) have been described.⁶¹ Syntheses of α - and β -naphthyl esters of some α, β -unsaturated acids,⁶² 2-(β -substituted acryloyl)-1-methacryloyloxynaphthalenes, which are cross-linking agents,⁶³ and 4-benzoylamino- α -naphthyl methacrylate,⁶⁴ which is an efficient thermostabiliser, are documented. Monomeric dyes of the anthraquinone series were obtained by the reaction of unsaturated acid chlorides with 4-amino-1,5-dihydroxy-2,6-diisobutyl-, 5-(3-aminophenylthio)-1,5-dihydroxy-2,6-diisobutyl- and 4,5-diamino-1,8-dihydroxy-2,7-diisobutylanthraquinones.⁶⁵ Copolymerisation of these dyes with styrene and butyl methacrylate yields polymers self-coloured in yellow, red and blue. Kimura *et al.*⁶⁶ have described 2- and 9-fluorenyl methacrylates. Upon their polymerisation in the presence of a telogen, the degree of telomerisation of the second monomer is lower. A number of monomers based on fluoranthene, including 3-fluoranthenyl methacrylate, produce polymers of the donor type, which form charge-transfer complexes possessing electrical properties with tetracyanoquinodimethane and tetracyanoethylene.⁶⁷

Methacrylates of the 8-hydroxyquinoline series⁶⁸ of the general formula



$\text{X} = \text{H}, \text{Br}, \text{Cl}, \text{I};$

$\text{R}' = \text{C}(\text{O})\text{CMe}=\text{CH}_2;$

$\text{R}'' = \text{H}, \text{Br}, \text{Cl}, \text{CH}_2\text{OMe}, \text{CH}_2\text{OEt}$

were synthesised in order to obtain subsequently medicinal preparations with prolonged action.^{69,70} Halogens were shown to favour polymerisation. Methacrylates of hydroxyphenyl derivatives of other nitrogen-containing heterocycles are also known, *e.g.*, 1,3-diphenyl-5-(4-methacryloyloxyphenyl)-2-pyrazoline.⁷¹ Of these, the most complex are acrylate and methacrylate of 5-(4-hydroxyphenyl)-10,15,20-triphenylporphyrin⁷² (the respective polymers possess semiconducting properties and adsorb oxygen at temperatures below 200 K) and of 5-(4-acryloyloxyphenyl)-15-phenyl-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin.⁷³

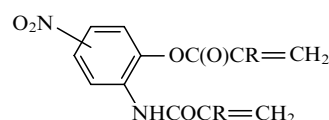
Some monomers contain the methacryloyloxy group bound directly to the heterocyclic ring, *e.g.*, 2-pyridyl methacrylate.⁷⁴ Aryl (meth)acrylates with the nitrogen-containing heterocyclic substituents in the *para*- and *meta*-positions of the benzene ring have been described.⁷⁵ The initial *N*-(hydroxyphenyl)imides were obtained by condensation of aminophenols with the corresponding anhydrides. Monomers were synthesised by acylation with unsaturated acid chlorides.

As regards aryl (meth)acrylates with nitrogen-containing substituents in the phenyl group, monomers with the nitro (see Refs 4, 10, 19) and cyano⁷⁶ groups have been described; a number of monomers with the azo (see Refs 77, 78), azoxy and azomethine groups⁷⁹⁻⁸² are also known. 4-Azidophenyl methacrylate,⁸³ salicinide,⁸⁴ *N*-benzyl- and *N*-phenyl-4-hydroxybenzamide acrylates and methacrylates⁸⁵ were synthesised.

4-Aminophenyl methacrylate proved to be sensitive to oxidation, which reduces the possibility of its practical application.⁸⁶ However, 3-(*N,N*-dimethylamino)phenyl methacrylate is fairly stable,⁷⁶ it forms charge-transfer complexes with electron acceptors and is promising for the synthesis of polymeric photoconductors.

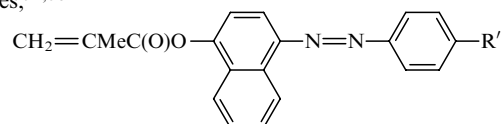
Many reactive monomers, *e.g.*, acylaminophenyl methacrylates of the general formula $\text{R}'\text{C}(\text{O})\text{NHC}_6\text{H}_4\text{OC}(\text{O})\text{CR}=\text{CH}_2$ ($\text{R}' = \text{H}, \text{Me}, \text{Et}, \text{Pr}, \text{Bu}, \text{C}_5\text{H}_{11}, \text{PhCH}=\text{CH}, \text{O}_2\text{NC}_6\text{H}_4$ and BrC_6H_4) were obtained by *N*-acylation of isomeric aminophenols with equimolecular amounts of carboxylic acid chlorides (in anhydrous acetone, methanol or DMF) with subsequent esterification by the Schotten-Baumann reaction with acryloyl or methacryloyl chlorides.⁸⁷⁻⁹⁰ If 4-, 3- or 2-aminophenols are esterified with methacrylic acid, both functional groups react to give 4-, 3- or 2-(meth)acryloylaminophenyl (meth)acrylates. These reactive monomers undergo cross-linking in the polymerisation.^{14, 91, 92} Di- and tri(meth)acryloyl derivatives of 2,4-diaminophenol (amidol) were synthesised by successive acylation.⁹²

Diacryloyl and di(meth)acryloyl derivatives of nitroaminophenols



were prepared⁹³ by acylation of 2-amino-4-nitro- and -5-nitrophenols with unsaturated acid chlorides in tetrahydrofuran in the presence of triethylamine.

Based on 4-amino- α -naphthol, azonaphthyl methacrylates,^{94,95}



$\text{R}' = \text{H}, \text{OMe}, \text{Br}, \text{NO}_2,$

imidonaphthyl methacrylates⁹⁴ and 4-benzoylamino- α -naphthyl methacrylate⁹⁵ were synthesised.

Thus, aryl (meth)acrylates with diverse functional groups in the aryl residue have been prepared to date.

III. Polymerisation of aryl (meth)acrylates

Aryl (meth)acrylates are relatively easily polymerised by a radical mechanism, the polymerisation rate being mainly determined by steric effects of substituents.⁹⁶ Thus *ortho*-substituted PMA are appreciably less reactive than the *para*-isomers, the chemical nature of the substituent does not play any substantial role, which has been confirmed by the results of polymerisation of nitro- and methoxyphenyl methacrylates.^{13, 97, 98} Polymerisation was carried out in block and in different solvents in the presence of benzoyl peroxide. Since the electronic effect of the nitro and methoxy groups is opposite, one could expect that the rates of polymerisation of *o*- and *p*-nitrophenyl methacrylates and *o*- and *p*-methoxyphenyl methacrylates would be different; however, polymerisation of *para*-derivatives occurred faster in both cases. The EPR spectra of radicals devoid of *ortho*-substituents, e.g., poly(phenyl methacrylate) (PPMA) and poly(4-methylphenyl methacrylate), are identical, whereas the spectra of radicals of 2,6-diisopropylphenyl methacrylate and 2,6-di-*tert*-butylphenyl methacrylate revealed differences related to the shielding of the growing end of the polymeric chain by the *ortho*-substituents and the α -methyl group.⁹⁹

The overall rate constant of the bulk polymerisation of alkylphenyl methacrylates (alkyl = Et, Prⁱ, Bu^t) is higher for the *para*-substituted monomers than for the *ortho*-substituted ones and is virtually independent of the substituent size, whereas for the *ortho*-isomers this constant decreases with the increase in the substituent size.¹⁰⁰ The reaction order with regard to the initiator (dilauryl peroxide) is 0.5 for non-substituted PMA, while it is 0.64–0.94 for the sterically hindered monomers. The presence of methyl groups in the *ortho*-position (e.g., in 2,6-dimethylphenyl methacrylate) decreases appreciably the ceiling temperature of polymerisation (down to 73 °C) compared to that of non-substituted PMA (140 °C).¹⁰¹ The overall activation energy (kJ mol⁻¹) increases in the following order: 2,6-diisopropylphenyl methacrylate (45.7) < 4-*tert*-butylphenyl methacrylate (49.9) < 4-(1,1,3,3-tetramethylbutyl)phenyl methacrylate (59.6) < 4-methyl-, 4-ethyl- and 4-isopropylphenyl methacrylates (70–76).^{102, 103}

Substitution of the cyclohexyl radical for the phenyl radical in the molecule of aryl methacrylate affects the polymerisation rate. For example, methacrylate of thymol, which contains a bulky isopropyl residue, is polymerised with difficulty, while methacrylate of menthol (hydrogenated thymol) analogous to the preceding monomer is polymerised easily under the same conditions.¹³ This is rationalised by the non-planarity of the cyclohexane ring and, consequently, by a lower rigidity of this monomer molecule compared to the methacrylate of thymol.

Block polymerisation of substituted PMA is accompanied by gel-effect, which is observed in 2,4,6-tribromophenyl, 4-tolyl, 4-cyclohexylphenyl and 4-methoxyphenyl methacrylates at 35%, 35%, 15% and 2% conversions of the monomer, respectively [the concentration of the polymerisation initiator, viz., azobisisobutyronitrile (AIBN) is 0.4%].¹⁰⁴ The kinetic parameters of PMA polymerisation in block and in solvent (60 °C, AIBN) were compared with those for alkyl methacrylates.¹⁰⁵ The overall polymerisation rate has an order of 0.5 with respect to the initiator and 1 with respect to the monomer, i.e., it is described by the usual equation of radical polymerisation. The ratio of the chain termination constant (k_t) to the squared chain propagation constant (k_p) increases in the following order: (phenyl < isobutyl $\approx$ *n*-butyl < ethyl < methyl) methacrylate. According to the radiometric analysis of the initiator fragments, the share of disproportionation in PMA is 89% [72% in methyl methacrylate (MMA)]. The initiation rate of radical polymerisation of PMA by

AIBN depends slightly on the nature of the solvent, while k_p (litre mol⁻¹ s⁻¹) increases in the following series of solvents: benzene (176) < fluorobenzene (180) < chlorobenzene (223) < anisole (230) < bromobenzene (235) < benzonitrile (243).¹⁰⁶ The magnitude of k_p was found to correlate with the difference in chemical shifts of β -alkene protons of monomers depending on the solvent.

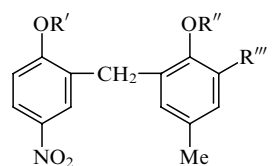
The MO LCAO method was used to calculate the stabilisation energy in the formation of complexes of a radical with a solvent; k_p was found to decrease with the increase in the complexation energy. It was shown later that this trend holds for MMA¹⁰⁷ and PMA.¹⁰⁸ The rate of radiation-induced polymerisation of PMA is proportional to the radiation dose to the power 0.65;¹⁰⁹ in the temperature range 20–34 °C, the activation energy of the process is equal to 14.15 kJ mol⁻¹, $k_p/k_t^{0.5} = 0.0198$. At high degrees of conversion, a three-dimensional network is formed owing to the involvement of the terminal double bonds.

Investigation of the influence of substituents on the radical polymerisation of PA has shown that the rate of this process increases in the order: methyl acrylate < 2-chlorophenyl acrylate < PA < 4-chlorophenyl acrylate.¹¹⁰ This is rationalised by changes in the flexibility of the propagating polymer chains. The increase in the overall polymerisation rate (toluene, 60 °C, lauryl peroxide) was found to increase in the following series:¹¹¹ (2-*tert*-butyl- < 2-isopropyl- $\approx$ 2-propyl- < 2-ethyl- < 2-methyl- < PMA < 4-methyl- < 4-isopropyl- < 4-*tert*-butyl- < 4-propylphenyl) methacrylate. The reaction order with regard to lauryl peroxide is 0.51–0.87 depending on the monomer concentration.

In the radical polymerisation of 2,4,5-trichlorophenyl methacrylate¹¹² in dioxane ($k_p = 2.73 \times 10^3$, $k_t = 7.22 \times 10^7$ litre mol⁻¹ s⁻¹), the polymerisation rate is proportional to the monomer concentration to the power 1.5, which is explained by the possible formation of complexes of the monomer with the solvent molecules. In the case of radical polymerisation of nitrophenyl methacrylates, at a low monomer concentration (0.01 mol litre⁻¹) one observes an inhibitory effect of the intra- and intermolecular chain transfer, the former being prevalent.^{113–115} For this reason, 2,6-dinitrophenyl, 2-methyl-4,6-dinitrophenyl and picryl methacrylates are not polymerised under these conditions, and the conversion of 2,4-dinitrophenyl methacrylate hardly reaches 2.6% in 2 h. The reaction orders of 4-biphenyl methacrylate polymerisation (in DMF with AIBN) are 0.55 and 1.1 with respect to the initiator and monomer respectively; the total activation energy is 58 kJ mol⁻¹ (see Ref. 8).

Replacement of an alkyl substituent by the electron-withdrawing acyl substituent in the benzene ring leads to an increase in the polymerisation rate of substituted phenyl (meth)acrylates because of the lower activation energy of the C=C bond cleavage.¹⁷ DTA studies of thermal bulk polymerisation of 4-acetylphenyl acrylate and methacrylate have shown¹¹⁶ that this process is the first-order reaction with respect to the monomer, the activation energies are equal to 228.1 and 120.5 kJ mol⁻¹, respectively. High polymerisation rates were observed for acylaminophenyl (meth)acrylates;^{87, 88} however, the rate of polymerisation decreased with increase in the length of the acyl radical. On the other hand, 4-diethylaminophenyl acrylate and methacrylate polymerised at a lower rate than non-substituted PMA.⁸⁹

Radical polymerisation of mixed diesters of 2,2'-methylene-diphenols with methacrylic and crotonic acids¹¹⁷



where R' and/or R'' are methacrylic and crotonic acid residues and R''' = H, Me, Bu^t, resulted in soluble polymers where R' = R'' (polymerisation involved the methacryloyl group alone),

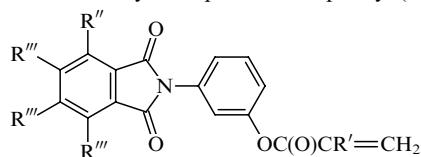
insoluble dimethacrylates where R' and R'' were the methacrylic acid residues and no polymerisation occurred where R' and R'' were the crotonic acid residues.

(Meth)acryloyl derivatives of *N*-hydroxyphenyl-substituted phthalimide¹¹⁸ $R'C_6H_4OC(O)CR=CH_2$ (R' = phthalimido)

Monomer	I	II	III	IV
R	H	H	Me	Me
Position of R'	<i>para</i>	<i>meta</i>	<i>para</i>	<i>meta</i>

and alicyclic diacylamines^{118, 119} polymerise at high rates and are more reactive than PMA, which seems to be due to the electron-withdrawing character of the imide fragment. The reactivity of monomers decreases in the following order: I > III > II > IV > *p*-acetylaminophenyl methacrylate (*p*-AAPMA), acrylates being more reactive than the corresponding methacrylates and the *para*-isomers more reactive than the *meta*-isomers.¹¹⁸

The reactivity of *m*-phthalimidophenyl (meth)acrylates¹²⁰



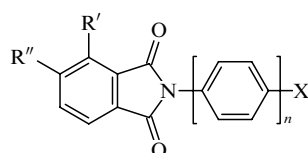
Monomer	R'	R''	R'''
I	H	H	H
II	Me	H	H
III	H	Cl	Cl
IV	Me	Cl	Cl
V	Me	Br	Br
VI	Me	NO ₂	H

decreases with in the series: IV > V > II > *m*-AAPMA > VI, i.e., with the weakening of the electron-withdrawing character of the phthalimido group. The reduced reactivity of the monomer with the nitro group in the phthalimide cycle may be explained by its inhibitory action.

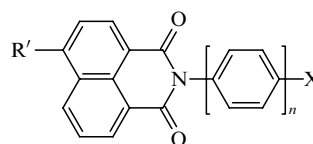
The polymerisation rate of imidonaphthyl (meth)acrylates is lower than that of analogous imidophenyl methacrylates, and, according to Vretik *et al.*,⁹⁴ this is due to the reduced reactivity of radicals because of a stronger electronic conjugation in the naphthyl-containing system. The most reactive of all the naphthyl (meth)acrylates studied proved to be bismethacrylate with an additional cycloalkene double bond. This compound was obtained by the reaction of endic dianhydride with 1-amino-4-methacryloyloxynaphthalene.⁹⁴

Irrespective of the initiation mode (thermal or photo-initiation), *m*-(succinimido)phenyl methacrylate (*m*-SIPMA) and acrylate (*m*-SIPA) occupy an intermediate position with regard to their reactivity between *m*-phthalimidophenyl methacrylate (*m*-PTIPMA) and acrylate (*m*-PTIPA), and acetylaminophenyl methacrylate (*m*-AAPMA) and acrylate (*m*-AAPA): *m*-PTIPMA > *m*-SIPMA > *m*-AAPMA > PMA; *m*-PTIPA > *m*-SIPA > *m*-AAPA > PA, i.e., there is correlation between the electron-withdrawing properties of the substituent and polymerisability of substituted phenyl (meth)acrylates.¹²¹ High reactivity of these aryl (meth)acrylates allows the introduction of the above-mentioned heterocyclic fragments into the side chains of macromolecules in order to impart definite photochemical, biological and other properties to the polymeric materials.

Based on imidoaryl (meth)acrylates,^{122, 123}



$X = OC(O)CR=CH_2$; $R', R'' = NO_2, NH_2$; $n = 1, 2$;



$X = NH_2, OC(O)CR=CH_2$; $R' = NO_2$; $n = 1, 2$

homopolymers were obtained with the controllable intramolecular energy transfer. In such polymers, movement of singlet or triplet excitons from one part of the macromolecule to another or from one unit chain to another is observed. The prerequisite for such a transfer is the presence of isolated aromatic systems with different excitation energies in each of the neighbouring units; the initial excitation should be generated in a definite element of the system. Such compounds are promising for the design of micro-electronic devices in which advantage is taken of photophysical processes at the molecular level.¹²⁴

Polymerisability of bifunctional monomers deserves special mention. Cross-linked polymers are formed upon polymerisation of *p*- and *m*-phenylene di(meth)acrylates; *o*-phenylene diacrylate can undergo cyclopolymerisation⁷ with the formation of ladder polymers; the extent of cyclisation increases with the decrease in the monomer concentration and the increase in the polymerisation temperature.¹²⁵ At a monomer concentration above 0.5 mol litre⁻¹, an insoluble polymer is formed. The intramolecular chain growth in the cyclopolymerisation follows mostly the 'head-to-tail' mechanism, and a small number of units are formed by the 'head-to-head' mechanism.

Radical polymerisation of 2-allylphenyl (meth)acrylates is a two-step process:¹²⁶ at an 18%–30% monomer conversion, a soluble low-molecular-mass polymer is formed, which is then cross-linked. The low molecular mass of the product and the absence of the gel-effect are associated probably with the ability of the allyl group to undergo chain transfer. A detailed study of the polymerisation of 2-allylphenyl acrylate in toluene at 60 °C in the presence of AIBN revealed high content of the residual double bonds in the pendent allyl groups of the polymer.¹²⁷ Subsequent cyclopolymerisation occurs due to the reaction of the C=C bonds of the acryloyl and allyl groups. Cyclopolymerisation of 2-allylphenyl, 2-(*o*-allylphenoxy)ethyl and 4-(*o*-allylphenoxy)butyl acrylates catalysed by alkylaluminium chlorides^{127–129} yields 8-, 11- and 13-membered rings; however, the catalyst's activity is insignificant for the formation of the 15-membered ring from 6-(*o*-allylphenoxy)hexyl acrylate.

Polymerisation of *ortho*-, *meta*- and *para*-(meth)acryloylaminophenyl (meth)acrylates initiated by AIBN occurs with the formation of cross-linked polymers.⁹² A decrease in the reactivity in the order *meta*- > *ortho*- > *para*-aminophenol di(meth)acrylates is associated with the character of conjugation in these monomers. Tri(meth)acryloyl derivatives of 2,4-diaminophenol (amidol) are more reactive than the corresponding (meth)acryloylaminophenyl (meth)acrylates, whereas di(meth)acryl derivatives of amidol (with a free OH group) do not polymerise. Upon polymerisation of monomers based on 2-amino-4- and -5-nitrophenols, no formation of cross-linked polymer is observed even at a 60% conversion,⁹³ as is the case of polymerisation of di(meth)acryloyl derivatives of 2-aminophenol. The presence of the nitro group decreases the number of active centres in the system resulting in the higher probability of chain transmission and formation of cycloliner structures in macromolecules.

Cinnamoylaminophenyl (meth)acrylates⁹⁰



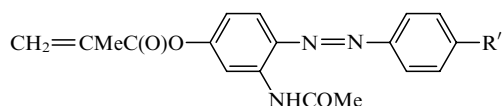
polymerise at a lower rate than di(meth)acryloyl derivatives of isomeric aminophenols; the early chain termination at low conversions appears to be due to the inability of the cinnamoyl C=C bond, which acts as a trap for free radicals, to polymerise. This conclusion is prompted by comparison of the IR spectra of

the monomer and the polymer. Photosensitivity of such monomers (photoinitiator, benzoin), like that of 4-cinnamoylamino-phenol, confirms the non-reactivity of the cinnamoyl double bond in radical polymerisation and its capability of photoaggregation.¹³⁰ The nitro group in 4-nitrophenyl cinnamate or in 4-nitro-1-naphthyl cinnamate exerts a photosensitising effect. These monomers are light-sensitive and belong to the group of self-sensitised ones.¹³¹ Poly(4-cinnamoylphenyl methacrylate) obtained in the presence of benzoyl peroxide as an initiator with a degree of conversion of 78% is insoluble in common organic solvents.¹³²

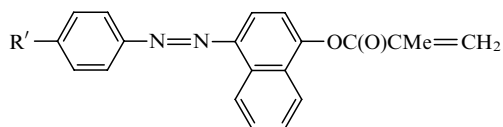
In contrast to MMA, radical telomerisation of aryl (meth)acrylates with the use of bromotrichloromethane as the telogen is not accompanied by the formation of lactones;¹³³ however, the distribution with regard to the degree of polymerisation and tacticity are analogous. Pyrolysis of telomers at 150–200 °C leads to the formation of unsaturated compounds and in part lactones.

The behaviour of 4-methacryloyl- and 4-acryloyloxybenzoic acids is highly specific under thermal treatment.¹³⁴ At 250 °C (above the upper limit of polymerisation temperature), the former undergoes polycondensation with the elimination of methacrylic acid and formation of a rigid-chain polymer, *viz.*, poly(4-hydroxybenzoate). The latter undergoes simultaneous polymerisation and polycondensation. In the polymerised state, both acids undergo polycondensation upon thermal treatment.

Methacrylic monomers with the azo group based on aminophenols^{77, 135}, and 4-amino- α -naphthol¹³⁶



R' = H, Me, NO₂;



R' = H, Br, OMe, NO₂

attract attention because of the possibility of using them for the preparation of 'self-coloured' polymers containing dye residues incorporated into the polymeric chain. Of the monomers based on azo compounds of 3-aminophenol, only the azo-coupling products at the *para*-position relative to the methacryloyl group can polymerise. The monomers based on 4-amino- α -naphthol are incapable of radical homopolymerisation because of a decreased reactivity of their radicals due to high electronic conjugation in the azo system. However, they copolymerise with styrene forming coloured polymers. Copolymers of *trans*-4-(phenylazo)-1-naphthyl acrylate and *trans*-4-(phenylazo)phenyl acrylate with (–)-menthyl acrylate are optically active.¹³⁷

The data on ionic polymerisation of aryl (meth)acrylates are scarce. They are known to polymerise by an anionic mechanism. Polymerisation of PMA on organolithium catalysts proceeds more slowly than that of alkyl methacrylates;¹³⁸ this process is characterised by the existence of a 'limit' of monomer conversion and the fact that the degree of polymerisation does not increase as the process proceeds further. Anionic polymerisation of PMA, cresyl acrylate^{139, 140} and 4-(α , α -dimethylbenzyl)phenyl methacrylate¹⁴¹ in the presence of *n*-butyllithium, as well as anionic polymerisation of *p*-cresyl methacrylate¹⁴² with naphthyllithium, butyllithium and LiAlH₄ in the hydrogen atmosphere are documented. Reduction of the polymers thus obtained with lithium aluminium hydride yields poly(α -methylalcohol) (in the case of *p*-cresyl methacrylate) and polyallylic alcohol (in the case of *p*-cresyl acrylate). Phenyl (meth)acrylate also polymerises readily with alkylaluminium chlorides by an anionic mechanism.¹⁴³ Some PA, *e.g.*, 4-nitrophenyl acrylate, do not polymerise by an anionic mechanism.¹⁴⁰

Comparative studies of radical and anionic polymerisation of 9-fluorenyl and 9-phenylfluorenyl methacrylates¹⁴⁴ in THF or toluene at temperatures from –78 to –60 °C in the presence of AIBN or butyllithium revealed substantial differences in the reaction course. Upon initiation with AIBN, the yield of polymers amounted to 60%–95%, the degree of polymerisation ranged from 9 to 37 with $M_w/M_n = 1.8$ –3.6, while upon initiation with butyllithium, the yield of polymers ranged from 3% to 40%, and $M_w/M_n = 1.9$ –2.0.

IV. Aryl (meth)acrylates in copolymerisation reactions

Aryl (meth)acrylates copolymerise easily with most monomers. For example, copolymers of PMA with ethylene¹⁴⁵ and butadiene¹⁴⁶ have been described. But of greatest interest are numerous data^{147, 148} on copolymerisation of substituted phenyl (meth)acrylates with styrene, acrylonitrile and MMA. Parameters of copolymerisation (AIBN, in bulk or in benzene at 60 °C) of PMA and its derivatives with substitutions in the ring with styrene are presented in Table 1.

It was noted that the reactivity of monomers towards styrene radical ($1/r_1$) is determined by the polar (σ) and resonance (E_r) effects of substituents and is satisfactorily described by the modified Hammett equation¹⁴⁹

$$\log \frac{1}{r_1} = \rho\sigma + \gamma E_r$$

for $\rho = 0.21$ and $\gamma = 1$. Low values of the copolymerisation constants r_1 and r_2 point to the tendency of aryl methacrylates for the alternation with styrene in the copolymerisation. The electron-donor substituents in PMA decrease polarity (e_2), while the electron-withdrawing substituents, especially those in the *para*-position, increase polarity. This is accompanied by a decrease in the frequencies of stretching vibrations of the $-\text{C}=\text{C}-$ and $>\text{C}=\text{O}$ groups.¹⁵⁰ Linear correlation is observed between the Hammett constants and the e_2 criteria as well as between $\log Q_2$ (Q_2 is the criterion of the monomer reactivity) and E_r .¹⁴⁷ In the case of *p*- and *m*-nitrophenyl methacrylates, the linear dependences are distorted because of the inhibitory effect of the nitro group. Introduction of several functional groups enhances the effect, as is observed for the criteria Q_2 and e_2 in 2,4,6-tribromophenyl and pentabromophenyl methacrylates.^{151, 152} The azo group manifests rather strong acceptor properties ($e_2 = 1.0$).¹⁵³ *ortho*-Substituents, *e.g.*, the carboxy group, strongly increase the values of Q_2 but virtually do not affect the e_2 values, which is well explained by considering the increased steric hindrances.^{154, 155}

In copolymerisation with styrene, 2-naphthyl methacrylate (2-NMA) manifests a weaker (compared to PMA) trend for alternation, which is, however, enhanced in polar solvents (*e.g.*, in acetonitrile).^{156–158} Irrespective of the solvent nature, the polydispersity and molecular mass increase with the increase in the content of 2-NMA. In complex aromatic systems, the methacryloyloxyphenyl group behaves in the usual manner, as it does in PMA.¹⁵⁹

Parameters of copolymerisation of substituted PA with styrene are presented in Table 2. Comparison of the data presented in Tables 1 and 2 shows that the values of the parameters Q and e are higher for PA than for the corresponding MA, which is associated with the absence of the effect of the α -methyl group.¹⁶⁰ For example, e_2 is equal to 1.32 for 2,4,6-tribromophenyl acrylate^{161–163} and to 0.91 for the corresponding methacrylate.

Copolymers of PA with MMA¹⁶⁴ are characterised by the predominance of MMA units ($r > 1$) in the macromolecule. In this case, the reactivity of substituted PA¹⁶⁵ is determined by their ability to form π -complexes with the double bond of MMA, which decreases in the series: PA > 2-chlorophenyl acrylate > 4-chlorophenyl acrylate. The values of parameter e increase in the same order (up to 1.46 for the latter member).

Table 1. Parameters of copolymerisation of substituted PMA with styrene.

Substituent in PMA	σ	E_r	r_1	r_2	$1/r_1$	Q_2	e_2	Ref.
—	—	—	0.30	0.60	3.33	1.17	0.51	147
4-Chloro	0.226	0.10	0.22	0.45	4.55	1.35	0.72	147
3-Chloro	0.373	0.08	0.21	0.40	4.76	1.36	0.77	147
2-Chloro	0.560	—	0.40	0.38	2.50	0.83	0.83	20
4-Nitro	0.778	0.41	0.19	0.22	5.26	1.27	0.98	147
3-Nitro	0.710	0.35	0.18	0.36	5.56	1.47	0.86	147
2-Nitro	0.650	—	0.13	0.36	7.69	1.90	0.95	20
2,4,6-Trichloro	—	—	0.19	0.34	5.26	1.40	0.86	20
Pentachloro	1.07	—	2.00	0.35	0.50	0.31	−0.20	152
2,4,6-Tribromo	—	—	0.20	0.27	5.00	1.27	0.91	151
Pentabromo	—	—	0.09	0.26	11.10	2.35	1.14	151
4-Methyl	0.170	0.03	0.30	0.70	3.33	1.23	0.45	147
4-Methoxy	0.268	0.11	0.28	0.60	3.57	1.23	0.53	147
2-Methoxy	—	—	0.33	0.66	3.03	1.13	0.43	20
4-Formyl	—	—	0.27	0.50	3.70	1.20	0.61	23
4-Acetyl	0.516	0.21	0.15	0.49	6.67	1.82	0.82	147
2-Isopropyl	—	—	0.34	0.16	2.94	0.75	0.90	20
2,6-Diisopropyl	—	—	0.39	0.13	2.56	0.79	0.66	20
2-Carboxy	—	—	0.16	1.18	6.25	2.22	0.50	154
2-Carboxy (DMSO)	—	—	0.80	0.41	1.25	0.54	0.25	155
2-Methoxycarbonyl	—	—	0.27	0.47	3.70	1.18	0.63	154
2-Phenyl	—	—	0.57	0.39	1.75	0.66	0.43	20
4-Phenylazo	—	—	0.29	0.14	3.45	1.28	1.00	153
2,4,6-Tricyano	—	—	0.18	0.10	5.55	1.56	0.82	76
4-(1,3-Diphenyl)-2-pyrazolyl-5	—	—	0.26	0.39	3.85	1.15	0.71	71
4,4-Bishydroxyphenyl- <i>o</i> -carboranyl	—	—	0.56	2.53	1.78	0.14	0.57	159
2-Naphthyl (dioxane)	—	—	0.49	0.34	2.04	0.70	0.54	158
2-Naphthyl (acetone)	—	—	0.63	0.54	1.58	0.69	0.24	158
4-Cinnamoylamino	—	—	0.62	0.31	1.61	0.58	0.48	90
4-Acetylamino	—	—	0.29	1.23	2.81	1.75	0.31	148
3-Acetylamino	—	—	0.63	4.45	1.59	—	—	148
3-Butyrylamino	—	—	0.38	0.75	2.67	1.08	0.33	148
4-Methacryloylamino	—	—	0.14	0.18	7.14	1.53	1.13	148
3-Methacryloylamino	—	—	0.26	0.03	3.85	0.66	1.39	148
4-Nitro-2-methacryloylamino	—	—	0.023	3.66	43.48	12.37	0.77	148
3-Methyltetrahydrophthalimido	—	—	0.55	0.21	1.82	0.56	0.67	119
3,5-Bis(<i>N,N</i> -dimethylamino)	—	—	0.32	0.28	3.13	1.03	0.75	

Note. The subscripts 1 and 2 in the parameters refer to the first (styrene) and the second (PMA) monomers, respectively; here and in other tables, the solvent for copolymerisation is indicated in parentheses.

Table 2. Parameters of copolymerisation of substituted PA with styrene.

Substituent in PA	r_1	r_2	$1/r_1$	Q_2	e_2	Ref.
—	0.37	0.50	2.70	0.96	0.50	20
2,6-Dimethyl	0.36	0.15	2.77	0.71	0.91	20
2,4,6-Trichloro	0.25	0.29	42.00	1.09	0.82	91
2,4,6-Tribromo	0.14	0.08	7.14	1.31	1.32	161
Pentachloro	0.90	2.11	1.11	—	—	163
Pentabromo	0.09	0.26	11.11	0.81	1.14	161
2,4,6-Tricyano	0.20	0	5.00	1.03	1.18	76
2-Carboxy (DMF)	0.49	0.61	2.04	0.85	0.30	160
2-Carboxy (DMSO)	0.20	0.53	5.00	1.50	0.70	155
2-Carboxy (benzene)	0.06	0.64	16.60	3.90	1.02	154
4-Cinnamoylamino	1.08	0.35	0.43	0.42	0.19	90
4-Propylamino	0.31	0.55	3.21	1.11	0.53	148
4-Butyrylamino	0.83	2.34	1.20	—	—	148
4-Nitro-2-acryloyl-amino	0.05	0.88	20.00	4.86	0.97	148

Note. The subscripts 1 and 2 in the parameters refer to the first (styrene) and the second (PA) monomer, respectively.

It was noted¹⁶⁵ that the presence of aromatic substituents in copolymers of MMA with phenyl (meth)acrylates increases the number of hetero- and isotactic sequences in macromolecules. As in the case of 4-phenylazophenyl methacrylate,¹⁵³ copolymers of MMA with 2-methacryloyloxybenzoic acid are enriched in the units of the latter ($r_1 = 0.74$, $r_2 = 1.22$). The rate of copolymerisation decreases with the increase in the content of the second component.¹⁶⁶ For 4-acetylphenyl methacrylate, the influence of the penultimate unit¹⁶⁷ was observed, which is due to strong steric hindrances and high polarisability of the aromatic oxo group.

Constants of copolymerisation of a number of substituted phenyl (meth)acrylates with acrylonitrile are presented in Table 3; their reactivity towards the acrylonitrile radical varies depending on the nature of the substituent group and its position in the ring.¹⁶⁸ The trend for alternation is not strong, the values of r_1 fit well the dependence

$$\log \frac{1}{r_1} = -0.98(\sigma + 1.66\Delta\sigma),$$

where σ is the Hammett polar constant, $\Delta\sigma$ is the difference between the Brown and Hammett constants for substituents. Accumulation of substituents in the ring of phenyl acrylates decreases even more strongly the trend for alternation, as is seen in the example of 2,4,6-tribromophenyl acrylate.¹⁶⁹ However, the

Table 3. Parameters of copolymerisation of substituted phenyl (meth)acrylates with acrylonitrile.^a

Substituent in phenyl methacrylates	r_1	r_2	$1/r_1$	Q_2	e_2	Ref.
Acrylates						
—	0.46	0.36	2.17	0.36	1.4	168
4-Chloro	0.33	0.94	3.03	0.37	−0.12	168
3-Chloro	1.26	0.86	0.79	—	—	168
2-Chloro	1.12	1.16	0.89	—	—	168
4-Bromo	0.82	1.02	1.22	0.07	−0.77	168
4-Methyl	0.73	0.80	1.37	0.11	−0.47	168
2,4,6-Tribromo	0.96	2.05	1.04	—	—	169
Methacrylates						
2,4,6-Tribromo	0.20	0.98	5.0	0.78	0.08	170
Pentabromo	0.28	0.12	3.57	1.09	0.64	171
2-Naphthyl (chloroform)	0.02	0.96	50.0	18.30	0.79	172
2-Naphthyl (benzene)	0.04	0.84	25.0	46.40	0.98	172
2-Naphthyl (acetone)	0.02	0.52	50.0	21.80	0.94	172
2-Naphthyl (acetonitrile)	0.03	0.51	33.3	53.00	1.09	172

Note. The subscripts 1 and 2 in the parameters refer to the first (acrylonitrile) and the second (PMA) monomer, respectively. ^a For acrylonitrile $e_1 = 1.2$, $Q_1 = 0.6$.

trend for alternation was observed for 2,4,6-tribromophenyl and pentabromophenyl methacrylates.¹⁷⁰

Copolymerisation of 2-NMA with acrylonitrile in chloroform or benzene proceeds with the formation of donor–acceptor complexes between the monomers; therefore, the values of r_1 and r_2 differ in different solvents.^{171, 172} Complexation was also found to occur in the copolymerisation of 2-NMA with monomethylitaconate,^{173, 174} thus the alternation of monomers of this pair is different in different solvents: in chloroform, $r_1 = 2.44 \pm 0.19$, $r_2 = 1.20 \pm 0.28$; in dioxane, $r_1 = 0.49 \pm 0.04$, $r_2 = 0.97 \pm 0.29$; in acetone, $r_1 = 0.15 \pm 0.01$, $r_2 = 0.28 \pm 0.03$ and in acetonitrile, $r_1 = 0.10 \pm 0.01$, $r_2 = 0.35 \pm 0.14$. Such changes in the copolymerisation constants reflect interactions between the monomer molecules and the corresponding solvent.

The constants of copolymerisation of PMA with methacrylic acid (MAA) are as follows: $r_1 = 0.40$ and $r_2 = 0.52$ (benzene), $r_1 = 0.21$ and $r_2 = 1.52$ (DMF/benzene), which points to a lower reactivity of MAA and higher reactivity of PMA in the presence of DMF, which appears to act as a complexation agent.¹⁷⁵ Copolymers of pentachlorophenyl acrylate with acrylic acid (AA) are enriched in the AA units.¹⁶³ In 2-butanone, PMA and glycidyl methacrylate give a copolymer enriched in PMA ($r_1 = 0.84 \pm 0.51$, $r_2 = 1.57 \pm 0.56$).¹⁷⁶ Optically active copolymers were obtained upon copolymerisation of phenyl, benzyl and 1-naphthyl methacrylates with maleic anhydride in the presence of β -cyclodextrin.¹⁷⁷ Copolymerisation of *N*-vinylpyrrolidone with 2-carboxyphenyl acrylate¹⁶⁰ and 2,4,5-trichlorophenyl acrylate¹⁷⁸ was also studied; in the latter case, copolymers with a high degree of alternation were obtained.

In copolymerisation of *p*- and *m*-phenylene diacrylates with styrene, a copolymer with acrylate pendent groups is formed in the initial stages; these groups then react with styrene to form a cross-linked copolymer, which precipitates from the reaction mixture in the form of a gel. *o*-Phenylene diacrylate forms a non-cross-linked ladder copolymer with styrene due to cyclopolymerisation. The smallest values of the polarity criterion e were obtained for the *ortho*-isomer.⁶ The values of the copolymerisation constants for isomeric phenylene diacrylates (PDA) are presented in Table 4.

Table 4. The values of copolymerisation constants for phenylene diacrylates (FDA) and styrene.

FDA isomer	Solvent	r_1	r_2	Q_2	e_2
<i>ortho</i> -	THF	0.55 ± 0.15	0.48 ± 0.19	0.74	0.37
	benzene	0.42 ± 0.28	0.45 ± 0.19	0.83	0.49
<i>meta</i> -	THF	0.33 ± 0.06	0.17 ± 0.02	0.78	0.90
	benzene	0.67 ± 0.11	0.15 ± 0.04	0.46	0.72
<i>para</i> -	THF	0.35 ± 0.06	0.21 ± 0.07	0.79	0.82
	benzene	0.30 ± 0.08	0.35 ± 0.09	1.00	0.70

Note. The subscripts 1 and 2 in the parameters refer to the first (styrene) and the second (FDA) monomer, respectively.

In radical copolymerisation of *p*-chlorophenyl methacrylate with ethylene glycol, 2,2-di(4-hydroxydiphenyl)propane and hydroquinone dimethacrylates,^{179, 180} the most reactive is ethylene glycol dimethacrylate as the second monomer, which is devoid of the mesomeric effect. The copolymer produced both upon catalytic and photochemical initiation is enriched in this compound ($r_1 = 0.29 \pm 0.03$ and $r_2 = 1.31 \pm 0.06$).

Methacrylamide¹⁸¹ and peroxide monomers can be used for subsequent cross-linking in copolymerisation with PMA. The constants of copolymerisation of PMA with *tert*-butyl *p*-vinylperbenzoate are as follows: $r_1 = 1.35$, $r_2 = 0.32$.¹⁸²

Copolymerisation of aryl methacrylates in donor–acceptor complexes bears a special character. For example, complexes of monomers and polymers of carbazoyl methacrylates with dinitrophenyl-containing monomers and polymers were obtained.¹⁸³ Charge-transfer complexes (CTC) are formed in copolymerisation of the donor monomers, *viz.*, *N*-(2-hydroxyethyl)carbazoyl acrylate (**1**) and -methacrylate (**2**) with the acceptor monomers, *viz.*, 2,4-dinitrophenyl acrylate (**3**) and methacrylate (**4**).^{114, 183, 184} The extent of intramolecular charge transfer in copolymers (according to the chemical shift values of aromatic protons in the ¹H NMR spectra of **3** and **4**) increases as the content of **4** in the alternating diads with **1** is increased and is larger in the **2–3** copolymer than in the **1–3** copolymer. In copolymers containing only methacrylate units, no intramolecular CTC are revealed, the most stable CTC are formed in copolymers having only acrylate units. In copolymerisation of **1** with **4**, the intermonomeric CTC are not added as a whole,¹⁸⁴ and the relative reactivity is determined solely by the sequence of distribution of units rather than by the configuration factors. With the increase in the temperature, the CTC present in the copolymer disintegrate due to the higher segmental mobility. Intramolecular CTC are also formed in the copolymerisation of picryl (meth)acrylate (incapable of homopolymerisation) with *N*-(2-hydroxyethyl)carbazoyl (meth)acrylate. The copolymerisation constants indicate that the most stable CTC are formed in dioxane.^{185–187} Photoconductivity of poly(*N*-vinylcarbazole) increases when electron-acceptor comonomers forming CTC are used, *e.g.*, isomeric 2,2-dicyanovinylphenyl (meth)acrylates (NC)₂C=CHC₆H₄OC(O)CR=CH₂ (see Ref. 188). Mixing of poly(*N*-vinylcarbazole) with the same amount of the low-molecular-weight acceptor leads to a less pronounced effect.

Directed intramolecular transfer of electronic triplet excitations was studied in a copolymer of 1-naphthyl acrylate (1-NA) and 4-acetylphenyl methacrylate.¹⁸⁹ The copolymer contains two π -electronic systems in which unidirectional transfer of electronic excitation is brought about. Upon selective excitation of the singlet level of 4-acetylphenyl methacrylate units, phosphorescence of only 1-NA units is observed. Such a molecular structure can function as a specific exciton gate.^{190–192}

In a ternary styrene–acrylonitrile–2,4,6-tribromophenyl (meth)acrylate system, the third component decreases the molecular mass and thermal stability of the terpolymers formed.^{193–195} In copolymerisation of phenyl, 4-butylphenyl, 4-nitrophenyl and

1-naphthyl acrylates with SO₂ and also in three-component copolymerisation of these monomers with hept-1-ene (see Ref. 196), the maximum content of sulfonyl monomeric units in copolymers ranges from 13% to 24% depending on the inductive steric effects. The composition of terpolymers varies within a wide range depending on the molar ratio of reagents and conversion. It is also possible to copolymerise PMA one with another.¹⁹⁷ Changes in the enthalpy and parameters of PMA copolymerisation with 2-methylphenyl and 2-ethylphenyl methacrylates were studied in the temperature range 80–100 °C.

The problems of the relationship between the structure of polymeric carriers based on cross-linked PA polymers and their copolymers with styrene and the reactivity of such carriers were reviewed.¹⁹⁸

V. Structure and properties of poly[aryl (meth)acrylates]

Esterification of atactic, syndiotactic and isotactic polyacrylic acids with phenols yields only atactic polymers. This points to the spatial isomerisation of the tertiary carbon atom in the course of esterification and the impossibility of obtaining stereoregular poly(aryl methacrylates) by polymer-analogous transformations.

Radical polymerisation of PMA yields an atactic polymer which contains nonetheless more syndiotactic structural blocks than the structurally similar poly(benzyl methacrylate) and poly(2-phenylethyl methacrylate).¹⁹⁹ This is related to the higher polarity ($\sigma = 0.6$) of the phenyl groups than that of the alkyl groups (σ varies from -0.3 to 0.215) rather than to their higher rigidity or small volume. Jimmy *et al.*²⁰⁰ studied the influence of the side groups and the size of the polymer coil of poly(benzyl methacrylate), poly(triphenylmethyl methacrylate) and poly(diphenylmethyl methacrylate). The overall activation energy of radical polymerisation of PMA is equal to 69.0 kJ mol^{-1} , which is somewhat lower than that for poly(methyl methacrylate) (PMMA).²⁰¹ In polymerisation with AIBN in the temperature range 30–100 °C, a Bernoulli distribution of stereochemical structures in the PPMA chains is observed. The content of iso- and syndiotactic triads in them decreases as the temperature increases, which is characteristic of α, α -disubstituted monomers. The triads are disposed in the chain in an isolated manner. The phenyl radical is oriented with its maximum polarisability axis along the direction of the main *trans*-chain.²⁰² In poly(aryl methacrylates), the content of isotactic, atactic and syndiotactic triads is 15%, 40% and 45%, respectively.²⁰³ The use of high-frequency NMR spectroscopy (500 MHz for ¹H and 125 MHz for ¹³C) allowed calculation of isotactic parameters for poly(phenyl acrylate) (PPA) ($P_m = 0.44$) and poly(4-fluorophenyl acrylate) ($P_m = 0.48$)²⁰⁴ obtained by radical polymerisation. Isotactic PPA can be obtained by anionic polymerisation in the presence of butyllithium.¹⁴⁰ Kempf and Harwood²⁰⁵ have shown that PPMA of a predetermined configuration can nonetheless be obtained from polymethacrylic acid if certain conditions are met.

Studies of the influence of solvents on the microstructure of poly(1-naphthyl methacrylate) and poly(2-naphthyl methacrylate) (1-PNMA and 2-PNMA, respectively) in comparison with poly[cumylphenyl methacrylate] and PMMA have shown^{206–208} that the polymerisation of 2-NMA in methanol, acetonitrile and nitromethane occurs heterogeneously. Even in the presence of non-polar solvents, the percentage of isotactic triads in 1-PNMA and 2-PNMA is higher and the percentage of syndiotactic triads is lower than in PMMA. Syndiotacticity of 2-PNMA is higher than that of 1-PNMA. In solvents with higher dielectric constants, PNMA with a still higher content of isotactic triads is obtained. Poly(1-naphthyl methacrylate) possesses a higher heterotacticity than 2-PNMA. In copolymerisation of 2-NMA with MMA ($r_1 = 1.93 \pm 0.16$, $r_2 = 0.33 \pm 0.08$), syndiotactic addition proved to be preferential.²⁰⁹ The behaviour of PA is analogous.²¹⁰ However, PPMA, poly(*p*-cresyl methacrylate), 2- and 4-methoxyphenyl methacrylates, obtained by polymerisation in the presence

of butyllithium at low temperatures in toluene, have an isotactic structure with 90% of isotriads,²¹¹ while syndiotactic polymers are formed in THF.²¹²

The temperature characteristics of poly[aryl (meth)acrylates] are determined by their structural peculiarities. As was indicated above,⁴ the thermostability is determined by the character of the substitution: in the *para*-substituted poly[aryl (meth)acrylates] the glass transition temperature (T_g) is always lower than in the *ortho*-substituted ones. This is explained by the shielding effect of *ortho*-substituents on the ester bond. T_g increases with the increase in the size of substituents and their polarity. Thus PPA, poly(*o*-tolyl acrylate) and its *para*-isomer have T_g values of 56.5, 51.5 and 24.5 °C, respectively. For 1-PNMA and 2-PNMA, T_g values are 135 and 119 °C, respectively.²¹⁴ The relationship between T_g and molecular mass (M) of poly(*o*-alkylphenyl methacrylates) is non-linear and may be described by the following equation:²¹⁵

$$T_g = T_g(0) + k \ln P,$$

where $T_g(0)$ is the temperature characteristic of the monomeric unit and P is the degree of polymerisation. For the infinitely large PPMA molecules, $T_g = 118$ °C, while for poly(2,6-dimethylphenyl methacrylate) (PMPMA) $T_g = 177$ °C. In copolymers of phenyl, 2-chlorophenyl and 4-chlorophenyl acrylates with MMA, T_g decreases with the increase in the concentration of MMA.²¹⁶ In this case, the concentration dependence of T_g obeys Johnson's equation, which considers the contribution of diads in the polymer chain to the glass transition effect. A comparative calorimetric study of substituted PPA²¹⁷ and poly(vinyl benzoates) made it possible to establish that the dependence of specific heat capacity (C_p) on temperature in the range of glassy state is described by the equation

$$C_p = A + BT + CT^2 + DT^2.$$

The increase in C_p in the glassy state was observed for all substituted polymers with increase in the volume of substituents. For a number of alkyl- and alkoxy-substituted PPA the values of T_g were found and the heat capacity jumps in the glass transition region and coefficients A , B , C and D in the proposed equation were determined.

Thermal stability of poly(aryl methacrylates) was studied by the TGA method;²¹⁸ the curves for poly(tolyl methacrylates) (PTMA) and poly(benzyl methacrylate) are S-shaped and similar to the curves for PMMA. For PPMA, the process was characterised by several ranges of decomposition. *ortho*-PTMA proved to be the most stable isomer. Effective activation energies of thermal destruction for the polymers studied vary from 81 to 159 kJ mol^{-1} (210 kJ mol^{-1} for PMMA).

Thermal destruction of poly(2-methacryloyloxybenzoic acid)²¹⁹ occurs in three steps in temperature ranges of 140–220, 250–330 and 350–450 °C with mass losses (according to TGA data) of 33%–35%, 30% and 30%, respectively, which corresponds to the stoichiometric content of salicylic acid in the polymer in the first two stages. The effective activation energy in the first stage is 79 kJ mol^{-1} . Upon destruction, fragments of the glutaric anhydride type accumulate first in the polymer (up to 330 °C); after this, the macrochains undergo disintegration.

Copolymers of PMA with MMA are more thermostable than the homopolymers;²²⁰ monomers are the main degradation products. At a low content of PMA, oligomers containing anhydride groups are also formed; with the increase in the PMA content the ability to form anhydrides drops. In contrast to homopolymers, the destruction of copolymers is characterised by relatively short kinetic chains of depolymerisation and the cleavage of the principal bonds in the macrochain. Among the copolymers of acrylonitrile with 2,3-dibromopropyl, pentabromophenyl and 2,4,6-tribromophenyl acrylates, the highest thermostability was observed for copolymers with the latter.²²¹

In studies of poly[aryl (meth)acrylates], a prominent place is occupied by the investigations of properties of their dilute solutions. By measuring the swelling degree, solubility para-

meters (δ) were determined and their dependence on the character of forces of interaction of polymer with solvent was confirmed.²²² Chloroform, tetrachloroethane, chlorobenzene and ethyl acetate are the best solvents for poly(aryl methacrylates). The values of δ for poly(alkylphenyl methacrylates) were determined in 20 solvents of different nature, considerably differing in their polarities (the contribution of δ_p) and ability to form hydrogen bonds (the contribution of δ_H), and in the widest possible range of the chain flexibility parameter σ . The magnitude of δ_H decreases slightly with the enhancement of the 'paraffinic character' of the solvent.²²³ The influence of alkyl residues is weakly manifested and the values of δ_H found differ somewhat from the calculated ones. Investigation of properties of dilute solutions by the osmometry and viscosimetry methods showed that the *ortho*-substituents in the benzene ring of the side chain increase appreciably the rigidity of the polymer. For PMPMA, the solubility parameter in toluene is equal to $9.6 \text{ cal}^{-1/2} \text{ cm}^{3/2}$ (see Ref. 224). The power index α in the dependence

$$[\eta] \approx M_w^\alpha,$$

where $[\eta]$ is the specific viscosity, increases as the thermodynamic quality of the solvent is enhanced (α is equal to 0.5 in toluene, 0.59 in THF and 0.69 in chlorobenzene). It was established that $\langle r_0^2 \rangle^{1/2}$ (characteristic chain ratio) and T_g increase upon transition from PPMA to PMPMA. For poly(2,6-diisopropylphenyl methacrylate), the solubility parameter in toluene is also equal to $9.6 \text{ cal}^{-1/2} \text{ cm}^{3/2}$ (see Ref. 225), while the Mark–Hauwink equation ($[\eta] = KM_n^\alpha$) (25 °C) has the following form for THF

$$[\eta] = 1.02 \times 10^{-4} M_n^{0.71},$$

for toluene

$$[\eta] = 1.22 \times 10^{-4} M_n^{0.69},$$

and the THF : water mixture (90.9 : 9.1)

$$[\eta] = 8.51 \times 10^{-4} M_n^{0.50},$$

for the ratio of the mean squared distance between the ends of the polymer coil and the molecular mass of the polymer (see Ref. 225)

$$\langle r_0^2 \rangle = 0.677 M^{1/2}.$$

For *p*-AAPMA²²⁶ in DMF at 25 °C

$$[\eta] = 1.40 \times 10^{-3} M_n^{0.85}.$$

Investigation of the influence of temperature on the thermodynamic properties and undisturbed dimensions of PPMA macromolecules in isobutyl methyl ketone showed²²⁷ that for all fractions an anomalous dependence of $[\eta]$ on temperature takes place at 20–35 °C, which becomes more pronounced with the increase in the molecular mass. The value of the coefficient K in the Mark–Hauwink equation is maximum at 25 °C, which implies changes in the character of hydrodynamic interactions inside the macromolecular coil, whereas the value of α is a minimum at the same temperature, which means drastic deterioration of the solvent quality. These phenomena point to a conformational transition associated with the increased chain flexibility resulting from the changes in specific interactions between the phenyl groups. The side chains in PMMA, poly(isobutyl acrylate) and poly(cyclohexyl methacrylate) have a strong influence on the temperature of the conformational transition and changes in the undisturbed dimensions of the chains, which is accompanied by the appearance of a jump in the temperature dependence of viscosity, refraction index and partial specific volume of polymers.²²⁸ Gargallo *et al.*²²⁹ analysed the influence of the size and the nature of the side groups in poly(alkylphenyl methacrylates) on the magnitude of partial volumes. The intramolecular character of the conformational transition is confirmed in the example of poly(4-*tert*-octylphenyl methacrylate).²³⁰ It was established for PPMA solutions that the conformational transition occurs owing to the changes in specific near-order interactions between the phenyl rings in the pendent

groups of the polymer studied.²³¹ Comparison of magnitudes and orientation of dipole moments related to the pendent groups of poly(chlorophenyl acrylates) revealed their strong dependence on the position of the substituent in the benzene ring.²³² The example of PPMA with the phenyl benzoate side groups showed²³³ that the influence of thermodynamic quality of the solvent on the dipole moment is characteristic of polymers with highly rigid polymeric chains and strong intramolecular interactions of the side groups.

For poly(2-biphenyl methacrylate), rather insignificant (5%–18%) variation of $[\eta]$ in different organic solvents was observed,²³⁴ whereas in other poly(aryl methacrylates) the variation of $[\eta]$ is 21%–61%, which is due to the presence of the bulky *o*-biphenyl group localised close to the basic chain. In poly(4-biphenyl methacrylate),²³⁵ the undisturbed dimensions of the chain calculated by the Stockmayer–Fixman method with consideration of the dependence of $[\eta]$ on M proved to be three times as large as those in the case of free rotation in the main valent chain, which is indicative of an appreciable inhibition of rotation in poly(aryl methacrylates). For this polymer, the temperature coefficient of undisturbed dimensions of the chain was determined (2.3×10^{-3} at 13–40 °C and 1.2×10^{-3} at 40–60 °C);²³⁶ similar calculations were performed for the *ortho*-isomer and for poly(2,4,5-trichlorophenyl methacrylate).²³⁷ In the case of poly(2-biphenyl methacrylate), the value of the chain flexibility parameter σ (2.8) was larger than that for poly(4-biphenyl methacrylate) ($\sigma = 2.7$), which points to a larger flexibility of the former due to a close position of the *o*-diphenyl groups to the basic chain.²³⁸ Studies of the mobility in poly(2-biphenyl methacrylate) by the DSC method pointed to the occurrence of four relaxation processes with the temperature increase, *viz.*, γ , β , α and ρ . The processes of α - and β -relaxation are related to vitrification and subvitrification, respectively.²³⁹

For PPA, it was found that the values of temperature coefficients of the undisturbed dimensions range from -3.4×10^{-3} to -4.7×10^{-3} , the upper critical temperature of dissolution Θ in ethyl lactate is 14 °C and the values of $[\eta]$ increase with the temperature increase within the range 7–77 °C.²⁴⁰ As for PMMA, the constants of the Mark–Hauwink equation for PPMA fit the van Krevelen equation.²⁴¹ The use of the light scattering method in ethyl lactate for PPA allowed determination of values of M_w , second virial coefficients A_2 , mean squared radii of inertia $\langle S^2 \rangle$ and coefficients of swelling at different temperatures.²⁴² This method was also applied to study PNMA solutions^{243,244} in comparison with polystyrene. The ratios of the threshold concentration c_0 in light scattering measurement to the second virial coefficient A_2 for these polymers were the same and equal (in non-polar solvents) to 0.93. For dilute solutions of homopolymers with the main methacrylate chain and methoxy-biphenyl mesogenic groups and their copolymers,²⁴⁵ the constants in the Mark–Hauwink equation, parameters of Flory–Huggins interaction and the mean squared distances between the chain ends $\langle r^2 \rangle$ were determined. The latter parameter is greater than that in PMMA, which indicates an appreciable increase in the rigidity of the polymethacrylate chain upon introduction of the mesogenic side groups. As regards PMA copolymers²⁴⁶ and substituted PMA,²⁴⁷ for them, too, the values of K , α and Θ were found in certain solvents, and the undisturbed dimensions of the polymer coils and parameters of the chain rigidity were calculated.

The data on electrical properties of poly(aryl (meth)acrylates) are scanty. The spectra of dielectric losses at different temperatures were studied for specimens of PPMA and polymers of *o*-, *m*- and *p*-PTMA²⁴⁸ and for polymethoxy-substituted PMA.²⁴⁹ Three relaxation processes were found to occur. The high-temperature process (α -relaxation) occurs in the glass transition range and is related to the micro-Brownian mobility in the basic chain of the polymer. The maximum temperature of this process increases in the following order: *m*-PTMA < *o*-PTMA < PPMA < *p*-PTMA; the crystallinity of polymers increases in the same order. In the middle-temperature range, β -relaxation is observed due to the micro-Brownian mobility of the side groups, which is particularly

manifested in *o*-PTMA. Increased activation energies of this process were observed for specimens of higher crystallinity (PPMA and *p*-PTMA). The low-temperature γ -relaxation is associated with the motion of the tolyl and methoxyphenyl pendent groups. Investigation of the dielectric relaxation of poly(phenyl and chlorophenyl acrylates) revealed that the intensity of the β -process in PPA and poly(4-chlorophenyl acrylate) is lower than in poly(2-chlorophenyl acrylate) and poly(3-chlorophenyl acrylate); in the last two polymers the intensity of β -process is higher than that of α -process. α -Relaxation is determined by the free volume and is well described by the binding model;²⁵⁰ in polymers the time of dielectric relaxation is always shorter than the time of mechanical relaxation.²⁵¹

Noticeable changes in the electrical characteristics of polyethylene in strong fields (electrical strength and I – V characteristics in the pre-breakdown voltage range) are observed when small amounts (1%–2%) of comonomers, such as pentabromophenyl and 2,4,6-tribromophenyl methacrylates, were introduced.²⁵² The maximum value of breakdown voltage is observed at the content of the former additive of 0.1%–0.2%, the doping action is produced by units of the above-mentioned PMA. Such an effect is not exerted by benzyl methacrylate.

In a magnetic field, a noticeable effect of the increase in spontaneous orientation of PPMA may be observed only in mesomorphic polymers, in particular in those with the phenyl benzoate pendent groups.²⁵³

Poly[aryl (meth)acrylates] are very transparent (transmission coefficient > 90%) and possess good mechanical properties.²⁵⁴ Therefore, copolymers containing up to 99% of these monomers are used as materials for manufacturing lenses.²⁵⁵ Some of them, in particular 1- and 2-NMA, determine the high refraction index of copolymers.²⁵⁶

Some aryl (meth)acrylates and their polymers may exist in the liquid-crystalline state with characteristic anisotropy of optical properties.^{31, 257} Their polymeric nature is manifested in considerable enhancement of thermal stability of the mesophase, its temperature range is restricted by the glass-transition and clarification temperatures and is determined to a considerable extent by the nature of the basic chain and its flexibility.²⁵⁸ In such polymers, structures of various mesophases and different variants of the packing of mesogenic groups can be realised. Most polymers can form lamellar structures of the smectic type. Nematic structures arise in polymers with shorter substituents and flexible hinges. In particular, all polymers with the lateral mesogenic groups possess nematic mesomorphism.²⁵⁹ Clarification temperatures of polymers with the same mesogenic groups but different chemical composition of the basic chain coincide, whereas in these cases the T_g values decrease with the increase in flexibility of the basic chain or the length of the terminal fragments of the mesogenic pendent groups.

For all the polymers having one mesogenic side unit per elementary unit of the chain, it was established that the global anisotropy is independent of steric inhibition of the α -methyl groups. A decrease in temperature results in a basic polymer chain extension normally to its mesogenic units, which thus acquires an elongated shape.²⁶⁰ According to the results of X-ray diffraction analysis, the macromolecules of polymers of phenyl and 4-alkoxyphenyl esters of acryloyloxybenzoates,²⁶¹ which form anisotropic systems on cooling of melts or concentrated solutions, represent cylinders 8–10 nm long and 2.5–3.9 nm in diameter formed by aperiodic helices.

Acrylic polymers that contain mesogenic phenyl benzoate groups with short alkyl substituents form only nematic mesophases.^{262, 263} In studies of the comb-like liquid-crystalline polymers, which differ in the nature of the basic chain (acrylate or methacrylate) but contain identical phenyl benzoate groups,^{264, 265} the low- and high-temperature smectic phases of polyacrylate are referred to the smectic types B and A, respectively. For polymethacrylates, the following scheme of polymorphic transformation was proposed: smectic F $\rightarrow$ smec-

tic C $\rightarrow$ smectic A $\rightarrow$ isotropic liquid. Investigation of conformational changes in poly(methacryloyloxyphenyl 4-*n*-alkoxybenzoates)²⁶⁶ in the temperature range including the glassy, liquid-crystalline and isotropic states revealed that the conformational changes are observed in the glassy state 40–80 °C before the transition to the liquid-crystalline state depending on the alkyl chain length and that they are accompanied by the homeotropic orientation in the polymeric films. Poly(biphenyl acrylate) prepared by the reaction of polyacryloyl chloride with 4-hydroxybiphenyl forms a smectic mesophase A at 144 °C, which is totally destroyed at 250 °C. The mesophase–isotropic transition is nearly fully reproduced in repeated cycles of heating.²⁶⁷ Poly(4-acryloyloxyazobenzene) is in turn in the mesomorphic state at 100–240 °C. Polyacrylates and polymethacrylates that contain the cyano-substituted aromatic azomethine and cyanobiphenyl mesogenic groups form liquid-crystalline phases of the nematic type and also of the smectic type A and C.^{268, 269} In polymethacrylate with the biphenyl fragments as mesogens in the side chains, a poorly ordered smectic phase exists at 136–157 °C and above these temperature, the isotropic phase.²⁷⁰

Thus, among poly[aryl (meth)acrylates] it is possible to find polymers that have mesophases in different temperature ranges. Such polymers are capable of reflecting selectively light in the IR, UV and visible parts of the spectrum, manifesting transitions induced by electric and magnetic fields, and in some cases they even possess ferroelectrical properties.²⁵⁸ Owing to such electrical and other effects, the field of application of these polymers in modern technology is extended.

VI. Chemical and photochemical properties of poly[aryl (meth)acrylates] and their copolymers

Chemical properties of poly[aryl (meth)acrylates] and their monomers are determined primarily by the presence of the ester group, the aromatic ring and its substituents. The rate of hydrolysis of the pendent groups in PPMA at different temperatures in aqueous DMSO is described by three different constants corresponding to the hydrolysis of the ester groups of the polymer with the adjacent 0, 1 and 2 hydrolysed ester groups.²⁷¹ The activation energies that correspond to these constants are equal to 40.6, 58.2 and 74.0 kJ mol^{–1}, respectively. Alkaline hydrolysis of PPMA with *p*-Cl, *p*-OMe, *p*-Me and *m*-NO₂ substituents in the aromatic ring is of the pseudo-first order;²⁷² the first two constants increase with the higher KOH concentration, whereas the third constant remains virtually unchanged. The values of these constants correlate well with the values of the Hammett constants for substituents.

Enzymatic hydrolysis of the side ester groups in copolymers of 4-nitrophenyl methacrylate with acrylamide²⁷³ in the presence of lipase did not take place, whereas esterase and α -chymotrypsin acted very slowly. The rate of alkaline hydrolysis increased with the higher content of acrylamide in the copolymer, which was due to the influence of acrylamide units on the reactivity of ester groups in the 4-nitrophenyl fragments. The action of α -chymotrypsin on 2-biphenyl methacrylate (BPMA) and its copolymers induced hydrolytic liberation of hydroxybiphenyl; the Michaelis constant for the copolymers was lower than for the homopolymer and decreased in the following series of comonomers: methacryloylglycine > vinyl acetate > methacryloylalanine > styrene.²⁷⁴ The catalytic effect of α -chymotrypsin was weaker in the case of poly(2-biphenyl acrylate).²⁷⁵ The possibility of modifying polymers and copolymers of 2,4,5-trichlorophenyl acrylate²⁷⁶ and 4-nitrophenyl methacrylate^{277–279} through their aminolysis has been demonstrated.

Optimisation of the reaction conditions makes it possible to introduce various substituents, for example, perfluoroalkyl groups,²⁸⁰ into the phenyl groups of PPMA. Reactive functional groups can be subjected to further transformations²⁸¹ and be used for the chelate formation.^{282, 283}

Chemical transformations of poly[aryl (meth)acrylates] under the action of different types of radiation are rather diverse. Investigation of the photobehaviour of phenyl-containing methacrylate polymers showed²⁸⁴ that the lifetime of the singlet state in polymers is shorter than in model small molecules, which is related to the higher sensitivity of this parameter to steric hindrances. A high yield of long-living triplet states was observed in the presence of naphthalene rings.²⁸⁵ The acetyl groups favour quenching of the triplet. 2,4-Diacetyl-1-naphthyl methacrylate units induce quenching even at their content ~ 1 mol. % with a quantum yield of 0.4.²⁸⁶ In poly(2-naphthyl methacrylate), insignificant migration of the singlet energy occurs.²⁸⁷ Because of a large difference in the energies of the excited singlet and triplet states, the singlet energy transfer to the ketone traps in a copolymer of 2-NMA with arylvinyl aromatic ketones and the triplet energy is transferred from these traps again to the naphthalene chromophores. The fluorescence (FL) spectrum of 2-PNMA²⁸⁸ is characterised by the presence of two bands which are attributed to monomeric (340 nm) and excimeric (400 nm) luminescence. The luminescence spectrum of copolymers strongly depends on the amount of a comonomer. In copolymers with MMA, the correlation between the excimeric and monomeric fluorescences is determined basically by the molar fraction of naphthyl methacrylate units.²⁸⁹ The ratio of intensities of excimeric and monomeric fluorescences is taken as the compatibility parameter of copolymers of naphthyl and anthryl methacrylates with MMA and *n*-butyl methacrylate (BMA).^{290,291} In copolymers of PMA,²⁹² the band of excimeric FL is at 355 nm. The FL spectra of copolymers of vinyl 3-(1- and 2-naphthyl)acrylate with vinyl hexanoate and vinyl acetate were analysed in order to reveal the monomeric and excimeric FL of the naphthalene groups at 340 and 390 nm, respectively. It was shown²⁹³ that the excimer is formed by two naphthalene groups bound to cyclobutane in the 1,2 or 1,3 positions *cis*-arranged relative to the cyclobutane ring. The curves of FL decay are well described by three exponents attributed to three fluorescence centres: excimers, monomeric chromophores capable of transition to the excimer form and isolated monomeric chromophores incapable of excimer formation.

Copolymers of 2-[(2,4,6-tricyanophenyl)thio]ethyl methacrylate with 3,5-bis(*N,N*-dimethylamino)phenyl methacrylate which are obtained in bulk phase and form rigid films possess photoconductivity. The photocurrent in such films was observed upon illumination with light with wavelengths of 200–700 nm.²⁹⁴

Photodestruction of PPMA in vacuum and in air occurs with the random scission of macrochains and is intensified under short-wave UV irradiation.²⁹⁵ The presence of chlorine atoms in the phenyl radical accelerates photodestruction. For 1-PNMA and its copolymers with BMA it was established that in contrast to thermodestruction leading to depolymerisation, the photo- and radiation destructions involve processes of the basic chain scission, the photodestruction rate depending on the intramolecular excimer formation.²⁹⁶ For this reason, the quantum yield of the chain scission decreases monotonically (down to 0.015) with the increase in the content of 1-NMA units. Excimers are not formed for the BMA–NMA–BMA sequences.^{297,298} Upon irradiation with electrons (20 keV) and UV light, the perfluoroalkylated PPA is cross-linked in contrast to the non-perfluoroalkylated one which is destroyed under these conditions.²⁹⁹

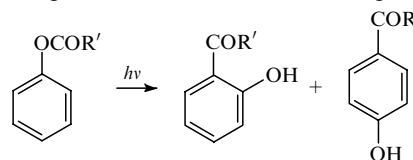
In the presence of oxygen, photooxidation of poly[aryl (meth)acrylates] occurs with the formation of carbonyl groups. Investigation of the photooxidation of 2-NMA copolymers with styrene, MMA and acrylonitrile revealed³⁰⁰ that where the content of 2-NMA was 7 mass %, the concentration of carbonyl groups was considerably higher than in polystyrene (0% of NMA) or in copolymers with 13% or 26% of 2-NMA. The number-average molecular mass is also most strongly decreased in copolymers with 7% of 2-NMA.

On the whole, poly[phenyl (meth)acrylates] are regarded as radiation-resistant materials,³⁰¹ however, their resistance is

sharply decreased upon introduction of halogens into the aromatic rings. Upon irradiation of poly(4-chlorophenyl methacrylate) with ionic beams,^{302,303} the primary process is the elimination of the chlorine atom with the formation of reactive centres in the basic chain under the action of atomic chlorine. Recombination of these two types of polymeric radicals leads to the cross-linking of the polymer. The radiation yield of the basic chain scission in the radiolysis of MMA copolymers with trichloro- and tetrabromophenyl methacrylates³⁰⁴ is strongly enhanced by small amounts of the latter, which is related to the important role of the processes of dissociative electron capture. The yield drops dramatically with the increase in the concentration of chlorine-containing monomer to 17% when the processes of cross-linking become noticeable. An analogous behaviour is displayed by halogen-substituted PPMA upon irradiation with a beam of electrons.³⁰⁵

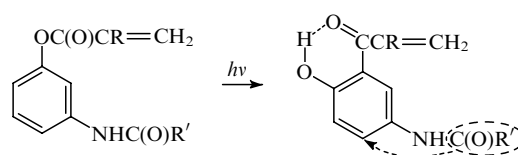
Homopolymers of 4-acryloyloxyazobenzene and 4-methacryloyloxyazobenzene copolymers with methyl acrylate³⁰⁶ and MMA,³⁰⁷ respectively, possess photochromic properties. The azo group in their units undergoes *trans*–*cis*-isomerisation under UV irradiation ($\lambda = 370$ nm). The increase in absorption is observed at $\lambda < 280$ nm and $\lambda > 400$ nm. Photoisomerisation occurs as the first-order reaction and is reversible, the rate constant for this reaction is independent of temperature. The reverse dark reaction (thermal *cis*–*trans*-isomerisation) is also of the first order. In homopolymers, the kinetics of photoisomerisation is of a more complex character. For them, this is an energetically more favourable process than for copolymers, which may be explained by the interaction of pendent groups. The absorption band of the azobenzene group corresponds to the π – π^* -transition and is shifted from 321.5 to 324 nm with the decrease in the content of the *trans*-isomer.³⁰⁷

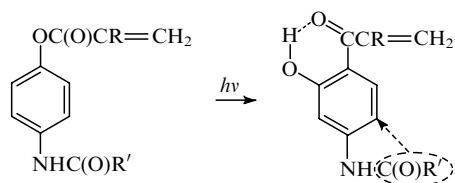
Like other phenyl esters, PA and PMA as well as their polymers and copolymers undergo the photochemical Fries rearrangement under the action of UV light^{308–313}



$R^1 = CR = CH_2$.

The rearrangement is inhibited after transformation of certain amount of phenyl esters into *o*- and *p*-hydroxyphenyl ketones (a 2:1 mixture). The ketones were identified by the appearance of absorption maxima at 265–270 and 294 nm in the UV spectra of irradiated monomers or new absorption bands at 1620 and 1660 cm^{-1} in the IR spectra of UV-irradiated poly[phenyl (meth)acrylates]. The stability of the polymer with respect to further UV irradiation is associated with the formation of hydroxy ketones on its surface and their photoshielding effect due to higher extinction coefficients. It is known³¹⁴ that 2-hydroxybenzophenones are good light stabilisers. It is presumed that their light-stabilising effect is related to the fast tautomerism of excited states. Spectral measurements showed³¹⁵ that under prolonged action of the UV light the molecules of *m*- and *p*-(*N*-acylamino)phenyl (meth)acrylates undergo the Fries rearrangement involving mainly the ester groups rather than the acylamino groups and resulting in the appearance of the hydroxy and amino groups, respectively.





R' = Me, Et, Pr.

Poly(1- and 2-naphthyl methacrylates) also undergo photochemical transformations by the Fries reaction upon UV irradiation.^{316,317} This reaction may be of practical value for the modification of polymeric materials. Yet another type of light-sensitive polymers, *viz.*, poly(methacryloyloxybenzylideneacetophenones)^{318,319} and copolymers of 4-methacryloyloxybenzylideneacetophenone with BMA,³²⁰ have been described. Upon UV irradiation, they become insoluble in organic solvents because of photodimerisation resulting in the formation of cyclobutane structures. Spectral sensitisation of such copolymers is possible with triplet sensitisers, *viz.*, 5-nitroacenaphthene, picramide, *N*-acetyl-4-nitronaphthylamine and some quinones. Evidently, this process is similar to the photoaggregation of cinnamates.

The polymers containing 4-acryloyloxybenzophenone units are highly efficient photoinitiators of polymerisation.^{321–323} After light absorption, the units of this monomer pass into the singlet-excited state with subsequent intercombinational conversion into π, π -triplet state and transition to n, π -triplet state, which may be quenched by oxygen molecules or be deactivated in the presence of a hydrogen donor with the formation of ketyl radicals.³²³ Homopolymer is the most efficient as the polymeric photoinitiator and its copolymers with 4-dimethylaminostyrene are also highly active.³²¹

Some PMA copolymers possess unusual photoluminescent properties, whereas the corresponding low-molecular-mass compounds and homopolymers do not luminesce under experimental conditions.³²⁴ The large diversity of properties opens wide possibilities for the application of poly[phenyl (meth)acrylates].

The data on liquid-crystalline aryl (meth)acrylates were generalised in a number of monographs (see, *e.g.*, Refs 59, 60), and this allows us not to go into details of this information.

VII. Practical application of aryl (meth)acrylates

At present, several types of phenyl (meth)acrylates are produced in small quantities and their variety increases continually. An analysis of most recent scientific and patent publications shows that these monomers and polymers, novel for modern industries, will find wide uses basically as modifiers of properties of polymers produced on a large scale.

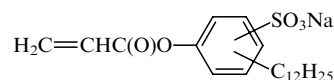
In order to manufacture lenses with high refractive indices (up to 1.67), thermal stability, resistance to shock and solvents and surface hardness, use is made of copolymers of the known monomers (MMA, styrene, *etc.*) with 3%–40% of PMA,^{325–328} halogenoaryl methacrylates,^{329–332} tribromophenyl methacrylate,^{333–337} brominated phenyl acrylates,³³⁸ as well as 1- and 2-naphthyl (meth)acrylates and benzylphenyl methacrylate.^{339,340} Pentachlorophenyl (meth)acrylates may be used as comonomers in the manufacture of light-conducting fibres.³⁴¹ PMA and PA may be the components of oxygen-permeable plastics intended for manufacturing contact lenses.³⁴² Poly(fluorophenyl acrylates) are used for manufacturing glass for aircraft port-holes.³⁴³

Halogen-containing phenyl (meth)acrylates [*e.g.*, 2,4,6-tribromophenyl (meth)acrylate] were recommended as components of rubbers³⁴⁴ and plastics³⁴⁵ in order to increase their fire resistance. For the same purpose, pentabromophenyl (meth)acrylates are incorporated as the third component into a styrene–acrylonitrile copolymer.^{346,347}

Aryl (meth)acrylates are introduced into plastics to improve their service properties, *e.g.*, shock resistance.³⁴⁸ Poly[3-pentadecylphenyl (meth)acrylates] are used as pressure-sensitive adhesives for binding various porous materials.³⁴⁹ 2,2-Di(4-hydroxyphenyl)propane di(meth)acrylates exert a particularly noticeable effect on general properties of plastics.^{350–352}

It is proposed to use di(meth)acryloyl derivatives of dihydroxybiphenyl oxides as cross-linking agents for polymeric materials. Fluoro-substituted diacrylates, for example, 1,3-bis(hydroxy-hexafluoropropan-2-yl)benzene diacrylate, are used for making coatings.³⁵³ It is proposed to use alkoxyated dimethacrylates of bisphenol-A,^{354–356} xylene dimethacrylates³⁵⁷ and aryl or naphthyl (meth)acrylates^{358,359} in compositions for photo-solidified coatings and glues. High-strength solidifying compositions may be prepared using hydroxyaryl (meth)acrylates that can form urethanes with diisocyanates or isocyanatoethyl methacrylate.³⁶⁰

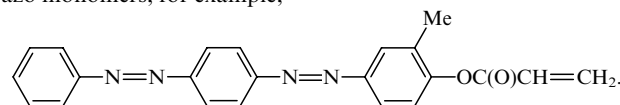
PMA and its derivatives and 2-NMA ($\geq 10\%$) are incorporated into copolymers used in the production of precision optical devices and video discs for recording information.^{361–364} Low-hygroscopic methacrylic polymers with the water absorption $\leq 0.58\%$ at 50 °C have been patented.³⁶⁵ Polymeric surfactants based on copolymers of hydrophilic and hydrophobic monomers are highly effective.³⁶⁶ These include di(meth)acrylates of hydroquinone containing in its ring such substituents as halogens, alkyls (C₁–C₂₀) and biphenyl. Copolymers which are components of hydrosol compositions with improved adhesive capacity and cohesive strength may contain 2-acryloyloxynaphthalene-2-sulfonic acid along with other monomeric acids.³⁶⁷ Emulsifying monomers of the general formula



accelerate polymerisation and increase the yield of the target polymer.³⁶⁸

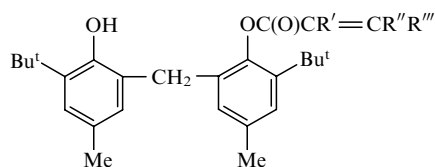
The adhesively strong coatings resistant to the action of water and ethanol were obtained based on film-forming aryl (meth)acrylate copolymers.^{369,370} Aqueous dispersions of such copolymers applied onto the polymer surface prevent sweating of plasticising agents from them.

Phenyl (meth)acrylates are used for the modification of well-known polymeric products. In order to prepare self-coloured polypropylene, polycaprolactam or polyethylene terephthalate fibres³⁷¹ and films,³⁷² these are grafted (with the aid of UV light) to azo monomers, for example,



Azo monomers are also used in the synthesis of polymeric luminophores.³⁷³ Units of tribromophenyl methacrylate are incorporated into polystyrene in order to improve its colourability.³⁷⁴ Coloured polymeric films were prepared by dispersing dyes based on 3,3'-diethoxydicarbocyanine iodide in PPMA.³⁷⁵

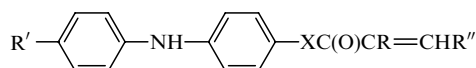
Phenyl (meth)acrylates containing groups with antioxidant or UV-stabilising activities may be introduced into macromolecules as intrachain stabilisers.^{376,377} This method of stabilisation is more efficient than the conventional introduction of antioxidants because it prevents their losses from polymers due to volatilisation during processing or diffusion in the course of their service. *p*-Anilinophenyl methacrylate³⁷⁸ may be regarded as one of the efficient thermostabilisers of this type for polyethylene.³⁷⁶ Copolymers of dienes and vinylarenes (styrene) are stabilised by introducing up to 1.5% of a complex acrylate³⁷⁹



$R', R'', R''' = \text{H, Alk}(C_1-C_{16}), \text{Ar, cyclo-Alk}(C_5-C_9), \text{AlkAr}(C_7-C_{12})$.

Monomeric amines of the type of 4-hydroxydiphenylamine (meth)acrylate belong to the group of non-sweating and non-washed off antioxidants for rubbers.³⁸⁰ 2-*tert*-Butyl-6-(3-*tert*-butyl-2-hydroxy-5-methylbenzyl)-4-methylphenyl acrylate is a high-temperature thermostabiliser belonging to the group of polymer-bound antioxidants of the phenol type.^{381, 382}

Aminophenyl (meth)acrylate derivatives have been used as antioxidants³⁸³



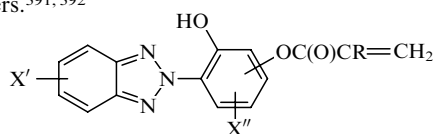
$R' = \text{H, Me, OMe}; R'' = \text{H, Me, Ph}; X = \text{NH, O}$.

Such antioxidants are not washed off from rubbers by solvents, are not evaporated and do not cause their bleaching, which is highly important in the technology of rubber processing.

Acylaminophenyl (meth)acrylates, imidophenyl (meth)acrylates and imidonaphthyl (meth)acrylates^{384, 385} are efficient light stabilisers for styrene. The mechanism of stabilisation is associated with the intramolecular energy transfer in molecules under the action of UV light. Aryl methacrylates introduced into the polystyrene macromolecule in the amount of 5 mass % undergo the Fries photorearrangement, which is accelerated owing to the intramolecular energy transfer of triplet excitations from the phenyl to the naphthalene moieties of the molecule. The photorearrangement rate is an order of magnitude higher in naphthyl (meth)acrylates than in phenyl (meth)acrylates.

The use of monomers providing for self-stabilisation upon exposure to natural conditions is rather promising for the preparation of copolymers.³¹⁶ Under the action of light, the Fries rearrangement occurs in films, for example, of copolymers of 1-NMA or 2-NMA with styrene or MMA, with the formation of structures of the type of 2-acetyl-1-naphthol with absorption at 320–400 nm. Even at a degree of conversion of $\sim 5\%$, one observes a substantial decrease in the photorearrangement rate, which leads to the increased light-resistance of NMA units situated at a distance of ~ 2.6 nm from the photoproduct.³⁸⁶ The application of such light stabilisers is advisable for coatings and fibres. Polymeric absorbers can also be obtained by copolymerisation of monomers which contain light-stabilising fragments or groups, *e.g.*, of phenyl 5-(meth)acryloyloxysalicylate with vinyl acetate, vinylidene chloride and vinyl chloride and of 2-hydroxy-4-(meth)acryloyloxybenzophenone with MMA.^{387, 388} The effect of light stabilisation is also achieved by grafting these monomers to polystyrene, polypropylene and polyethylene; the activity of methacrylate is higher and this is explained by additional stabilisation of the radical owing to hyperconjugation with the methyl group.³⁸⁹ An analogous effect is also observed for di(meth)acryloyl derivatives of 2,4-dihydroxybenzophenone.³⁹⁰

To prepare transparent articles with improved UV absorption and weather resistance, it is proposed to introduce phenyl (meth)acrylates with benzotriazole substituents into copolymers.^{391, 392}



$X', X'' = \text{H, Hal, Alk, Ar}$.

The photochemical behaviour of numerous monomers and polymers with benzotriazole fragments has been described in

several publications.^{393–395} It was shown that the light-protective effect of polymeric UV absorbers depends on the nature of the groups which determine the nearest environment of the fragment and their influence on the strength of the intramolecular hydrogen bond in the benzotriazole fragment. Polyethylene used for manufacturing a packing material containing 4-acryloyloxybenzophenone units (from 0.1% to 40%), which is destroyed under the action of light in 120 h, has been patented.³⁹⁶

Monomers with the nitro groups, for example, 4-nitrophenyl methacrylate³⁹⁷ or 4-nitro-1-naphthyl methacrylate can be used as photosensitisers. Monomers with 4-dialkylaminobenzylidenacetophenone residues, *e.g.*, 4-(4-dimethylaminobenzylidenecarbonyl)phenyl methacrylate can be used as³⁹⁸ photoinitiators, including the intrachain ones,^{399, 400} sensitive to light with a wavelength of 488 nm.

Aryl (meth)acrylates undergo photopolymerisation, which makes them promising components of photopolymerisable compositions (PPC) for printed circuit boards and photoresists. Di(meth)acrylates of the general formula $\text{H}_2\text{C} = \text{CRC}(\text{O})\text{NH} - \text{C}_6\text{H}_4\text{OC}(\text{O})\text{CR} = \text{CH}_2$ are introduced into PPC for improving the technology of manufacturing offset type forms,⁴⁰¹ upgrading printing-technical properties of compositions for obtaining thin copying layers.⁴⁰² It was proposed to introduce 3-acetylaminophenyl acrylate into PPC for the same purpose.⁴⁰³ Dimethacrylates of isomeric aminophenols are also used as light-sensitive compounds in compositions for ideally transparent planographic printed circuit boards.⁴⁰⁴ Two preparative methods for obtaining light-sensitive polymers containing *p*-phenylene diacrylate groups (PDAG) have been described. Under the action of radiation from an argon laser, PDAG is photodimerised with a quantum yield of 0.44, which allows one to use these polymers as resists.⁴⁰⁵ Comparison of the reactivities of PA in UV-compositions with alicyclic and aliphatic analogues (including diacrylates) showed its highest efficiency.⁴⁰⁶ A copolymer of 4-nitrophenyl methacrylate with 2-cinnamoyloxyethyl methacrylate is an efficient negative photoresist with a sensitivity of $17-34 \text{ mJ cm}^{-2}$ and a resolution of $1.5-3 \mu\text{m}$ for a layer $0.5-1 \mu\text{m}$ thick.⁴⁰⁷ Homo- and copolymers of 4- or 2-*tert*-butoxycarbonyloxyphenyl (meth)acrylates are used as binding agents in irradiation-sensitive polymer mixtures and depending on the development technique of the irradiated photoresists, negatives or positives are obtained.⁴⁰⁸ The use of phenyl acrylates in resists for X-ray microlithography with the plasma-based development makes it possible to attain submicron resolution ($\sim 0.5 \mu\text{m}$) at a sensitivity of 2.5 mJ cm^{-2} (see Ref. 409). The content of aryl (meth)acrylate in X-ray resists reaches 30%.⁴¹⁰ Positive photoresists with high sensitivity and resolution are obtained by polymerisation of esters of 2-cyanoacrylic acid in the presence of sulfur-containing compounds.⁴¹¹

Irradiation of poly(halogenophenyl methacrylates) with electrons induces their cross-linking;⁴¹² therefore, such polymers may be used as negative electron resists. Poly(4-chlorophenyl methacrylate) is an example. However, the increase in the number of chlorine atoms in the ring makes destructive processes more pronounced and the resist may become negative. Poly(phenyl methacrylates) with the perfluoroalkyl groups are also regarded as negative electron resists. The sensitivities of C_3F_7 - and $\text{n-C}_6\text{F}_{13}$ -containing polymers are 20 and $7 \mu\text{C cm}^{-2}$, respectively.⁴¹³ In the case of copolymers, the fluorine atoms may be present in comonomer units. For example, a copolymer of PMA containing up to 50% of α -trifluoromethylacrylic acid is an electron resist with a sensitivity of $10 \mu\text{C cm}^{-2}$ at a zero residual thickness.^{414, 415} The halogen-free poly[aryl (meth)acrylates] are positive electron resists with an insufficiently high electron sensitivity. It is $50 \mu\text{C cm}^{-2}$ for PPMA, $200 \mu\text{C cm}^{-2}$ for PNMA, $65 \mu\text{C cm}^{-2}$ for poly(fluorenyl methacrylate), $550 \mu\text{C cm}^{-2}$ for poly(anthryl methacrylate) and differs considerably from that for PMMA ($10 \mu\text{C cm}^{-2}$).⁴¹⁶ Introduction of halogen, *e.g.*, by chloromethylation, changes drastically the situation.⁴¹⁷ Electron-ray resists become negative with a sensitivity of $3.7-11.0 \mu\text{C cm}^{-2}$; their sensitivity increases up to a 20%

content of chloromethyl groups. The crucial role in the cross-linking process is played by recombination of free radicals formed as the result of cleavage of the carbon – halogen bond. In contrast to vinyl and epoxide polymers, virtually no postirradiation chain polymerisation, which decreases the resolution obtained, occurs in 2-PNMA. In this particular case it reaches 0.5 μm . This polymer may be sensitised to the action of light with $\lambda = 365\text{ nm}$ (3% of Michler's ketone), the resultant sensitivity is $\sim 100\text{ mJ cm}^{-2}$. The above-considered polymers may be used in the so-called hybrid lithography, where relatively large details of microrelief are obtained under the action of UV light, while fine details are obtained with the aid of a well-focused electron beam.

Copolymers of ethylene with halogenoalkyl-substituted PMA are excellent dielectrics.^{418, 419} Polymers of 4-hydroxystyrene or its halogen derivatives esterified with methacryloyl chloride,⁴²⁰ exhibit good dielectric properties, heat and fire resistance. These are also suitable for manufacturing bases for semiconductor devices. As in the case of copolymers of styrene with 2,4,5-trichlorophenyl acrylate,⁴²¹ modification of functional groups makes it possible to prepare electron-conducting metallocomplexes. Polymethacrylates, containing aromatic amino groups in the side chain, were found to possess the hole-type photoconductivity with rather high mobility of charges comparable to that in polyvinylcarbazole.⁴²²

There are data on piezoelectrical⁴²³ and magnetic⁴²⁴ properties of poly[aryl (meth)acrylates]. Specific behaviour of such polymers with liquid-crystalline properties in electric and light fields allows prediction of their wide use in electronics and optics, in particular, in birefringent and colour displays using the 'guest – host' effect, phase lenses and high-resolution laser devices.^{425, 426}

Like phenols, phenyl (meth)acrylates are antiseptics. Introduction of chlorine atoms into the aromatic rings increases biocidal activity; however, the low rate of the ester bond hydrolysis⁴²⁷ of poly[aryl (meth)acrylates], e.g., 2,4,5-trichlorophenyl methacrylate, may lead to the total loss of this activity. Nonetheless, materials based on copolymers of styrene with pentachlorophenyl acrylate,^{428, 429} *p*-chloro-, *p*-cresyl or biphenyl acrylate and analogous copolymers with MMA and acrylates⁴²⁹ possess noticeable antimicrobial activities. Homo- and copolymers of pentachlorophenyl methacrylate⁴³⁰ and 2-carboxyphenyl methacrylate⁴³¹ are analogous in this respect. It is proposed to use polymers of 2- and 4-(meth)acryloyloxyphenylacetic acids^{432, 433} and their alkyl esters as bactericidal agents for the purification of sewage.

High fungicidal activity is displayed by copolymers of pentachlorophenyl (meth)acrylate⁴³⁴ with vinyl acetate, ethyl and butyl acrylates, MMA and MAA. Their emulsions possess good film-forming properties and may be used as components of fungus-resistant dyes⁴³⁴ for indoor and outdoor work, while copolymers with acrylamide⁴³⁵ are applied for impregnation of paper.

It is proposed to use 2,2-bis(4-methacryloyloxyphenyl)propane in compositions for fillings in dentistry.^{436–438} Dentists also make use of solidified compositions which possess enhanced adhesion to metals and the dental tissue and contain from 0.5% to 10% of hydroxybenzoic (meth)acrylate⁴³⁹ or aromatic di(meth)acrylates.⁴⁴⁰ A hemocompatible polymeric material for coating blood-contacting surfaces was obtained from dimethyl (2-hydroxyethyl)ammonium salt of poly(2-acryloyloxybenzoic acid).⁴⁴¹ Some phenyl methacrylates, e.g., 4-azidophenyl methacrylate, are components of copolymers possessing hemoglobin function.⁴⁴² Others, e.g., 4-nitrophenyl acrylate, are introduced into polymeric carriers for the isolation of biologically specific molecules such as proteins, which may be used for radiodiagnostics of thrombi, antigens and tumours⁴⁴³ or for immobilisation of enzymes, amino acids, proteins^{444, 445}, e.g., serum albumin.^{446, 447} Polymers based on 2,4,5-trichlorophenyl, 4-nitrophenyl or 2,4-dinitrophenyl (meth)acrylates are X-ray contrasting preparations.⁴⁴⁸

Introduction of residues of unsaturated acids into medicinal substances and subsequent polymerisation yield drugs with prolonged action.^{69–70} Resorption of polymers of acrylic acid

with β -naphthyl acrylate as potential coatings of such medicinal preparations was studied by liquid chromatography by monitoring the liberation of the β -naphthol upon hydrolysis of the copolymer.⁴⁴⁹

Thus, aryl (meth)acrylates possess a very broad spectrum of useful properties and their further studies are highly advisable.

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Ternary and quaternary chalcogenides of Group IB elements

V A Starodub

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Abstract. Methods of synthesis, molecular and electronic structures and electrophysical, optical and magnetic properties of ternary and quaternary chalcogenides based on copper, silver and gold are considered. The possibility of the synthesis of chalcogenide analogues of high-temperature superconductors is discussed. The prospects of searching for new high-temperature superconductors in $Ln-Cu-X$ systems, where Ln is a rare-earth element and X is S, Se or Te, are shown. The bibliography includes 148 references.

I. Introduction

The discovery of the high-temperature superconductivity in 1986¹ has given powerful impetus to the development of solid-state chemistry. This has awakened great interest in metal oxide systems with the perovskite-like structures. High-temperature superconductors (HTSCs) with the superconducting transition temperatures (T_c) of up to 150 K (see Ref. 2) were synthesised (the data, while unconfirmed, on the synthesis of HTSCs with T_c of up to 250 K are also available in the literature^{3,4}). It has since become clear that the properties of new superconducting materials cannot be explained within the framework of the BCS theory (Bardeen–Cooper–Schrieffer). Apparently, the RVB (resonance valence bond) model proposed by Anderson⁵ is most realistic.^{5–9} This model assumes the occurrence of mixed-valence states in the system of chemically bonded atoms as an essential prerequisite for the high-temperature superconductivity. The mixed valence is necessary not only for the provision of the required carrier concentration and the equivalent positions for the carrier motion but also provides the basis for the coupling mechanism. In this connection, it becomes apparent that solid-state chemistry is of paramount importance in the solution of both theoretical and applied problems of physics of superconductivity.

In spite of the ten-year history of HTSCs, much in the chemistry of these materials remains unclear. Suffice it to mention that the problem associated with the estimation of the degree of oxidation of copper in metal-oxide samples, which is of importance for constructing the theory of HTSCs, is still debated. Leaving aside the details of this problem, let us mention a study,¹⁰

in which the authors used X-ray emission spectroscopy for estimating the degree of oxidation of copper atoms in HTSCs. This method is free from the drawbacks of X-ray photoelectron spectroscopy (XPS), which is most often used for these purposes.

The role of oxygen atoms in HTSCs also remains unclear. In the available chemical models of superconductivity of HTSCs, which are based on Anderson's ideas,^{11–13} the possibility of formation of weakly bound O_4 complexes upon transformation of HTSCs into the superconducting state is considered. The bond strength in these complexes is determined, on the one hand, by the sizes of the cations and, on the other hand, by the concentration of holes, which disturb the antiferromagnetic order in the initial dielectric system. Taking into account the greater ability of sulfur and selenium atoms to form polychalcogenide ions, chalcogenide analogues of HTSCs would be expected to possess stronger electrophysical characteristics compared to those of oxide HTSCs. This idea was proposed, for example, in the study;¹⁴ simultaneously, it was assumed that the structural characteristics remain unchanged. The prospects for synthesising HTSCs based on thio-, seleno- and tellurocuprates are very attractive because chalcogenides of transition metals, in particular, copper chalcogenides, provide substantially greater possibilities for the preparation of compounds possessing various physicochemical properties compared to those of the corresponding oxides. The most essential differences consist in the higher covalence of the metal–chalcogen bonds, the ability of chalcogen atoms to form bonds with each other resulting in molecular anions and the higher ability of metal atoms to form metal–metal bonds (due to the lower formal charge). Owing to these facts, chalcogenides of Group IB metals can exhibit a broad spectrum of electrical (from dielectric to superconducting¹⁵) and magnetic properties (from diamagnetism to temperature-independent paramagnetism).

Table 1 gives the structural and electrophysical characteristics of selected superconductors based on chalcogenides of transition metals, *viz.*, chalcogenides of copper and rare-earth elements, which are structural elements of HTSCs, as well on some ternary chalcogenides characterised by high T_c values. Analysis of these data suggests that a search for HTSCs in $M-Ln-X$ systems, where M is IB Group metal, Ln is a rare-earth element and X is chalcogen, may have promise. Thus, in the studies of the $Cu_2S-La_2S_3$ system performed in 1968–1972,^{19–21} ternary sulfides, *viz.*, the hexagonal $Cu_2La_4S_7$ and monoclinic $CuLaS_2$ phases, were detected. However, Andreev²² studied the same system in 1988 and found only the $CuLaS_2$ phase. Later on, Andreev published the paper entitled 'The Cu_2S-BaS system as a possible HTSC',²³ where he demonstrated that two phases, *viz.*, the tetragonal $BaCu_2S_2$ and orthorhombic $BaCu_4S_3$ phases, exist

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Table 1. Structural and electrophysical characteristics of selected chalcogenide superconductors.^{16–18}

Compound	T_c /K	Density of states /cm ⁻³	Lattice type	Composition
CuS	1.65	$\sim 10^{20}$	hexagonal	$\text{Cu}_4^+ \text{Cu}_2^{2+} \cdot (\text{S}_2^{2-})_2 (\text{S}^{2-})_2$
CuS ₂	1.48–1.53	$\sim 10^{21}$	pyrite, cubic	$\text{Cu}^{2+} (\text{S}_2^{2-})$
CuSe ₂	2.30–2.43	$\sim 10^{21}$	the same	$\text{Cu}^{2+} (\text{Se}_2^{2-})$
CuTe ₂	1.25–1.3	$\sim 10^{21}$	"	$\text{Cu}^{2+} (\text{Te}_2^{2-})$
YS	1.9	$\sim 10^{22}$	NaCl, cubic	$\text{Y}^{2+} / \text{Y}^{3+}$
YSe	2.5	$\sim 10^{22}$	the same	$\text{Y}^{2+} / \text{Y}^{3+}$
YTe	2.05	$\sim 10^{22}$	"	$\text{Y}^{2+} / \text{Y}^{3+}$
LaS	0.87	$\sim 10^{22}$	"	$\text{La}^{2+} / \text{La}^{3+}$
LaSe	1.02	$\sim 10^{22}$	"	$\text{La}^{2+} / \text{La}^{3+}$
LaTe	1.48	$\sim 10^{22}$	"	$\text{La}^{2+} / \text{La}^{3+}$
La ₂ Se ₃	1	semicon-	cubic	$\text{La}^{2+} / \text{La}^{3+}$
		ductor		
La ₃ S ₄	8–11.5	6×10^{21}	the same	$\text{La}^{2+} / \text{La}^{3+}$
La ₃ Se ₄	7.63–9.4	$10^{21} - 10^{22}$	"	$\text{La}^{2+} / \text{La}^{3+}$
La ₃ Te ₄	4.61	–	–	–
AgMo ₄ S ₅	8.9	–	–	–
Cu _{1–1.9} Mo ₃ S ₄	10.9–10.5	–	–	–
Li _x Ti _{1.1} S ₂	10–13	–	hexagonal	$\text{Ti}^{3+} / \text{Ti}^{4+}$
(0.1 < x < 0.3)				

in this system. In 1994, Chinese researchers²⁴ at the National Laboratory of Superconductivity synthesised a series of oxyselenides LnCuSeO ($\text{Ln} = \text{La}, \text{Sm}, \text{Gd}$ or Y). The structures of the latter contain the alternating $[\text{Ln}_2\text{O}_2]$ and $[\text{Cu}_2\text{Se}_2]$ layers. Analogous layers have been found previously by Popovkin²⁵ in oxyselenide BiCuSeO . Attempts were undertaken to perform partial replacement of oxygen atoms in HTSCs by halogen or chalcogen atoms. These attempts often cast doubt from the chemical standpoint^{14, 26, 27} and do not solve the problem because they allow only an insignificant amount of oxygen to be replaced by chalcogen. The effect of the latter in these systems can be considered only as a weak perturbation, which was in essence found in the above-mentioned studies.

As early as 1991, we attempted to synthesise chalcogenide analogues of HTSCs, in particular, $\text{La}_2\text{CuS}_{4+\delta}$ and $\text{YBa}_2\text{Cu}_3\text{S}_{6+\delta}$.²⁸ However, because of difficulties associated with the preparation of a single phase and the lack of data on simpler systems (for example, $\text{Ba}-\text{Cu}-\text{S}$ and $\text{Cu}-\text{Ln}-\text{S}$), we turned our attention primarily to ternary systems consisting of chalcogenides of Group IB metals and chalcogenides of alkali, alkaline-earth or rare-earth metals.

Nevertheless, even regardless of the problem of HTSCs, the success achieved in the chemistry of ternary and quaternary chalcogenides based on Group IB elements within the last decade is so impressive that it makes sense to expose not only chemists and physicist involved in studies of HTSCs but also researchers working in other fields to the results obtained. The present review is devoted to analysis of methods of synthesis and molecular and electronic structures of chalcogenides in relation to their magnetic and electrophysical properties.

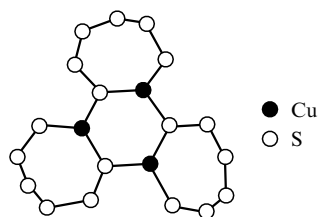
Molecular polychalcogenides are considered first because it is in this class of compounds that sulfides and selenides differ most sharply from the corresponding oxides. We next consider the coordination polymers based on polychalcogenides of Group IB metals. Finally chalcogenides containing only X^{2-} and/or X_2^{2-} ions, i.e., the structural elements identical to those in oxide HTSCs, are considered. Tellurides are considered at the end of each chapter for two reasons. First, tellurium has peculiarities and the properties of tellurides differ from those of the corresponding

sulfides and selenides and second, these compounds are poorly known.

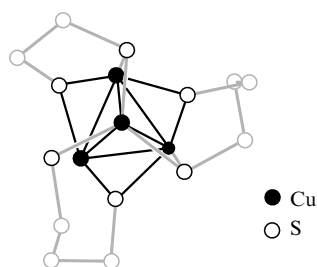
II. Molecular copper, silver and gold polychalcogenides

Molecular polychalcogenides of Group IB metals containing isolated $[\text{M}_n\text{X}_m]^{q-}$ clusters ($\text{M} = \text{Cu}, \text{Ag}$ or Au ; $\text{X} = \text{S}, \text{Se}$ or Te) were virtually unknown up to the early 1980s.²⁹ (The synthesis of polynuclear copper sulfide complexes was reported for the first time in 1983.)

The $(\text{Et}_4\text{N})_3[\text{Cu}_3(\text{S}_6)_3]$ complex was prepared by the reaction of copper(II) acetate with an ethanolic solution of polysulfides.³⁰ The complex contains the complex $[\text{Cu}_3(\text{S}_6)_3]^{3-}$ ion in which the Cu^+ ions are chelated by the hexasulfide ions (Fig. 1). One of the terminal sulfur atoms of each S_6^{2-} ion acts as a bridge and is involved in formation of the central six-membered Cu_3S_3 ring. In the following year,³¹ researchers succeeded in isolating salts, which contain $[\text{Cu}_3(\text{S}_4)_3]^{3-}$ ions and are structurally similar to $[\text{Cu}_3(\text{S}_6)_3]^{3-}$. In this study, the $(\text{Ph}_4\text{P})_4[\text{Cu}_2\text{S}_{20}]$ salt containing the $[\text{S}_6\text{CuS}_8\text{CuS}_6]^{4-}$ ions in which two CuS_6 rings are bound to each other through the bridging S_8^{2-} anion was also described. Analogous silver salts containing the $[\text{Ag}_2\text{S}_{20}]^{4-}$ ions were also obtained.³² Note that in all these salts, the copper and silver atoms adopt the coordination number of 3, which is rarely observed in the chemistry of coordination compounds.

**Figure 1.** Structure of the $[\text{Cu}_3(\text{S}_6)_3]^{3-}$ anion.²⁹

Müller and coworkers synthesised a series of four-nuclear clusters of the general formula $[\text{Cu}_4(\text{S}_4)_{3-x}(\text{S}_5)_x]^{2-}$. These clusters contain the tetrahedral Cu_4 core in which the copper atoms are chelated by the bridging S_4^{2-} and/or S_5^{2-} ions. All members of this series were isolated, viz., salts with $x = 0,^{31} 1, 2^{33}$ and $3.^{34}$ The structure of the $[\text{Cu}_4\text{S}_4(\text{S}_5)_2]^{2-}$ cluster is shown in Fig. 2. It should be noted that these clusters provide rare examples of coexistence of the MS_4 and MS_5 chelates.

**Figure 2.** Structure of the $[\text{Cu}_4\text{S}_4(\text{S}_5)_2]^{2-}$ anion.³³

In 1984, the $(\text{Ph}_4\text{P})_2[\text{Cu}_6(\text{S}_4)_3\text{S}_5]$ salt was synthesised virtually simultaneously at the laboratories headed by Henkel³⁵ and Müller.³⁶ This salt can be prepared either by the reaction of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ with a threefold excess of NaSR ($\text{R} = \text{Et}$ or CH_2Ph) in methanol³⁵ or by the reaction of $\text{Cu}(\text{acac})_2$ with an ethanolic solution of polysulfides.³⁶ In both cases, the salt was isolated as orange-red crystals upon addition of a solution of Ph_4PBr to the

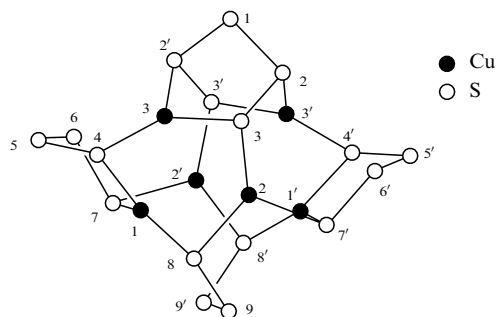


Figure 3. Structure of the $[\text{Cu}_6(\text{S}_4)_3\text{S}_5]^{2-}$ anion.³⁶

reaction mixture. In this complex, a new coordination mode was found (Fig. 3). Six copper atoms form two distorted tetrahedra, whose vertices are occupied by the Cu(1), Cu(2), Cu(3), Cu(1'), Cu(2') and Cu(3') atoms. These tetrahedra are linked *via* the shared Cu(3)–Cu(3') edge. The metal atom is coordinated by the tetrasulfide ions only through the terminal atoms, while the pentasulfide ions are coordinated to the metal atoms through four sulfur atoms [S(2), S(2'), S(3) and S(3')].

In the laboratory headed by Henkel,³⁷ the $(\text{Ph}_4\text{P})_4[\text{Cu}_{12}\text{S}_8]$ salt containing the $[\text{Cu}_{12}\text{S}_8]^{4-}$ cluster ions was synthesised. This salt was prepared as wine-red needles by the reaction of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ with a threefold excess of NaSEt in methanol ($\sim -78^\circ\text{C}$) followed by addition of Li_2S and (after completion of the reaction) of a solution of Ph_4PBr . The $[\text{Cu}_{12}\text{S}_8]^{4-}$ anion has the ideal O_h symmetry. The sulfur atoms occupy the vertices of the cube and the copper atoms occupy the centres of the edges.

Later on, Marbach and Strähle³⁸ isolated an analogous gold complex as the tetraphenylarsonium $(\text{Ph}_4\text{As})_4[\text{Au}_{12}\text{S}_8]$ salt. The $[\text{Au}_{12}\text{S}_8]^{4-}$ and $[\text{Cu}_{12}\text{S}_8]^{4-}$ anions have identical structures. In 1992, Kanatzidis and Huang³⁹ prepared the $(\text{Et}_4\text{N})_3[\text{NaAu}_{12}\text{Se}_8]$ complex, which is the selenium analogue of the $(\text{Ph}_4\text{As})_4[\text{Au}_{12}\text{S}_8]$ salt. The larger size of the selenium atom compared to that of the sulfur atom allows Na^+ ions to occupy the centres of the $[\text{Au}_{12}\text{Se}_8]^{4-}$ cuboctahedra. Hence, this complex is one of a few examples of inorganic cryptands. The Na^+ ion occupies the inversion centre. The distances from the sodium ion to the gold ions are shorter than those to the selenium atoms. Apparently, the interactions between the sodium ion and the twelve Au^+ ions are stronger. The authors³⁹ believed that this fact reflects the general tendency of the Au^+ ions to interact with alkali-metal ions. Note that the Au^+ or Cu^+ ions in the $[\text{M}_{12}\text{X}_8]^{4-}$ complexes ($\text{M} = \text{Au}$ or Cu) have a typical linear coordination.

An example of a supposedly extremely large copper chalcogenide cluster was described in the study.⁴⁰ The authors succeeded not only in isolating the $[\text{Cu}_{146}\text{Se}_{73}(\text{Ph}_3\text{P})_{30}]$ cluster but also in characterising it structurally. Although this compound is not a purely chalcogenide cluster because it contains the triphenylphosphine group, it corresponds to the subject of this review because this compound is formally a derivative of copper selenide $\text{Cu}_2\text{Se} - \{[\text{Cu}_{146}\text{Se}_{73} \cdot 30(\text{Ph}_3\text{P})]\}$. This cluster is also of interest because it is a semiconductor with the conductivity $\sigma_{RT} = 1.5 \times 10^{-2} \Omega^{-1} \text{cm}^{-1}$. The selenium atoms in this cluster form three planar layers consisting of 21, 31 and 21 atoms (*ABA* packing) arranged in a close packed fashion. The copper atoms occupy the cavities in this packing. In the crystal, the clusters are arranged in such a way as to form cavities (channels) with a diameter of 1.6 nm. When crystallisation is performed from organic solvents, channels are occupied by the solvent molecules, which can be, however, removed under mild conditions without destruction of the crystal lattice. For example, 42 tetrahydrofuran molecules can add per formula unit of the cluster.

In the above-considered examples, the specificity of the Cu^+ , Ag^+ and Au^+ ions is not manifested. Let us consider examples of chalcogenides, in which this specificity is apparent. The Au^+ ion, like the Cu^+ ion, forms a complex with the tetrasulfide ion with

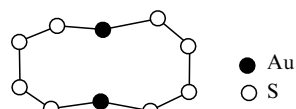
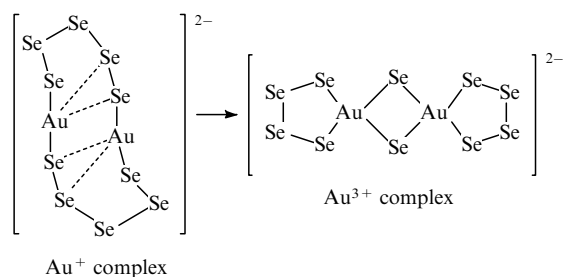


Figure 4. Structure of the $[\text{Au}_2(\text{S}_4)_2]^{2-}$ anion.³⁴

composition $[\text{Au}_2(\text{S}_4)_2]^{2-}$.³⁴ Unlike analogous copper complexes, the gold(I) tetrasulfide complex can be described as a ten-membered ring, in which the Au^+ ion has a nearly linear coordination (Fig. 4).

The gold(I) pentaselenide complex was isolated as the $[(\text{Ph}_2\text{P})_2\text{NPh}_2]_2[\text{Au}_2\text{Se}_{10}]$ salt. However, according to the data of X-ray diffraction analysis,⁴¹ this complex is in fact an Au^{3+} derivative and contains coordinated selenide and tetraselenide ions. It was suggested that the Au^+ complex with the Se_5^{2-} ions in which the Au^+ ion has linear coordination, was actually formed at the initial stage. However, the subsequent intramolecular two-electron transfer from the Au^+ ion to the terminal Se–Se bond afforded the Au^{3+} and Se^{2-} ions and the Se_4^{2-} ions were formed from the Se_5^{2-} ions. The complex $[\text{Se}_4\text{AuSe}_2\text{AuSe}_4]^{2-}$ ion is planar, like the majority of $\text{Au}(\text{III})$ complexes.



Oxidation of $\text{Au}(\text{I})$ with the pentaselenide ion proceeded unusually. The reaction of AuCl_3 with Na_2Se_5 upon addition of a Ph_4PBr solution to the reaction mixture afforded gold and the product of oxidation of the pentaselenide ion, *viz.*, $(\text{Ph}_4\text{P})_2\text{Se}_{11}$, *i.e.*, Au^{3+} was reduced with the pentaselenide ion. Apparently, the only analogous reaction is the reaction in the $\text{Ti}^+ - \text{I}_3^-$ system in which Ti^{3+} ions were completely reduced with I^- ions to Ti^+ . However, Ti^+ ions reacted with an excess of I_3^- ions to form the Ti^{3+} complex with composition $[\text{TiI}_4]^-$.⁴¹

Polyselenide $\text{Au}(\text{I})$ complexes were prepared with the use of polyselenides Se_n^{2-} with $n = 1-4$.⁴² Thus, the reaction of AuCN with a Na_2Se_2 or Na_2Se_3 solution in the presence of Ph_4PCl yielded the $(\text{Ph}_4\text{P})_2[\text{Au}_2\text{Se}_2\text{Se}_3]$ salt containing the seven-membered cyclic $[\text{Au}_2\text{Se}_2\text{Se}_3]^{2-}$ anions (Fig. 5). The complex anion adopts an envelope conformation with the linear coordination of the Au^+ ions. The reaction performed under analogous conditions with the use of K_2Se_4 instead of Na_2Se_2 or Na_2Se_3 gave the $(\text{Ph}_4\text{P})_2[\text{Au}_2\text{Se}_2\text{Se}_4]$ salt. This salt contains the eight-membered cyclic anion in which two Au^+ ions are symmetrically coordinated by the diselenide and tetraselenide ions.

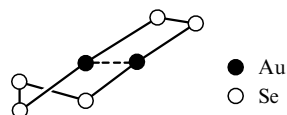
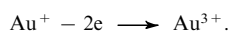


Figure 5. Structure of the $[\text{Au}_2\text{Se}_2\text{Se}_3]^{2-}$ anion.⁴²

Finally, the reaction with the use of pentaselenide K_2Se_5 gave the $\text{K}_2[\text{Au}_2\text{Se}_2(\text{Se}_4)_2]$ complex. Unlike the two above-described complexes, the latter complex contains the Au^{3+} ion as a result of the higher oxidising capacity of the Se_5^{2-} ion compared to those of the Se_4^{2-} and Se_3^{2-} ions.⁴³



In addition to the above-mentioned $[\text{Ag}_2\text{S}_{20}]^{4-}$ anion, the Ag^+ complex with hexasulfide ions with composition $[\text{Ag}_2(\text{S}_6)_2]^{2-}$ is known. In this complex, the coordination of the S_6^{2-} ligands is analogous to that observed in the $[\text{Cu}_3(\text{S}_6)_3]^{3-}$ anion, with the only difference that the binuclear $[\text{Ag}_2(\text{S}_6)_2]^{2-}$ anion contains the four-membered Ag_2S_2 rings.⁴⁴

The coordination of the tetraselenide anions by the Ag^+ cations is also very similar to that observed in Cu^+ salts. Thus, four-nuclear silver tetraselenides $(\text{Et}_4\text{N})_4[\text{Ag}_4(\text{Se}_4)_4]$ and $(\text{Pr}_4\text{N})_2[\text{Ag}_4(\text{Se}_4)_3]^{2-}$ were isolated.⁴⁵ The $[\text{Ag}_4(\text{Se}_4)_4]^{4-}$ anion is formed by four Ag^+ ions, which occupy the vertices of the planar rhombus and which are linked *via* the bridging Se_4^{2-} ligands (Fig. 6). The silver atoms in this cluster are nonequivalent. The coordination environment about two of them $[\text{Ag}(1)$ and $\text{Ag}(1')]$, see Fig. 6) is a tetrahedron, while two other atoms $[\text{Ag}(2)$ and $\text{Ag}(2')]$ have a planar-trigonal coordination. Analogously, the Se_4^{2-} ions are also nonequivalent. Two of them link three silver ions each and the remaining two complex ions link two silver ions each.

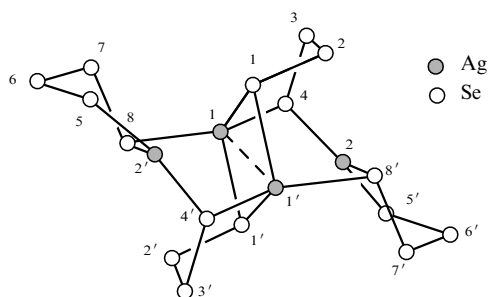


Figure 6. Structure of the $[\text{Ag}_4(\text{Se}_4)_4]^{4-}$ cluster.⁴⁵

The structure of the cluster $[\text{Ag}_4(\text{Se}_4)_3]^{2-}$ ion (Fig. 7) is based on the tetrahedral cage formed by the Ag^+ ions, which are linked *via* three Se_4^{2-} ligands. This cage, in turn, forms the distorted adamantane-like central Ag_4Se_6 core in which all silver atoms adopt a planar-trigonal coordination.

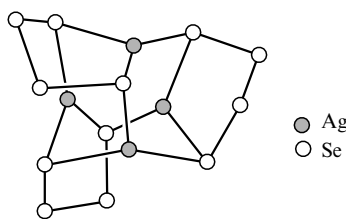


Figure 7. Structure of the $[\text{Ag}_4(\text{Se}_4)_3]^{2-}$ cluster.⁴⁵

The complex copper and silver selenides, *viz.*, $[\text{Cu}_2\text{Se}_4(\text{Se}_5)_2]^{4-}$, $[\text{Cu}_4(\text{Se}_4)_{2.4}(\text{Se}_5)_{0.6}]^{2-}$ and $(\text{Ph}_4\text{P})_2. [\text{Ag}_4(\text{Se}_4)_{3-x}(\text{Se}_5)_x]$, which are related to the above-described copper sulfides $[\text{Cu}_4(\text{S}_4)_{3-x}(\text{S}_5)_x]^{2-}$, were also described.^{46, 47} These salts were prepared by the reaction of CuCl with a melt of polyselenide Li_2Se_n or by fusing a mixture of CuCl_2 , sodium and selenium. Their structures are similar to those of the corresponding sulfides.

The mononuclear complexes with the nonasulfide ion are known only for gold and silver. Marbach and Strähle isolated cyclic nonasulfidoaurate(I) $(\text{Ph}_4\text{As})[\text{AuS}_9]$.⁴⁸ Its structure is shown in Fig. 8. The Au^+ ion binds the terminal sulfur atoms of the ligand and has a nearly linear coordination [the $\text{S}(1)\text{AuS}(9)$ angle is 176°]. The analogous silver salt $(\text{Ph}_4\text{P})[\text{AgS}_9]$ is also

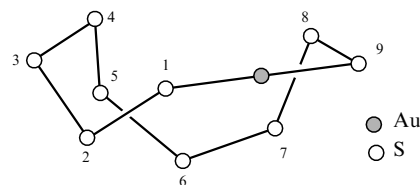


Figure 8. Structure of the $[\text{AuS}_9]^{9-}$ anion.⁴⁸

known.²⁹ However, the anions in the crystal of this salt are substantially disordered.

Finally, let us consider a few examples of molecular polytellurides, which are presently known only for gold. In 1985, the first gold polytelluride $(\text{Ph}_4\text{P})_4[\text{KAu}_9\text{Te}_7]$ containing isolated cluster ions was described.⁴⁹ The reaction of a methanolic solution of K_2AuTe_2 with a solution of Ph_4PBr afforded an orange precipitate. Additional treatment of the latter with DMF and a solution of Ph_4PBr in MeOH gave two products. One of them, which was isolated as triangular red platelet-like crystals, has the composition $(\text{Ph}_4\text{P})_4[\text{KAu}_9\text{Te}_7]$. The structure of the $[\text{KAu}_9\text{Te}_7]^{4-}$ anion (Fig. 9) can be considered as that derived from the cubic structure of the above-described $[\text{M}_{12}\text{S}_8]^{4-}$ ions ($\text{M} = \text{Cu}$ or Au) in which one vertex and three edges are removed. The ideal cubic structure is distorted due to the contraction along the threefold axis passing through the absent vertex and the centre of the ion. This contraction is responsible for the pronounced $\text{Au}-\text{Au}$ interaction. The $\text{Au}-\text{Au}$ distances in the triangles (see Fig. 9) vary from 0.3039 to 0.3221 nm. The average distance (0.313 nm) is close to the $\text{Au}-\text{Au}$ distance in metallic gold (0.288 nm) and is substantially shorter than that in the hypothetical $[\text{Au}_{12}\text{Te}_8]^{4-}$ ion (0.363 nm). Like $[\text{NaAu}_{12}\text{Se}_8]^{3-}$, the $[\text{Au}_9\text{Te}_7]$ framework incorporates the encapsulated potassium ion, the $\text{Au}-\text{K}$ distances being shorter than the $\text{Au}-\text{Te}$ distances, which reflects the higher electronegativity of gold compared to that of tellurium (2.4 and 2.1, respectively). It is believed that the above-described encapsulation is responsible for the formation of a cryptand with this composition because the K^+ ion is too large to be encapsulated into the hypothetical $[\text{Au}_{12}\text{Te}_8]^{4-}$ ion.

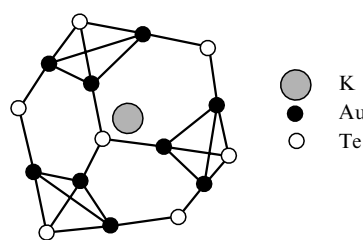


Figure 9. Structure of the $[\text{KAu}_9\text{Te}_7]^{4-}$ anion.⁴⁹

The electrochemical preparation of the $(\text{Ph}_4\text{P})_2[\text{Au}_2\text{Te}_4]$ and $(\text{Bu}_4\text{N})_3[\text{Au}_3\text{Te}_4]$ salts with the use of AuTe_2 as the electrode was reported in a study.⁵⁰ The $[\text{Au}_3\text{Te}_4]^{3-}$ anion is gold(I) telluroditelluride (Fig. 10a) and the $[\text{Au}_2\text{Te}_4]^{2-}$ anion is gold(I) bistelluride (Fig. 10b). In both cases, the gold atoms have a linear coordination typical of Au^+ ions. However, the tendency for the trigonal coordination through the $\text{Au}-\text{Au}$ bonds is also pronounced. The lengths of these bonds (see Fig. 10a, b) are only slightly larger than the $\text{Au}-\text{Au}$ distances in metallic gold.

Treatment of gold tellurides KAuTe and K_3AuTe_2 with ethylenediamine or DMF afforded salts containing the $[\text{Au}_2(\text{Te}_2)_2]^{2-}$ and $[\text{KAu}_9\text{Te}_7]^{4-}$ anions and the $[\text{K}_2\text{Au}_4\text{Te}_4]^{2-}$ anion in which the $[\text{Au}_4\text{Te}_4]^{4-}$ rhombi are linked in infinite stacks through the K^+ ions.^{49, 51}

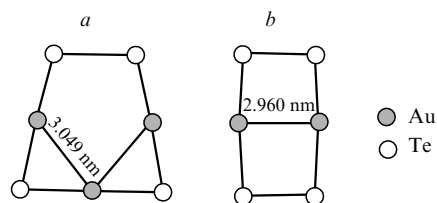


Figure 10. Structures of the $[\text{Au}_3\text{Te}_4]^{3-}$ (a) and $[\text{Au}_2\text{Te}_4]^{2-}$ (b) anions.⁵⁰

The reaction of AuCN with polytellurides Te_n^{2-} in DMF in the presence of PET_3 and NET_4Cl yielded the $(\text{NET}_4)_3[\text{AuTe}_7]$ salt.⁵² The $[\text{AuTe}_7]^{3-}$ anion is planar, which is typical of Au(III) complexes (Fig. 11 a). The fact that the degree of oxidation of gold is equal to +3 is indirectly supported by the Au–Te bond lengths (0.2638–0.2664 nm), which are comparable with those in the known Au(III) compounds, for example, in AuTeI (0.2642–0.2684 nm), and is also confirmed by the data of Mössbauer spectroscopy on ^{197}Au nuclei. Hence, the anion under consideration is bisditelluridotritelluridoaurate(III).

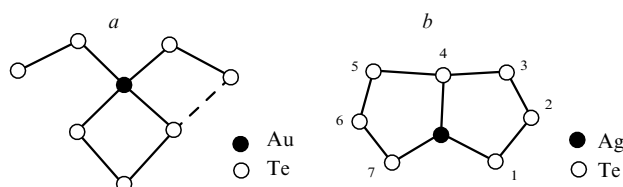


Figure 11. Structures of the $[\text{AuTe}_7]^{3-}$ (see Ref. 52) (a) and $[\text{AgTe}_7]^{3-}$ (b) anions.⁵⁴

The structure of the analogous silver complex $[\text{AgTe}_7]^{3-}$ isolated as the $(\text{Ph}_4\text{P})_2(\text{Et}_4\text{N})[\text{AgTe}_7]$ salt (Fig. 11 b)^{53,54} differs from that of the $[\text{AuTe}_7]^{3-}$ anion. In this silver complex, the Ag^+ ion adopts a trigonal coordination. Based on the charge of the $[\text{AgTe}_7]^{3-}$ anion, the charge of –4 should be assigned to the ligand and the ligand can be considered as $\eta^3\text{-Te}_7^{4-}$. The $\text{Te}(4)\text{--Te}(5)$ and $\text{Te}(4)\text{--Te}(3)$ bond lengths (0.2866 and 0.3230 nm, respectively) are substantially different, whereas this difference in the corresponding bonds in the analogous $[\text{HgTe}_7]^{2-}$ complex is insignificant (0.3050 and 0.2997 nm, respectively⁵³). Therefore, the nature of the bonds in the new polytelluride $\eta^3\text{-Te}_7^{4-}$ ligand is still unknown. Polyhalide ions, in particular, such as I_8^{3-} , are the closest analogues of this ligand. The concept of hypervalence is used for describing the nature of bonds in these compounds, in particular, in S_2N_2 , S_4N_4 , polyhalides, xenon halides, etc.⁵⁵ In accordance with this concept, the $\text{Te}(3)\text{--Te}(4)\text{--Te}(5)$ bond can be considered as a three-centre four-electron bond, whereas the $\text{Te}(2)\text{--Te}(3)$ and $\text{Te}(5)\text{--Te}(6)$ bonds are usual two-centre two-electron bonds.

Copper and silver tetratellurides containing the $[\text{Te}_4\text{M}(\mu\text{-Te}_4)\text{MTe}_4]^{4-}$ ions ($\text{M} = \text{Cu}$ or Ag) were also prepared.⁵⁶ The structures of these ions are similar to that of the $[\text{S}_6\text{Cu}(\mu\text{-S}_8)\text{CuS}_6]^{4-}$ ion. In these tellurides, the copper(I) and silver(I) atoms are trigonally coordinated through the chelating and bridging Te_4^{2-} ions.

III. Coordination polymers based on polychalcogenides of Group IB elements

Coordination polymeric polychalcogenides are intermediate between low-molecular-weight polychalcogenides and chalcogenides containing only X^{2-} and/or X_2^{2-} ions. These ions are bound to metal ions through substantially covalent bonds due to which these compounds are virtually insoluble in the usual organic solvents.

Polymeric polychalcogenides containing the $[\text{CuS}_4]^-$ anion have been known since the early 20th century.⁵⁷ However, their structures were established only late in the 1980s. Generally, polymeric polychalcogenides were prepared from solutions. However, the procedure for the synthesis of these compounds from melts of alkali metal polychalcogenides, which act simultaneously as the solvent and the reagent, was proposed in 1989.⁵⁸ This method appears to be more promising and allows one to prepare more perfect single crystals suitable for X-ray diffraction study. Coordination polymeric polychalcogenides can be synthesised in the temperature range of 150–350 °C. At lower temperatures, molecular polychalcogenides are obtained. At higher temperatures, mono- and dichalcogenides of Group IB metals are formed.

Oxidation of copper in a melt of K_2S_4 at 215 and 250 °C affords two modifications (α and β , respectively) of the $\text{K}[\text{CuS}_4]$ salt. These modifications are insoluble in usual organic solvents and stable to hydrolysis and oxidation with atmospheric oxygen. Both phases have quasi-one-dimensional structures (Fig. 12).

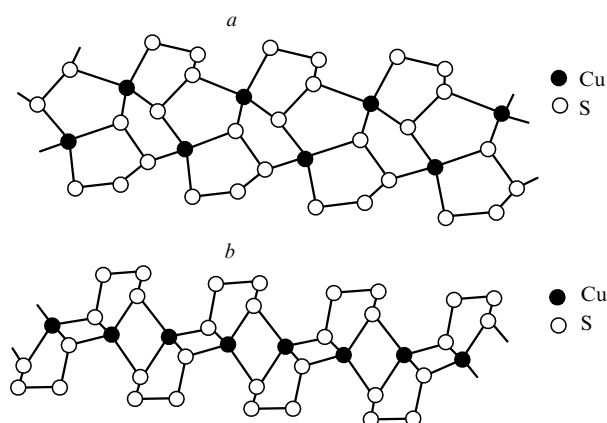


Figure 12. Infinite $\alpha\text{-}[\text{Cu}(\text{S}_4)]_n^-$ (a) and $\beta\text{-}[\text{Cu}(\text{S}_4)]_n^-$ (b) chains.⁵⁸

The $\alpha\text{-K}[\text{CuS}_4]$ salt is isostructural to the $(\text{NH}_4)[\text{CuS}_4]$ salt described previously⁵⁹ and contains the tetrasulfide ligands chelating the copper(I) ions (Fig. 12 a). The $[\text{CuS}_4]^-$ ions form infinite noncentrosymmetrical chains extended along the a axis. These chains can be considered as a sequence of fused five-membered CuS_4 and Cu_2S_3 rings. Therefore, the S_4^{2-} ion in this structure plays the unprecedented role of a bridge that links three Cu^+ ions.

The structure of $\beta\text{-K}[\text{CuS}_4]$ contains centrosymmetrical one-dimensional $\beta\text{-}[\text{CuS}_4]_n^-$ chains with a nearly linear (the CuCuCu angle is 173.5°) arrangement of the copper atoms linked through the bridging S_4^{2-} ligands (Fig. 12 b). Unlike the α -phase, the $\beta\text{-}[\text{CuS}_4]_n^-$ chains consist of the five-membered (CuS_4) and four-membered (Cu_2S_2) rings. Since the β -modification is formed at higher temperature, it can be suggested that this phase is thermodynamically more stable. Heating of crystals of $\alpha\text{-K}[\text{CuS}_4]$ above 250 °C results in transition to the β -phase. However, cooling of crystals of the β -phase do not lead to the reverse transition. The K_2S_4 solvent is of considerable importance in the $\alpha \rightarrow \beta$ -transition. Heating of crystals of $\alpha\text{-K}[\text{CuS}_4]$ in the absence of the solvent *in vacuo* resulted in their decomposition to CuS and K_2S_x .⁵⁸

Treatment of an alkaline solution of the $(\text{NH}_4)[\text{CuS}_4]$ salt with solutions of salts containing bulky cations afforded low-molecular-weight polysulfides, for example, $(\text{NMe}_4)_2[\text{Cu}_4(\text{S}_6)_3] \cdot 4\text{H}_2\text{O}$, $(\text{Et}_3\text{NBn})_2[\text{Cu}_4(\text{S}_4)(\text{S}_5)_2] \cdot 4\text{H}_2\text{O}$ and $(\text{Ph}_3\text{PBN})_2[\text{Cu}_6(\text{S}_6)_4] \cdot 12\text{H}_2\text{O}$.⁶⁰ The authors failed to prepare single crystals suitable for X-ray diffraction study and hence, the formulas were proposed by analogy with the known $[\text{Cu}_4(\text{S}_4)_x(\text{S}_5)_{3-x}]^{2-}$ and $[\text{Cu}_6(\text{S}_4)_3(\text{S}_5)_3]^{2-}$ salts.^{31,35,36} Metal cations bulkier than alkali

metal cations were used, apparently, with the aim of achieving more complete isolation of depolymerisation products from solutions.

The $[(\text{NH}_3)_2\text{C}_2\text{H}_4][\text{CuS}_5]_n \cdot 4\text{H}_2\text{O}$ salt was synthesised as orange-red single crystals.⁶¹ In the $[\text{CuS}_5]_n^{n-}$ anion formed as an infinite sequence of the $-\text{Cu}-\text{S}-\text{Cu}-\text{S}-$ bonds, each S_5^{2-} ion links three Cu^+ ions (Fig. 13). Therefore, the $[\text{CuS}_5]_n^{n-}$ chains consist of the five-membered CuS_4 and Cu_2S_3 rings. Analogous anionic chains were also observed in the crystals of the $(\text{NMe}_4)[\text{AgS}_5]$ ⁶² and $(\text{NMe}_4)[\text{AgSe}_5]$ salts.⁶³

These examples demonstrate that the properties of the above-described polysulfides are relatively independent of the nature of the outer-sphere cations.

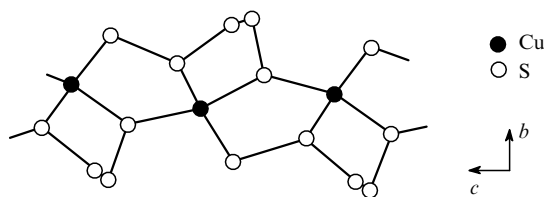


Figure 13. Infinite $[\text{CuS}_5]_n^{n-}$ chains.⁶¹

Treatment of copper with a melt of cesium polysulfide with composition Cs_2S_{11} at 270°C afforded the $\text{Cs}[\text{CuS}_6]$ salt.⁶⁴ In the crystal, the $[\text{CuS}_6]_n^{n-}$ anions form one-dimensional centrosymmetrical $[\text{CuS}_6]_n^{n-}$ chains (Fig. 14) separated by Cs^+ ions. The Cu^+ ions are chelated by the terminal sulfur atoms of the S_6^{2-} ions to form the seven-membered CuS_6 rings. In this case, the terminal sulfur atoms of the S_6^{2-} ion each act also as a bridge between the adjacent copper atoms resulting in the formation of the four-membered Cu_2S_2 rings. The $\text{Cs}[\text{CuS}_6]$ salt is one of a few examples of coordination polymers containing such long polychalcogenide ions.

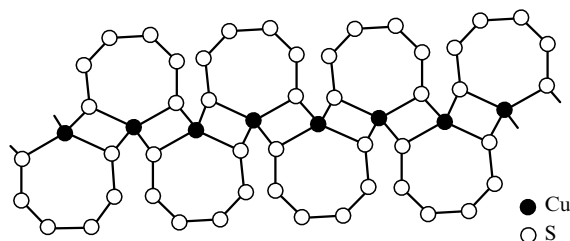


Figure 14. Infinite $[\text{CuS}_6]_n^{n-}$ chains.⁶⁴

In the crystals of the $\{(\text{Ph}_4\text{P})[\text{AgSe}_4]\}_n$ salt, the trigonal coordination about the silver(I) atom is formed by the Se_4^{2-} ions. However, only five-membered rings occur in this case (Fig. 15). Only one of the terminal selenium atoms of the Se_4^{2-} ion acts as a bridge.⁶⁵

Polymeric silver selenides with stack structures were prepared with the use of ethylenediamine in the supercritical state as the solvent.^{66, 67}

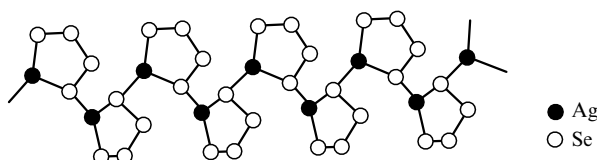
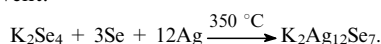


Figure 15. Infinite $[\text{Ag}(\text{Se}_4)]_n^{n-}$ chains.⁶⁵

The crystals of $\text{K}_2\text{Ag}_{12}\text{Se}_7$ contain the 18-membered $\text{Ag}_{12}\text{Se}_6$ rings. The seventh Se^{2-} ion occupies the centre of this ring. In the crystal structure, the rings are packed in stacks resulting in the formation of channels. These channels are occupied by K^+ ions. The sulfide with the same composition, which was prepared under analogous conditions, has quite a different structure.⁶⁸

Oxidation of gold with a melt of potassium polyselenides at 250°C afforded polymeric gold polyselenides KAuSe_5 and $\text{K}_3\text{AuSe}_{13}$ containing the $[\text{AuSe}_5]_n^{n-}$ and $[\text{AuSe}_{13}]_n^{3n-}$ ions, respectively.⁶⁹

Unlike the analogous copper and silver pentachalcogenides, the Au^+ ions in the $[\text{AuSe}_5]_n^{n-}$ anions are linearly coordinated (the SeAuSe angle is 179°) by the bridging Se_5^{2-} ions (Fig. 16a), the latter being coordinated only through the terminal selenium atoms. The structure of the $[\text{AuSe}_5]_n^{n-}$ ions is analogous to that of the $[\text{AuSe}]_n^{n-}$ ions with the formal replacement of the Se^{2-} ions by the Se_5^{2-} ions. The $[\text{AuSe}_5]_n^{n-}$ chains are linked through $\text{Au}-\text{Au}$ interactions. The $\text{Au}-\text{Au}$ distance (0.295 nm) is close to that in metallic gold (0.288 nm) and is substantially shorter than the corresponding distances in KAuSe^{70} and in α - and β - AuSe^{69} . Therefore, the presence of $\text{Au}-\text{Au}$ contacts leads to dimerisation of polymeric $[\text{AuSe}_5]_n^{n-}$ ions. In this case, the gold atom has the d^{10} configuration and this dimerisation is one of a few examples of $d^{10}-d^{10}$ interactions. Formally, a combination of two filled d -orbitals of the gold atom gives bonding and antibonding orbitals resulting in the absence of a bond. However, it is known that the relativistic effects are essential in the case of heavy elements, such as gold,⁷¹ and the reasoning regarding the electronic structures of silver complexes, which is based on the nonrelativistic approach, is incorrect. Pekka⁷¹ examined the role of relativistic effects in studies of the structural molecular characteristics. If these effects are taken into account, the bond lengths are decreased, the value of this decrease being proportional to the square of the charge on the atomic nucleus and varying from 0.250–0.300 nm for AuH to 0.450–0.500 nm for Au_2 . Correspondingly, the force constant and the dissociation energy of the Au_2 molecule increase by factors of more than four and two, respectively. The role of the relativistic effects decreases as the bond ionicity increases. Therefore, this role should be noticeable in gold chalcogenides in which the degree of covalence of the $\text{Au}-\text{X}$ bonds is large. Dimerisation of the $[\text{AuSe}_5]_n^{n-}$ ions is a prominent example of this phenomenon.

The presence of these bonds between ions with closed shells was also described for other gold compounds, in particular, for the complex $[\text{Au}_2\text{Se}_5]^{2-}$ and $[\text{Au}_2\text{Se}_6]^{2-}$ anions,⁷² and for the sulfide $\text{Ti}_2\text{Au}_4\text{S}_3$.⁷³ Since this phenomenon is unknown in the chemistry of other elements, it was suggested⁷² that the term 'aurophilic attraction' to be used for the $\text{Au}^+ - \text{Au}^+$ interaction. The authors believed⁷² that the aurophilic attraction is a result of correlation effects, which are ignored in the Hartree–Fock approximation.

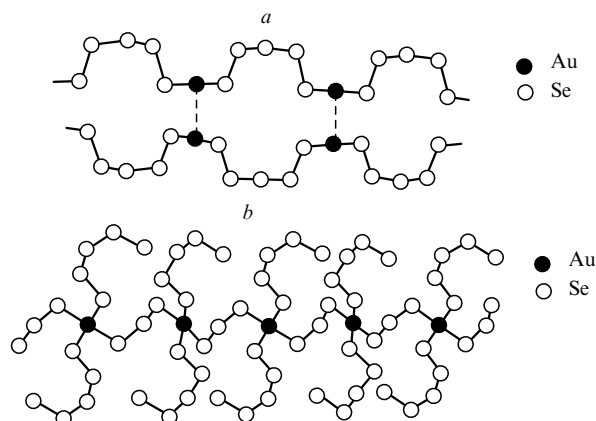
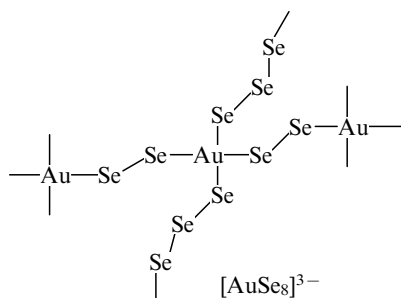


Figure 16. Structure of the $[\text{AuSe}_5]_n^{n-}$ (a) and $[\text{AuSe}_{13}]_n^{3n-}$ chains (b).⁶⁹

However, the authors restricted themselves only to nonrelativistic calculations. Hence, the above-considered interpretation, in which the importance of the relativistic effects in chemistry was emphasised, is, admittedly, more reliable (see also the study⁷⁴).

The $[\text{AuSe}_{13}]_n^{3n-}$ ion also has an unusual structure. This ion can be described as the catenabis(pentaseleido- μ -triseleido-aurate)(III) ion $[\text{Se}_5\text{Au}(\mu\text{-Se}_3)\text{AuSe}_5]_n^{3n-}$. This is the only known complex containing simultaneously the monodentate Se_5^{2-} ions and the bridging Se_3^{2-} ions coordinated to the Au^{3+} ions (Fig. 16 b).

The reaction performed under the same conditions (ethylenediamine in the supercritical state) with the use of sodium polyselenides instead of potassium polyselenides afforded Na_3AuSe_8 .⁷⁵ The crystals of this complex contain polymeric chains formed by the planar-square Au^{3+} complexes. Two Se_3^{2-} ions are coordinated in a monodentate fashion.



The polymeric complexes $(\text{Me}_4\text{N})[\text{MTe}_4]$ ($\text{M} = \text{Cu}$ or Ag) containing tetratelluride ions were prepared for the first time in 1993.⁴³ These complexes, unlike the analogous tetrasulfides and tetraselenides, have layered structures (see Fig. 17). The layers consist of the five-membered MTe_4 rings. Each Te_4^{2-} ligand links three copper atoms. An interesting feature of this structure is the presence of cavities formed by 14-membered rings (see Fig. 17). The size of the cavity is determined by the shortest distances between the opposite tellurium atoms (0.6034 and 0.6195 nm). The $(\text{Me}_4\text{N})[\text{MTe}_4]$ salts are diamagnetic semiconductors with the width of the forbidden band of 0.80 and 0.90 eV for $\text{M} = \text{Cu}$ and Ag , respectively.

In attempting to prepare mixed copper sulfidotelluride complexes from melts of $\text{Cs}_2\text{S}_x\text{Te}_y$, the authors⁶⁴ isolated the $\text{Cs}_6\text{Cu}_2(\text{S}_6)_2(\text{TeS}_3)_2$ complex containing the dimeric $[\text{Cu}_2(\text{S}_6)_2(\text{TeS}_3)_2]^{6-}$ anion (Fig. 18). In this anion, two Cu^+ ions are chelated by two Se_6^{2-} ions (the seven-membered CuS_6 rings) and are linked to each other through two bridging TeS_3^{2-} ions. Only one sulfur atom of each TeS_3^{2-} ion is involved in coordination, i.e., the four-membered Cu_2S_2 rings are formed. The trithiotellurite ion differs sharply in this property from the isoelectronic SO_3^{2-} ion.

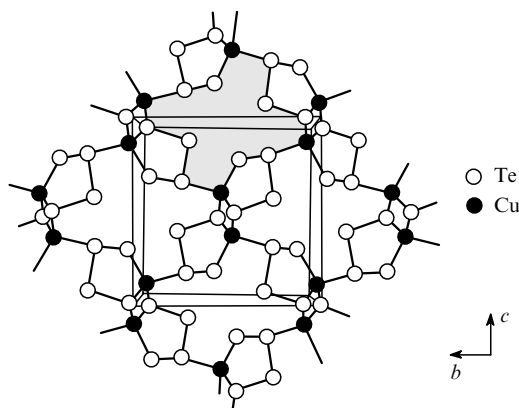


Figure 17. Structure of the $[\text{CuTe}_4]^-$ layers.⁴³ One of the 14-membered rings is hatched.

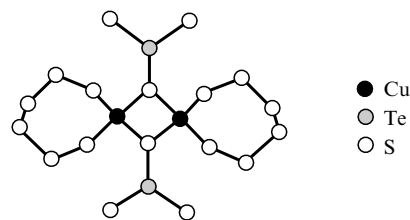


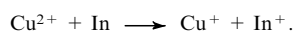
Figure 18. Structure of the $[\text{Cu}_2(\text{S}_6)_2(\text{TeS}_3)_2]^{6-}$ ion.⁶⁴

Unfortunately, successful attempts to prepare mixed selenidotelluride complexes are as yet unknown although their syntheses are quite possible because selenium and tellurium differ in properties to a lesser degree than sulfur and tellurium. For example, mixed sulfidoselenide complexes were formed in the $\alpha\text{-CsCu}(\text{S}_x\text{Se}_{4-x})$ and $\text{CsCu}(\text{S}_x\text{Se}_{6-x})$ systems.⁷⁶

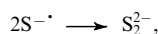
IV. Chalcogenides containing only X^{2-} and/or X_2^{2-} ions

The majority of compounds of this type give crystals with essentially covalent $\text{M}-\text{X}$ bonds. Many of these compounds possess metallic properties and exhibit superconducting properties at low temperatures (Table 1). According to the RVB theory,⁵⁻⁹ the metallic state in these crystals can occur on condition that the metal atoms exhibit a mixed valence.

It is well known that the simplicity of the electronic structures of chalcogenides, such, for example, as CuS or CuS_2 , is more apparent than real. Thus, according to the X-ray diffraction data, the formula $\text{Cu}_4^+\text{Cu}_2^+(\text{S}_2^{2-})_2(\text{S}^{2-})_2$ should be assigned to covellite CuS , i.e., both the metal and chalcogen atoms in this compound exhibit mixed valences.¹⁷ However, after the results of the study performed by Jellinek were reported,⁷⁷ the question about the electronic structures of copper chalcogenides became a matter of discussion. Based on the results of X-ray photoelectron spectroscopy, Jellinek assigned the degree of oxidation of +1 to the copper atoms in all chalcogenides (for example, in CuS , CuSe , CuTe , CuS_2 , KCu_4S_3 , etc.). To satisfy the principle of electronegativity of the salts, Jellinek had to represent the structures of the copper chalcogenides by formulas, which are absurd from the chemical standpoint, such as, for example, Cu^+Te^- for CuTe , $\text{Cu}_3^+(\text{S}_2^{2-})\text{S}^-$ for CuS or $\text{K}^+\text{Cu}_4^+\text{S}_2^{2-}\text{S}^-$, where S^- and Te^- are nothing but radical ions, which should be dimerised to the S_2^{2-} and Te_2^{2-} ions, respectively. I do not share the opinion of Jellinek and believe that one of the reasons for the absence of lines from the Cu^{2+} ions in the X-ray photoelectron spectra⁷⁷ is a mistake in the procedure for the preparation of samples. Thus, ground samples of the dichalcogenides were applied to the freshly purified surface of indium. In this case, it is quite possible that the chalcogenide reacted with indium as a result of which Cu^{2+} was reduced to Cu^+ on the surface:



The authors⁷⁷ did not perform subsequent treatment of the surface of the samples under study with Ar^+ ions (to remove the surface layer containing the adsorbed molecules) until this treatment ceased to affect the spectral patterns. Note also that the formulas proposed by Jellinek do not allow one to explain the fact that the above-mentioned chalcogenides possess the metallic conductivity. Since both the Cu^+ and S_2^{2-} ions have filled electron shells, only the S^- ions (actually, these ions are the S^{2-} radical anions) can be responsible for the charge transfer. Interactions between the orbitals of the adjacent S^- species would necessarily lead to the formation of the covalent bond



and hence, the formulas proposed by Jellinek would be more properly written as $\text{Cu}_2^+(\text{Te}_2^{2-})$ or $\text{Cu}_6^+(\text{S}_2^{2-})_3$. However, in this

case, the copper chalcogenides would exhibit dielectric properties and, moreover, the above-considered formulas are contradictory to the structural data.¹⁷

The fact that the approach proposed by Jellinek is inadequate gave impetus to the more accurate determination of the structure of CuS. Thus, Gotsis *et al.*⁷⁸ attempted to redetermine the structure of CuS by the high-resolution X-ray powder diffraction method and calculated the electronic structure using density functional theory. Based on the results obtained, the authors reasoned that the $\text{Cu}^+ - \text{S}_2^{2-} - \text{Cu}^+$ formula is more realistic for CuS (the authors believed that this formula is also appropriate for CuSe). However, this interpretation of the charge state of CuS suffers from drawbacks analogous to those of Jellinek's interpretation. Liang and Whangbo⁷⁹ believed that the $\text{Cu}_3^+(\text{S}_2)\text{S}^{2-}$ formula is more adequate than the formula suggested by Jellinek [$\text{Cu}_3^+(\text{S}_2^+)\text{S}^-$]. Although the authors noted the substantially covalent character of the Cu–S bond, they concluded that holes in the valence band are associated with oxidation of only sulfur, *i.e.*, the authors did not assume the mixed-valence state for copper.

A study⁸⁰ was devoted to the electronic structures of copper chalcogenides and their relationship with the conductivity. The authors calculated the electronic structures of copper sulfides with the use of the extended Hückel method and demonstrated that holes are approximately equally distributed over copper and sulfur atoms due to substantial overlap between the $3p$ orbitals of the sulfur atoms and the $3d$ orbitals of the copper atoms. This indicates that the classical formula for CuS is more realistic and, as will be seen from the data given below, agrees with the existence of charge density waves (CDWs) in conducting chalcogenides based on copper.

The X-ray photoelectron spectra of samples of highly pure CuS, which was synthesised according to a procedure reported in the handbook,⁸¹ have lines at 932.2 and 933.7 eV with the intensity ratio of 1.3 : 1.¹⁰ These lines correspond to the energies of the $2p_{3/2}$ levels of copper [$\text{ECu}(2p_{3/2})$]. The first and second lines can be assigned to the Cu^+ and Cu^{2+} ions, respectively. Note that the $\text{ECu}(2p_{3/2})$ value given for CuS (932.8 eV) in the handbook⁸² is the average of the values determined in the study.¹⁰ Jellinek⁷⁷ reported an obviously unrealistic value of 931.4 eV, which is even smaller than that for Cu_2S (*cf.* 932.0 eV⁷⁷ and 932.9 eV⁸²).

To summarise, it can be noted that the problem of the determination of the charge state of copper in chalcogenides is in essence identical to that for oxide HTSCs based on copper. However, in the case of chalcogenides the situation is more complex because the Cu–X bonds in these compounds are more covalent than those in the corresponding oxides.

Taking into account the complexity and ambiguity of the determination of charge states of the copper and chalcogen atoms in chalcogenides, hereinafter the following approach will be used.

Chalcogenides are considered to be compounds of monovalent copper if the sum of the degrees of oxidation of the cations is equal to twice the number of the chalcogen atoms (*i.e.*, on the assumption that the degrees of oxidation of the chalcogen and copper atoms are -2 and $+1$, respectively). If this sum is smaller than twice the number of the chalcogen atoms, chalcogenides are considered as mixed-valence compounds in which the degree of oxidation of copper is larger than $+1$ and the degree of oxidation of chalcogen is larger than -2 . Thus, according to this approach, sulfide NaCu_5S_3 contains the Cu^+ and S^{2-} ions, whereas sulfide NaCu_4S_3 is a mixed-valence compound. This approach is known in the literature as Zintl's concept (according to Ref. 83).

Ternary copper chalcogenides can be divided into two groups: compounds with chain structures and compounds with layered structures. At the same time, according to the above-proposed approach, these compounds can be separated into copper(I) chalcogenides and mixed-valence copper chalcogenides (the degree of oxidation of copper is larger than unity). The fruitfulness of this approach is apparent. Thus, virtually all copper(I) chalcogenides are semiconductors, whereas mixed-valence copper chalcogenides possess the metallic conductivity.

All chalcogenides of the general formula $\text{MCu}_2\text{X}_{n+1}$ (where M is alkali metal, X is chalcogen, $n = 1-3$) have layered structures. The following layered ternary copper chalcogenides are known: TlCu_2Te_2 ,⁸⁰ TlCu_2Se_2 ,⁸⁴ TlCu_2S_2 , TlCu_2SeS ,⁸⁵ TlCu_4S_3 , TlCu_4Se_3 ,^{80,86} KCu_4S_3 ,⁸⁷ KCu_4Se_3 ,⁸⁶ RbCu_4S_3 ,⁸⁸ RbCu_4Se_3 , CsCu_4S_3 , CsCu_4Se_3 ⁸⁶ and TlCu_6S_4 .⁸⁹ Since the total charge of the cations in the compounds of this series is one less than twice the number of the chalcogen atoms, these chalcogenides should be considered as mixed-valence compounds. It is therefore concluded that the valence band contains holes. Hence, these chalcogenides should exhibit metallic properties.

Selenide TlCu_2Se_2 was prepared⁸⁴ by heating ($< 1050^\circ\text{C}$) stoichiometric amounts of TlSe, copper and selenium *in vacuo* followed by slow cooling. The crystals of TlCu_2Se_2 consist of the Cu–Se layers. The Tl^+ ions are located above and below the layers. The Cu–Se bonds within the layers are substantially covalent. The copper atoms are located inside the tetrahedra formed by the selenium atoms, only three-fourths of positions being occupied (the ThCr_2Si_2 structural type) (Fig. 19).

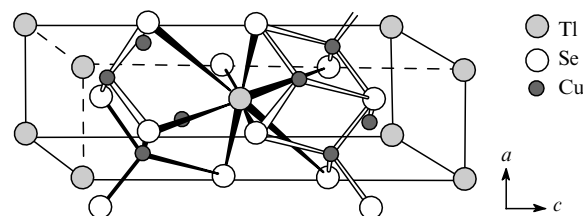


Figure 19. Crystal structure of TlCu_2Se_2 .⁹⁰

It was found⁹⁰ that the TlCu_2Se_2 salt exhibits metallic properties. To account for this fact, Brun *et al.*⁹⁰ assumed the coexistence of Tl(I) and Tl(III) selenides in the lattice. However, this assumption is contrary to the structural data and the results of electrophysical measurements.⁹¹ Selenide TlCu_2Se_2 possesses the rather high conductivity ($\rho_{RT} = 5 \times 10^{-5} \Omega \text{ cm}$). The temperature dependence of the conductivity, which was measured down to liquid helium temperature, is typical of metals. No substantial difference between the conductivities measured for single crystals and for pressed powders of TlCu_2Se_2 was observed, which is indicative of the weak anisotropy of the resistance of crystals. For TlCu_2Se_2 , the Hall effect was measured and it was demonstrated that this selenide is a metal with hole conductivity (one hole per formula unit, like in the isostructural TlCu_2Te_2 compound⁹¹). This fact rules out the existence of two forms of thallium suggested in the study⁹⁰ because if this were the case, electrons, which fill the conduction band, would act as carriers.

Isostructural sulfide TlCu_2S_2 was prepared by Berger.⁸⁵ Thus, heating a one-phase sample of Tl_4S_3 , which has been synthesised beforehand, with powdered copper and sulfur afforded TlCu_3S_2 the subsequent treatment of which with a concentrated ammonia solution and a 30% H_2O_2 solution yielded TlCu_2S_2 . This compound is unstable⁸⁵ and reversibly decomposes to three phases, *viz.*, to TlCuS , TlCuS_2 and TlCu_4S_3 , on heating to 330 K.

Sulfide TlCu_2S_2 , like the selenide and telluride, exhibits metallic properties.

Later on, chalcogenides TlCu_2X_2 ($\text{X} = \text{S}$ or Se) and mixed chalcogenide TlCu_2SSe were prepared⁹² and studied by X-ray photoelectron spectroscopy. According to Jellinek's concept, the authors⁹² assigned the degree of oxidation of $+1$ to the thallium and copper atoms in TlCu_2SSe . The X-ray photoelectron spectrum of this compound has two lines in the $\text{ECu}(2p_{3/2})$ region. The authors attributed these lines to the difference in the environment about the copper atoms and suggested that one line belongs to the copper atom bound to the selenium atom and the second line belongs to the copper atom bound to the sulfur atom. However, this assignment of the lines implies the structural ordering in the

crystals of the mixed chalcogenide and the equality of the two lines, which was not observed experimentally.

The metal–nonmetal transition should occur on addition of one electron to the valence band of chalcogenide MCu_2X_2 (M is alkali metal) because the valence band becomes completely filled. Actually, the replacement of alkali metal by alkaline-earth metal causes this transition and chalcogenides BaCu_2S_2 and BaCu_2Se_2 exhibit dielectric properties.^{83, 93–95}

Single crystals of BaCu_2X_2 develop an orange colour in transmitted light and a metallic-black colour in reflected light, which is characteristic of semiconductors. In the study,⁹³ chalcogenides BaCu_2X_2 were prepared by heating stoichiometric amounts of barium and copper chalcogenides with metallic copper. In this case, orthorhombic crystals with a chain structure were formed.

Sulfide BaCu_2S_2 was prepared by the reaction of BaCO_3 and CuO with sulfur at 700 °C under a stream of CS_2 .⁹⁴ However, this procedure afforded the tetragonal phase of BaCu_2S_2 ,⁹⁵ which has the layered structure^{83, 95} analogous to the structure of TiCu_2X_2 (the ThCr_2Si_2 structural type).

The conductivity of sulfide BaCu_2S_2 was measured⁹⁶ and this compound was found to exhibit metallic properties in the range of 40–293 K. This result is difficult to explain on the basis of the accepted notion of the electronic structure of chalcogenides because sulfide BaCu_2S_2 does not contain holes in the valence band and can be represented by the formula $\text{Ba}^{2+}\text{Cu}_2^+\text{S}_2^{2-}$. At the same time, it was demonstrated⁸³ that this compound exhibits semiconducting properties at 77–293 K. This discrepancy in the results was accounted⁸³ for by the procedure for the synthesis used in the study,⁹⁶ which afforded a mixture of $\text{Ba}_{0.96}\text{Cu}_{2.01}\text{S}_{1.94}$ and $\text{Ba}_{0.95}\text{Cu}_{3.91}\text{S}_{2.97}$ in a ratio of 17:3. The resistance of the sulfide increases insignificantly (by a factor of ~ 2.7) as the temperature decreases from 300 to 77 K, from which an approximate estimate of the activation energy can be obtained ($E_a \sim 0.01$ eV). This estimate was not made in the study.⁸³ For BaCu_2S_2 , the magnetic susceptibility was measured and the superconductivity was found to be absent to 2 K. The temperature dependence of the magnetic susceptibility is described by the following equation

$$\chi_{\text{exp}} = \frac{C}{T} + \chi_{\text{dia}} + \chi_0,$$

where C is the Curie constant, χ_{dia} is the diamagnetism of the core and χ_0 is the temperature-independent paramagnetism. Judging from the value of the Curie constant ($C = 5.83 \times 10^{-3}$ emu K mol⁻¹), the paramagnetic contribution results from admixtures whose concentration was $\sim 1.5\%$ and BaCu_2S_2 possesses diamagnetic properties. Hence, Zintl's concept appears to be true for both polymorphous modifications of BaCu_2S_2 , which justifies its use in the present review.

Chalcogenides NaCuSe , NaCuTe , KCuSe , KCuTe ⁹⁷ and KCuS ⁹⁸ in which the degrees of oxidation of the copper and chalcogen atoms are +1 and -2, respectively, are similar in electronic properties to BaCu_2X_2 . In spite of the formal similarity, these compounds have different structures. Thus, chalcogenides NaCuSe and NaCuTe belong to the PbFCl structural type, whereas KCuS , KCuSe and KCuTe belong to the Ni_2In structural type (contain zigzag Cu–S chains). The authors related this change in the structural type caused by the replacement of sodium by potassium to the difference in the ionic radii and noted that this change is unusual because only intermetallic compounds rather than salts belong to the Ni_2In structural type. These chalcogenides, judging from their colour, are narrow-band semiconductors. All these compounds were isolated as bright black crystals.

Chalcogenides of the general formula MCu_4X_3 (M is alkali metal and X = S or Se) were described for the first time by Rüdorff.⁹⁹ He isolated the KCu_4S_3 and RbCu_4S_3 salts. The CsCu_4S_3 ⁸⁸ and TiCu_4S_3 ⁸⁶ salts and the selenium analogues MCu_4Se_3 (M = Tl, K, Rb or Cs)⁸⁶ were described. The majority of these compounds were synthesised according to Rüdorff's

carbonate method. Copper and chalcogen were mixed with carbonate of the corresponding metal and the mixture was heated to 650–700 °C. The resulting product was isolated as platelet-like black crystals. The thallium salts were synthesised with the use of Ti_2S or TiSe . Unlike the sulfide, the selenide CsCu_4Se_3 , which was prepared according to the carbonate method, was not a one-phase compound.⁸⁶ The KCu_4Se_3 salt was prepared⁸⁶ also by fusing stoichiometric amounts of K_2Se , Cu and Se in a sealed evacuated quartz tube at 800 °C.

All the above-mentioned chalcogenides have layered structures. The double layers consist of sulfur atoms, which form tetrahedra linked *via* shared edges. The copper atoms are located inside the tetrahedra and the alkali metal or thallium atoms are located between layers. Due to mutual repulsions between the like-charged $[\text{Cu}_4\text{X}_3]_n^{n-}$ layers, it is required by the sizes of the M^+ ions that the M–X distances will be larger than the sum of their ionic radii. Thus, the Na^+ ion is too small to screen mutual repulsions between the layers and hence, NaCu_4X_3 salts do not exist.

Goodenough (according to Ref. 86) suggested the $D_0(n, l)$ criterion, which depends on the electronic configuration of the metal atom and the nature of the bridging ligand. This criterion determines the possibility of the nonmetal–metal transition. According to this criterion, Cu^{2+} sulfide complexes with the d^9 configuration can exhibit metallic properties if the internuclear distances Cu–Cu < 0.31 nm. In sulfide KCu_4S_3 , four Cu–Cu distances are 0.276 nm and one Cu–Cu distance is 0.297 nm. These data satisfy Goodenough's criterion well and, consequently, KCu_4S_3 can exist in the metallic state. Hence, taking into account also the mixed-valence state of the copper and chalcogen atoms (the formal degree of oxidation of copper is +1.25), it can be suggested that chalcogenides MCu_4X_3 are metals. Actually, as early as 1952 Rüdorff found⁹⁹ that KCu_4S_3 and RbCu_4S_3 exhibit metallic properties. According to Rüdorff, the specific resistance ρ_{RT} of KCu_4S_3 and RbCu_4S_3 at ~ 20 °C is 2.5×10^{-2} and 1.67×10^{-2} Ω cm, respectively.

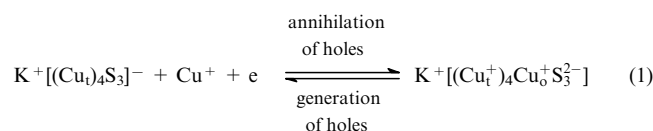
Later on, the major metallic state of KCu_4S_3 was confirmed:⁸⁷ $\rho = 2.5 \times 10^{-4}$ and 1.67×10^{-5} Ω cm at 293 and 20 K, respectively. The specific resistance changes linearly with temperature throughout the temperature range. Sulfide KCu_4S_3 exhibits temperature-independent paramagnetism (Pauli paramagnetism) and shows metallic reflection in the visible and near UV regions. Rüdorff obtained higher values of the electrical resistance because he performed measurements with the use of the double-contact method, which ignored the thermoelectromotive force.

In 1983, it was established¹⁰⁰ that other alkali thiocuprates MCu_4S_3 also exhibit metallic properties. Their electrical resistance changes linearly with temperature in the range of 150–300 K. At ~ 293 K, the resistance is 6.25×10^{-4} , 7.14×10^{-4} and 8×10^{-4} Ω cm for KCu_4S_3 , RbCu_4S_3 and CsCu_4S_3 , respectively. All three salts show temperature-independent paramagnetism.

Selenide CsCu_4Se_3 was prepared¹⁰¹ by the hydrothermal synthesis. Alkali metal polyselenide M_2Se_x (M = Na or K; $x = 2, 4$ or 5), CsCl and copper were placed in a tube with water. The tube was evacuated, sealed and heated at ~ 120 °C for five days. Needle-like crystals of α - CsCu_4Se_4 and platelet-like crystals of CsCu_4Se_3 were isolated from the reaction mixture. The increase in the temperature to 170 °C resulted in an increase in the yield of CsCu_4Se_3 to 80% but the compound was formed as polycrystals. The Cu–Cu distances in selenides MCu_4Se_3 (0.2895 and 0.3071 nm¹⁰¹) satisfy Goodenough's criterion. Hence, taking into account also the mixed-valence states of the copper and selenium atoms, these selenides can be considered as metals.

The crystal structures of the MCu_4X_3 salts¹⁰² are characterised by the presence of octahedral cavities (one cavity per formula unit) between the $[\text{Cu}_4\text{X}_3]_n^{n-}$ layers. The size of the cavity is large enough for an additional copper atom to occupy this cavity. The insertion of copper atoms into the octahedral cavities should lead to annihilation of holes in the valence band and, consequently, should cause the metal–nonmetal transition. According to Zintl's

criterion, chalcogenide MCu_5X_3 contains the $\text{M}^+\text{Cu}_5^+\text{X}_3^{2-}$ ions with the closed shells. The electrochemical reaction



metal
(Pauli paramagnetism)

semiconductor
(diamagnetic)

afforded¹⁰³ chalcogenide KCu_5S_3 (Cu_1 and Cu_0 are the copper atoms occupying the tetrahedral and octahedral positions, respectively); the back reaction, *viz.*, anodic oxidation of KCu_5S_3 , gave the initial sulfide KCu_4S_3 . According to the X-ray diffraction data,¹⁰³ the tetragonal symmetry of the crystals is retained in the course of the reaction. The unit-cell volume decreases from $140.4 \times 10^9 \text{ nm}^3$ for KCu_4S_3 to $129.6 \times 10^9 \text{ nm}^3$ for KCu_5S_3 due to additional attractions between the charged layers caused by the copper ions occupying the octahedral cavities between the layers. The specific resistance increases from $7.34 \times 10^{-4} \Omega \text{ cm}$ for KCu_4S_3 to $1.90 \times 10^{-3} \Omega \text{ cm}$ for KCu_5S_3 , the sign of the temperature resistance coefficient changing to minus, *i.e.*, KCu_5S_3 is a semiconductor.

As mentioned above, the NaCu_4S_3 salt does not exist. However, the $\text{Na}_2\text{Cu}_4\text{S}_3$ and NaCu_5S_3 salts are known.^{104,105} Both these salts can be considered as analogues of the KCu_5S_3 salt, in which octahedral cavities are occupied either by Na^+ or by Cu^+ ions. The NaCu_5S_3 salt was prepared by the hydrothermal synthesis and the $\text{Na}_2\text{Cu}_4\text{S}_3$ salt was synthesised from a carbonate melt.

Crystals of NaCu_5S_3 belong to the hexagonal system (unlike tetragonal crystals of KCu_5S_3) (Fig. 20). There are two crystallographically nonequivalent copper atoms per asymmetric unit. The $\text{Cu}(1)$ atoms are almost linearly coordinated by two sulfur atoms. The $\text{Cu}(2)$ atoms are coordinated by three sulfur atoms (as in $\text{Na}_2\text{Cu}_4\text{S}_3$) to form a trigonal pyramid. The $\text{Cu}(1)$ atoms each have four $\text{Cu}(2)$ neighbouring atoms, whereas the $\text{Cu}(2)$ atoms each are surrounded by six $\text{Cu}(1)$ atoms. The $\text{Cu}-\text{Cu}$ distances (0.27 nm) satisfy Goodenough's criterion. However, according to Zintl's criterion, both salts contain ions with closed shells and, consequently, the NaCu_5S_3 and $\text{Na}_2\text{Cu}_4\text{S}_3$ salts are, apparently, semiconductors. This is also true for selenide TiCu_5Se_3 .⁸⁵

Annihilation of holes in the valence band of MCu_4X_3 can be also induced by the replacement of alkali metal by alkaline-earth metal. Sulfide BaCu_4S_3 was prepared¹⁰⁶ by heating a mixture of BaS , copper and sulfur in a sealed evacuated tube at 800°C as crystals, which develop a red colour in transmitted light and exhibit metallic lustre in reflected light. According to the X-ray diffraction data, these are two different phases, *viz.*, the α and β phases. The α phase, which is stable at room temperature, is transformed into the β phase at 640°C . Both phases belong to the

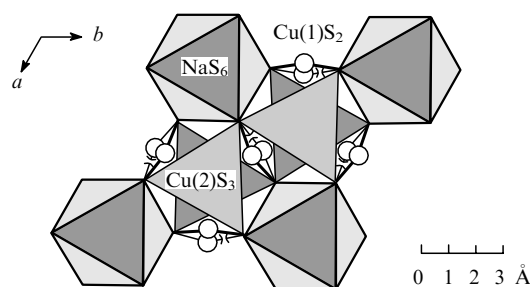


Figure 20. Crystal structure of NaCu_5S_3 projected onto (001). The NaS_6 octahedra (the Na atoms at $z/c = 1/4$ and $3/4$), the linear coordination in $\text{Cu}(1)\text{S}_2$ (the Cu(1) atoms at $z/c = 1/4$ and $3/4$) and the $\text{Cu}(2)\text{S}_3$ pyramids [the Cu(2) atoms at $z/c \sim 0$ and $1/2$].

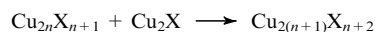
orthorhombic system. Their structures are similar and consist of chains formed by the BaS_6 trigonal prisms linked to each other *via* shared triangular faces. The copper atoms form infinite zigzag chains in the α phase ($\text{Cu}-\text{Cu}$, 0.275 nm) and infinite linear chains in the β phase ($\text{Cu}-\text{Cu}$, 0.29 nm). In spite of the filled valence band (as follows from the formula $\text{Ba}^{2+}\text{Cu}_4^+\text{S}_3^{2-}$), the short $\text{Cu}-\text{Cu}$ contacts are responsible for the noticeable conductivity ($\rho_{RT} = 0.2 \Omega \text{ cm}$) of the crystals of BaCu_4S_3 , which is virtually independent of the temperature.

Only one salt belonging to the $\text{MCu}_{2n}\text{X}_{n+1}$ series with $n = 3$ is known, *viz.*, TiCu_6S_4 .⁸⁹ This salt was prepared by fusing a mixture of TiS_2 , copper and sulfur in a quartz tube. Its structure is similar to those of the preceding members of the series with $n = 1$ or 2. The crystal contains layers consisting of the CuS_4 tetrahedra alternating with layers of the thallium atoms. The TiCu_6S_4 salt should exhibit metallic properties because it is a mixed-valence compound with the $\text{Cu}-\text{Cu}$ distances of 0.2783 and 0.2917 nm. Actually, the electrical resistance of single crystals of TiCu_6S_4 varies (although not quite linearly) proportional with temperature. The crystals are characterised by a plus sign of the Hall constant. The concentration of holes was determined from this constant (+1.29 per formula unit). Berger and Eriksson⁸⁹ noted that the effective radius of sulfur increases in the series $\text{TiCu}_{2n}\text{S}_{n+1}$ as n increases and related this effect to a change in the concentration of holes in the valence band per sulfur atom. A decrease in the ratio from +0.5 at $n = 1$ to +0.25 at $n = 3$ correlates with an increase in the radius (the closer the charge of sulfur to -2 , the larger the radius). This interpretation is reasonable. However, from this interpretation it does not follow that holes are localised exclusively on the sulfur atoms.

In chalcogenides TiCu_7X_4 ($\text{X} = \text{S}$ or Se), which are derivatives of the TiCu_6S_4 salts, additional copper atoms occupy cavities, which leads to filling of the valence band and causes the metal–nonmetal transition.⁸⁵ The mineral crookesite with composition $\text{TiCu}_{6.8}\text{Se}_4$, in which 80% of vacancies are occupied, possesses metallic properties⁸⁹ because the valence band is only partially filled (there are +0.2 holes per formula unit in the crystal).

The members of the MCu_6X_4 series are represented only by thallium salts. However, the ammonium analogue of TiCu_7X_4 , *viz.*, the $\text{NH}_4\text{Cu}_7\text{S}_4$ salt, is known. This salt satisfies Zintl's criterion and, consequently, has a filled valence band.⁸⁷ Judging from the $\text{Cu}-\text{Cu}$ bond lengths (0.283 and 0.294 nm), this salt possesses semiconducting properties.

Since no salts of the $\text{MCu}_{2n}\text{X}_{n+1}$ series with $n > 3$ are available, the question of whether these salts can exist was considered theoretically.⁸⁰ The formal analogy of the reactions of the type



was drawn to the so-called isodesmic reactions, which are well known in theoretical organic chemistry. In these reactions, the number of bonds of a particular type remains invariant, but their relative arrangement changes. For example,

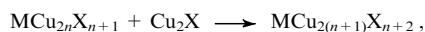


It was demonstrated that this concept is applicable to two layers of the $\text{Cu}_{2n}\text{X}_{n+1}^{q-}$ anions ($q = 1$ or 2) and the energy effects of the isodesmic reactions with the participation of these anions were calculated (the extended Hückel method).⁸⁰

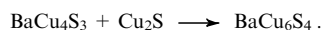


Reaction	(2)	(3)	(4)
$\Delta E/\text{eV}$ ($q = 1$)	−0.320	−0.159	−0.061
$\Delta E/\text{eV}$ ($q = 2$)	−0.023	−0.002	0.000

The results of calculations are in complete agreement with the experimental data. Thus, these reactions are most favourable for compounds with $q = 1$, viz.,



where M is a single-charged ion (alkali metal or thallium). These reactions are less favourable for analogous barium salts ($q = 2$). Thus, the absence of the BaCu_6S_4 salt is attributable to fact that the gain in energy is virtually absent for the reaction



Judging from the very low energy of reaction (4), MCu_8S_5 salts, most probably, do not exist.

The absence of compounds of the $\text{MAG}_{2n}\text{X}_{n+1}$ series lends support to the validity of the approach, which we applied to the determination of the electronic structures of ternary copper chalcogenides. In these compounds, silver should possess mixed valence because the oxidation state of this element in chalcogenides is no greater than +1. However, when hydrogen sulfide was passed through a melt of $\text{Ba}[\text{Ag}(\text{CN})_2]$ in a mixture with KNCS (500 °C, 30 min), the sulfide BaAg_2S_2 (CaAl_2Si_2 structural type), which meets Zintl's concept, was obtained.¹⁰⁷ The structure of CaAl_2Si_2 is characterised by the presence of the $[\text{Al}_2\text{Si}_2]^{2-}$ structural elements in which three crystallographically equivalent Si–Al bonds are shorter than the fourth bond directed along the c axis. An analogous situation was observed in the crystals of BaAg_2S_2 , with the only difference that three equivalent S–Ag bonds (0.2686 nm) are longer than the fourth bond (0.2659 nm). The data on the conductivity were not reported in the study.¹⁰⁷ However, based on Zintl's concept and taking into account the dark-red colour of the crystals, it is believed that sulfide BaAg_2S_2 is a semiconductor.

Chalcogenides $\text{K}_2\text{Ag}_4\text{S}_3$ ^{87, 110} (Fig. 21 *a*) and KAg_4Se_3 ¹⁰⁹ (analogues of $\text{Na}_2\text{Cu}_4\text{S}_3$) as well as RbAg_5S_3 ¹⁰⁸ (an analogue of NaCu_5S_3) and CsAg_7S_4 ¹⁰⁸ (an analogue of TlCu_7S_4) satisfy Zintl's criterion. The $\text{M}_2\text{Ag}_6\text{S}_4$ salts ($\text{M} = \text{Na}$ or K) containing an alkali metal atom instead of the seventh silver atom were reported.⁶⁶ These chalcogenides were prepared according to the carbonate procedure by heating a mixture of powdered silver, chalcogen and the corresponding alkali metal carbonate to 1000 °C for ~ 6 h. Since the resulting anthracite-like bright crystals are unstable in air, the authors¹⁰⁹ failed to isolate the $\text{K}_2\text{Ag}_4\text{Se}_3$ salt as single crystals suitable for X-ray diffraction analysis.

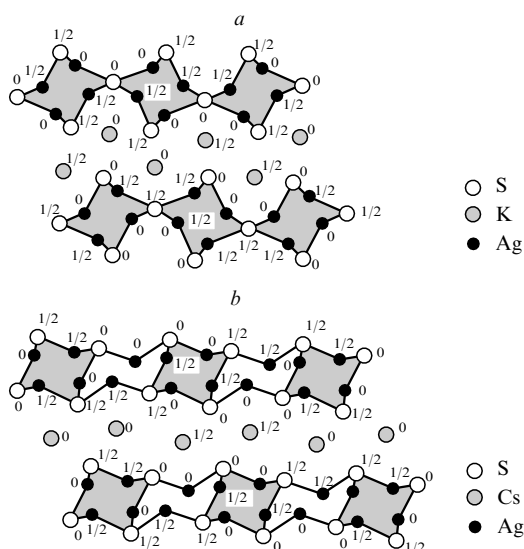


Figure 21. Projections of the structures $\text{K}_2\text{Ag}_4\text{S}_3$ (*a*) and CsAg_3S_2 (*b*) along the b axis.

The RbAg_5S_3 and CsAg_7S_4 salts were prepared as dark-red needle-like crystals according to the carbonate procedure by heating in an autoclave (~ 300 °C, 84 h) with the use of ethylenediamine in the supercritical state as the solvent.

The hexagonal crystals of RbAg_5S_3 contain the Ag_6S_6 twelve-membered rings in which the silver and sulfur atoms adopt the coordination number of 3. The rings are linked to each other through the silver atoms (the coordination number is 2) with the nearly linear coordination and are packed in stacks. The structure contains channels with a diameter of ~ 0.7 nm. These channels are occupied by the Rb^+ ions (Fig. 22). The Ag–Ag distances vary from 0.296 to 0.307 nm, which may indicate the presence of covalent interactions between the Ag^+ ions with the d^{10} configuration. It was noted¹⁰⁸ that the potassium analogue KAg_5S_3 has an analogous structure.

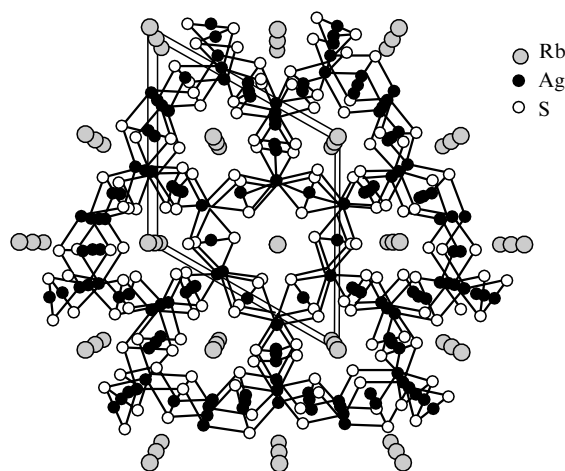
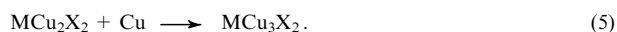


Figure 22. Projection of the structure of RbAg_5S_3 along the c axis;¹⁰⁸ columns containing Rb^+ ions are shown.

The structure of the cesium salt CsAg_7S_4 is unique. The crystals contain the eight-membered Ag_4S_4 rings in which the silver and sulfur atoms adopt the coordination numbers of 2 and 3, respectively. These rings, as in the structure of RbAg_5S_3 , are linked to each other through the silver atoms, which have a nearly linear coordination. The $\text{Ag}^+ - \text{Ag}^+$ contacts, as in the rubidium salt, are in the range of 0.2961–0.3087 nm.⁹⁹ The rings are packed in infinite stacks. The channels (with a diameter of ~ 0.6 nm) formed in the structure are occupied by the cesium ions (Fig. 23).

Analysis of these structures allows the conclusion to be drawn about the similarity of the structural motifs of ternary copper and silver chalcogenides satisfying Zintl's concept. The ions with the d^{10} configuration have the linear or trigonal coordination, whereas the copper ions, which exist in a formal oxidation state greater than +1, are tetrahedrally coordinated.

The compounds of the series of chalcogenides of the general formula MB_3X_2 (M is alkali metal or thallium; $\text{B} = \text{Cu}$ or Ag ; $\text{X} = \text{S}$ or Se) can be considered as chalcogenide derivatives MCu_2X_2



As in the case of reaction (1), the insertion of an additional copper atom leads to annihilation of holes in the valence band and causes the metal–semiconductor transition. Since the compounds of the MB_3X_2 series meet Zintl's criterion, i.e., contain only B^+ ions, these compounds may be thought to possess a structural motif identical to that of the above-considered silver salts.

The first compounds of this series to be prepared by the carbonate procedure were the silver salts RbAg_3S_2 and CsAg_3S_2 .¹¹¹ Their structures are isotypic and are in many respects similar to the structure of $\text{K}_2\text{Ag}_4\text{S}_3$. In both cases, the sulfur and silver atoms form layers between which the alkali metal atoms are

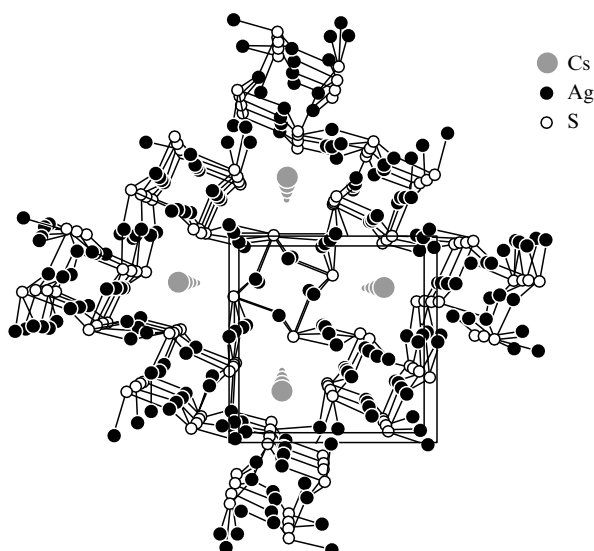


Figure 23. Projection of the structure of CsAg_7S_4 along the c axis;¹⁰⁸ channels formed by eight-membered rings are shown.

located, with the only difference that these layers in MAg_3S_2 are parallel to the (001) plane, whereas these layers in $\text{K}_2\text{Ag}_4\text{S}_3$ are parallel to the (100) plane (see Fig. 21 *a, b*). However, the structures of the layers are different. Thus in the structure of $\text{K}_2\text{Ag}_4\text{S}_3$, the eight-membered Ag_4S_4 rings are linked to each other *via* shared vertices through the bridging sulfur atoms, whereas the analogous rings in MAg_3S_2 are linked *via* shared edges. In Fig. 21 *a, b*, the fused Ag_4S_4 rings, which are similar in appearance but crystallographically nonequivalent, are hatched.

The first compound of the series of copper chalcogenides to be synthesised was sulfide KCu_3S_2 , which was prepared by heating a mixture of K_2CO_3 , copper and sulfur to 850 °C under an Ar atmosphere.¹¹² When the reaction was performed at a temperature lower than 780 °C, sulfides KCu_4S_3 and $\text{K}_3\text{Cu}_8\text{S}_6$ were obtained⁹⁹ (see below). The KCu_3S_2 salt exists as bright black needle-like crystals insoluble in water. These crystals as well as the crystals of MAg_3S_2 ($\text{M} = \text{Rb}$ or Cs) belong to the same structural type (X-ray diffraction data).

Later on,⁸⁸ the cesium salt CsCu_3S_2 was prepared by the carbonate procedure. It was found that brief heating (up to 1.5 h) at 700 °C afforded CsCu_4S_3 . However, an increase in the duration of annealing and in the temperature (4 h, 800 °C) resulted in the CsCu_3S_2 salt, which was free from admixtures. Unlike the blue-black crystals of CsCu_4S_3 , the crystals of CsCu_3S_2 are transparent and almost colourless. Since these crystals are oxidised in air and develop a dark-brown colour, they are stored under an inert atmosphere. From the colour of the crystals and their composition, which satisfies Zintl's criterion, CsCu_3S_2 can be unambiguously assigned to compounds possessing dielectric properties.

In spite of the formal similarity to KCu_3S_2 , the crystal structure of CsCu_3S_2 is quite different (the CdI_2 structural type). The sulfur atoms form hexagonal close packing. Half of octahedral positions are occupied by layers of Cs^+ ions. The layers with unoccupied octahedral positions, which remain unoccupied in the structure of CdI_2 , are filled with copper atoms located at the centres of the edges of the octahedra (Fig. 24). The sulfur (the coordination number is 3) and copper (the coordination number is 2) atoms form layers perpendicular to the c axis. The copper ions have a linear coordination, which is uncommon in the chemistry of alkali chalcogenides of copper. It is evident from the above-considered examples of chalcogenides, which meet Zintl's criterion, that trigonal coordination or trigonal coordination combined with the linear coordination is more typical of these compounds.

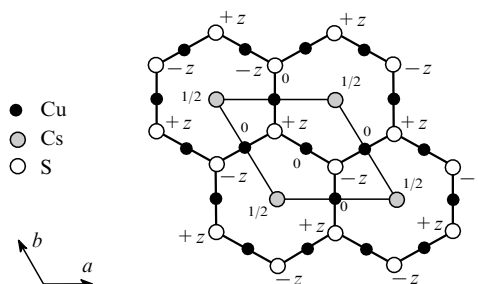


Figure 24. Projection of the structure of CsCu_3S_2 along the c axis.⁸⁸

In the above-considered sulfide KCuS , the copper atoms have a linear coordination (the SCuS angle is 179 °). However, the crystal structure consists only of chains, which impart the quasi-one-dimensional structure to this salt. The $\text{Cu}-\text{S}$ distances in KCuS (0.213 and 0.216 nm) and in CsCu_3S_2 (0.217 nm) are virtually identical and are typical of copper sulfides with covalent bonds.

The thallium chalcogenides TlCu_3X_2 ($\text{X} = \text{S}$ or Se) described previously^{85, 113–117} were synthesised in two stages. Initially, Tl_4S_3 was prepared from the elements. Then, the fusion of the latter with copper and sulfur afforded sulfide TlCu_3S_2 .

These chalcogenides are very sensitive to oxidising agents. Thus, the selenide is oxidised in air, whereas active oxygen formed upon decomposition of hydrogen peroxide is required to oxidise the sulfide. The reaction

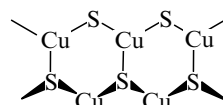


can be performed by oxidation (including electrochemical oxidation^{116, 117}). Berger called this reaction 'extraction' of copper from TlCu_3X_2 . This reaction is analogous to the above-described process (1) for the $\text{KCu}_5\text{S}_3-\text{KCu}_4\text{S}_3$ system and can be formally represented by Scheme (5). To perform chemical oxidation, powdered TlCu_3S_2 was deposited on a glass filter (with the aim of performing the process in a dynamic mode) and an ammonia solution of hydrogen peroxide, which decomposed under the action of the sulfide, was added dropwise. Ammonia that was released coordinated the Cu^{2+} ions, which were formed as result of oxidation, thus facilitating their extraction into a solution.

Selenide KCu_3Se_2 was synthesised by heating (910 °C, 3 h) a mixture of powdered copper, potassium and copper selenide in a quartz tube.¹¹⁸ The KCu_3Se_2 salt was obtained as well-faceted black platelet-like crystals. Its crystal structure is analogous to that of TlCu_3S_2 (X-ray diffraction data).

The data on other copper selenides MCu_3Se_2 are unavailable in the literature. However, analogous silver selenides RbAg_3Se_2 and CsAg_3Se_2 were reported.¹⁰⁹ Both salts crystallise as dark anthracite-like crystals and are readily oxidised in air. Their structures are similar to those of the analogous sulfides. The selenium and silver atoms form layers separated by layers of the M^+ ions.

Sulfide $\text{Na}_2\text{Cu}_3\text{S}_3$, which crystallised as needles, was described in a pioneering study.⁹⁹ More recently, it was demonstrated¹¹⁹ that this sulfide has in fact the composition $\text{Na}_3\text{Cu}_4\text{S}_4$ and its structure contains the $[\text{Cu}_4\text{S}_4]^{3n-}$ stacks. Below is schematically shown the formation of these stacks from the *cis*- CuS chains. The coordination about the copper atoms is planar-trigonal.



The stacks are separated by the Na^+ ions, thus imparting the quasi-one-dimensional electronic structure to the crystals. The shortest $\text{Cu}-\text{Cu}$ distances (0.2619–0.306 nm) satisfy Goode-nough's criterion. Besides, the $\text{Na}_3\text{Cu}_4\text{S}_4$ salt is a mixed-valence compound. As was noted in the study,¹¹⁹ all copper atoms in the

structure are equivalent, which is typical of metallic bonds (electrons delocalised along the $[\text{Cu}_4\text{S}_4]_n^{3n-}$ stacks), and sulfide $\text{Na}_3\text{Cu}_4\text{S}_4$ should exhibit metallic properties.

The electrophysical properties of this sulfide were examined.^{100,120} The electrical resistance of single crystals of $\text{Na}_3\text{Cu}_4\text{S}_4$ was found¹²⁰ to change linearly as the temperature decreased over the range from 300 to 150 K. Below 150 K, the $\rho(T)$ dependence becomes weaker, tends to saturation and reaches $3.3 \times 10^{-6} \Omega \text{ cm}$ at 15 K.¹⁰⁰

The electrical resistances for tableted samples at 293 K ($\rho_{RT} = 3.3 \times 10^{-3} \Omega \text{ cm}$) and 15 K ($\rho_{15} = 6.7 \times 10^{-4} \Omega \text{ cm}$) were reported.¹⁰⁰ For single crystals, the electrical resistance along the crystal axis, *i.e.*, along the stacks, was measured ($\rho_{RT} = 6.5 \times 10^{-5} \Omega \text{ cm}$). This $\rho(T)$ dependence is characteristic of metals.

Although Ghosh and Chaudhury¹⁰⁰ failed to measure $\rho_{\perp}$ (the resistance perpendicular to the stacks), the noticeable difference (by a factor of ~ 50) in the resistance of tableted samples and single crystals is indicative of the substantial anisotropy of the electrical resistance. The temperature-independent paramagnetism, which was found in the studies^{100,120} (150×10^{-6} and $170 \times 10^{-6} \text{ emu mol}^{-1}$, respectively), is also evidence in favour of the metallic state of $\text{Na}_3\text{Cu}_4\text{S}_4$.

It should be noted that the change in the specific electrical resistance according to the law

$$\rho = \rho_0 + \rho' T \quad (7)$$

is typical of normal metals, unlike quasi-one-dimensional molecular metals, whose specific resistance changes quadratically. The authors^{100,120} used the approach proposed by Jellinek in studies of sulfide $\text{Na}_3\text{Cu}_4\text{S}_4$ as a salt containing only Cu^+ ions and mentioned that the oxidation state of +2 for copper atoms was not revealed by X-ray photoelectron spectroscopy. Curiously, the authors¹²⁰ considered all sulfur atoms as being also identical, whereas Jellinek's concept requires the presence of S^{2-} and S^- ions in the structure. However, this is quite reasonable when it is considered that the compound under study is a metal and the electrons are delocalised along the stacks. In this case, the valence fluctuations $\text{Cu}^{2+} \rightarrow \text{Cu}^+$ within the stack occurred in $\sim 10^{-16} \text{ s}$.

The absence of the metal–nonmetal transition up to 13 K and the peculiarities in the $\rho(T)$ dependence associated with the formation of charge density waves (CDWs) are not understood. It is known¹²¹ that the so-called Peierls instability, which is manifested in the structural distortion of the one-dimensional chain associated with the increase in its period, is characteristic of quasi-one-dimensional metals. If the degree of filling of the band with electrons or holes is n^{-1} , a decrease in the temperature leads to n -merisation of the chain accompanied by splitting of the conduction band in such a way that the metal–nonmetal transition occurs. In this case, the larger is n , the smaller the gain in energy.

The reasons for the absence of the Peierls transition in the crystals of $\text{Na}_3\text{Cu}_4\text{S}_4$ up to 13 K were theoretically examined.¹²² In particular, it was noted that $\text{Na}_3\text{Cu}_4\text{S}_4$ is a one-dimensional metal because the shortest distance between the adjacent one-dimensional $[\text{Cu}_4\text{S}_4]_n^{3n-}$ stacks (0.423 nm) in this salt is substantially larger than the sum of the van der Waals radii of sulfur atoms (0.360 nm). Calculations within the framework of the extended Hückel method demonstrated that the Fermi level intersects two bands, each being formed half by the 3d orbitals of the copper atoms and half by the 3p orbitals of the sulfur atoms. Hence, Whangbo and Canadell¹²² believed that the hybrid formula including both the Cu^{2+} and S^- ions, *viz.*, $\text{Cu}_3^+\text{Cu}^{2+}\text{S}_4^{2-}$ and $\text{Cu}_4^+\text{S}_3^{2-}\text{S}^-$, is more adequate than Jellinek's formalism. This view is similar to our approach to the interpretation of the electronic structures of copper chalcogenides, which do not meet Zintl's concept.

Whangbo and Canadell¹²² believed that the state with CDWs preceding the Peierls transition is not formed due, probably, to the fact that the stabilisation of the electronic energy is exactly

compensated by the deformation energy of the stack. In the case of one-dimensional metals in the absence of states with CDWs, an alternative possibility consists in the formation of spin density waves (SDWs), which is generally observed at lower temperatures. In a review,¹²¹ we noted that the spin–lattice interaction responsible for the spin-Peierls transition is more efficient than the electron–lattice interaction at $t \approx U$, where t is the integral of the electron transition between the nearest electronic states and U is the interaction energy of two electrons located at one node. In one-dimensional conductors $[\text{MS}_4\text{C}_4(\text{CF}_3)_4]\text{TTF}$ ($\text{M} = \text{Cu}$ or Au ; TTF is tetrathiafulvalene), the spin-Peierls transition is observed at 12 (Cu) and 2.1 K (Au). I believe that the deviation of the $\rho(T)$ dependence from the linearity for $\text{Na}_3\text{Cu}_4\text{S}_4$ at $T < 80 \text{ K}$ is, probably, caused by fluctuations preceding the spin-Peierls transition at $T < 13 \text{ K}$.

A series of ternary copper sulfides M_nCuS with the Cu : S ratio of 1 : 1 can be distinguished based on formal attributes. In this series, all members with n from 0 (CuS) to 1 (KCuS) are known, the n value varying with a step of 0.25. Thus, the above-considered sulfide $\text{Na}_3\text{Cu}_4\text{S}_4$ corresponds to $n = 0.75$, whereas the above-considered layered sulfides MCu_2S_2 (the first members of the $\text{MCu}_{2n}\text{X}_{n+1}$ series) are characterised by $n = 0.5$. Finally, sulfide NaCu_4S_4 synthesised in 1996¹²³ corresponds to $n = 0.25$. It should be noted that the M_nCuS series can be distinguished only formally because the insertion of alkali metal into the lattice of CuS leads not only to a change in the electronic properties but also to a change in the structure. Thus, unlike $\text{Na}_3\text{Cu}_4\text{S}_4$, which has a quasi-one-dimensional stack structure, NaCu_4S_4 has a layered structure, though formally contains the same Cu_4S_4 structural elements.

Heating of a mixture of copper, Na_2S and BaS with sulfur (taken in a ratio of 1 : 3 : 0.5 : 6, respectively) in an evacuated glass tube (500 °C, 4 days) followed by cooling at a rate of 4 °C/h afforded a melt, which was freed off from polysulfides with water and DMF under a nitrogen atmosphere. As a result, platelet-like black crystals of NaCu_4S_4 were obtained in 79% yield.

The crystals consist of trigonal-symmetrical layers of CuS alternating with layers of Na^+ ions (Fig. 25). The structure of $\text{Na}_{0.25}\text{CuS}$, like CuS, contains both sulfide and disulfide ions. The $[\text{Cu}_4\text{S}_2(\text{S}_2)]^-$ layers have the sandwich structure: the Cu_2S_2 layers (the *anti*-GaS structural type) are located between two CuS layers (the BN structural type). These layers are linked through the copper atoms from the *anti*-GaS layer and through the sulfur atoms from the BN layer to form the Cu–S bond resulting in four-coordinate S^{2-} ions with the unusual inverted tetrahedral geometry. Unlike the structurally similar CuS salt in which the Cu_2S_2 layers of the *anti*-GaS type alternate with the CuS layers of the BN type, half of the *anti*-GaS layers in NaCu_4S_4 are replaced by layers of Na^+ ions. Therefore, the structure of NaCu_4S_4 contains two crystallographically nonequivalent copper atoms,

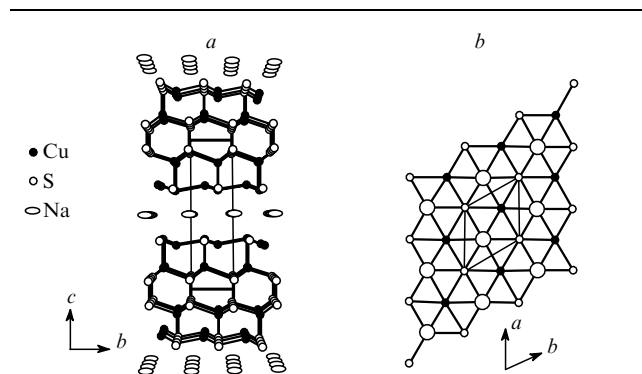


Figure 25. Packings of the atoms in NaCu_4S_4 (a) and in the $[\text{Cu}_4\text{S}_4]^-$ ions (b) along the c axis (large and small empty circles denote S atoms from two different layers).

viz., the copper atom tetrahedrally coordinated by one S^{2-} ion and three S_2^{2-} ions and the trigonally coordinated copper atom.

Sulfide $NaCu_4S_4$ is a metal with the hole conductivity. Its electrical resistance increases linearly with temperature in the range from 4.2 to 250 K. From measurements of the thermoelectromotive force it follows that holes act as charge carriers. This salt possesses the Pauli paramagnetism, $\chi_M = 6.2 \times 10^{-5} \text{ emu mol}^{-1}$.

Sulfide $BaCuS_3$, which we prepared¹²⁴ by heating a mixture of BaS , CuS and sulfur taken in stoichiometric amounts (800 °C, 2 h), has no analogues. This sulfide was formed as black bright platelet-like crystals belonging to the monoclinic system. Since the composition of this sulfide does not satisfy Zintl's criterion, it is believed that this compound is a metal. Actually, the specific resistance ($\rho_{RT} = 9.4 \times 10^{-2} \Omega \text{ cm}$) of the samples, though large, decreases as the temperature decreases and reaches $0.037 \Omega \text{ cm}$ at 15 K. Unlike other ternary copper sulfides, the $\rho(T)$ dependence is described by a fractional-rational rather than by a linear function

$$\rho(T) = \frac{1 + \alpha T}{\beta + \gamma T}, \quad (8)$$

where $\beta^{-1} = \rho(0)$, *i.e.*, $\beta = \sigma(0)$, $\alpha/\gamma = \rho(\infty)$.

Equation (8) can be rewritten in a more customary form

$$\rho(T) = \rho_\infty + \frac{a}{b + T} \quad (9)$$

with the 'Curie-like' second term. The magnetic susceptibility of metals containing paramagnetic centres is described by this formula. In the case of $BaCuS_3$, the following parameters were obtained for Eqn (9): $\rho_\infty = 0.136 \Omega \text{ cm}$, $a = -18.98 \Omega \text{ cm K}^{-1}$ and $b = 178.3 \text{ K}$.

Note that the temperature dependence of the electrical resistance described by Eqn (9) is untypical of all conducting materials, and not just of ternary sulfides. Analysis of the published data makes it possible to reveal analogous $\rho(T)$ dependences for $Cu_{1.5}Co_{1.5}S_4$,¹²⁵ which has the spinel structure, for $Rb_4Mo_{18}Se_{20}$ ¹²⁶ consisting of Mo_6Se_8 clusters and for spinel-like $CuRh_2S_4$ and $CuRh_2Se_4$.¹²⁷ The dependences reported in these studies are well described by Eqn (9). Apparently, the authors¹²⁷ failed to approximate the $\rho(T)$ dependence throughout the temperature range because the high-temperature region was described by the linear function (7), the temperature range with $T < 20 \text{ K}$ was described by the function

$$\rho(T) = \rho_0 + AT^n \quad (10)$$

with $n = 3$, whereas the temperature range from 20 to 250 K was not interpreted. The authors considered this dependence as the supporting evidence for the applicability of the Wilson model. However, the $\rho(T)$ dependence for single crystals of $BaCuS_3$ as well as that for chalcogenides studied in Refs 125–127 are described by Eqn (9) throughout the temperature range (from 300 K up to the superconducting transition). This result should give impetus to theoretical studies in the field of solid-state physics.

Sulfide $K_3Cu_8S_6$, which was the first representative of ternary copper chalcogenides of the general formula $M_3Cu_8X_6$ (M is alkali metal and $X = S$ or Se), was synthesised as early as the mid-nineteenth century.¹²⁸ Later on, this sulfide, along with other salts described above, was prepared according to the carbonate procedure and studied by the X-ray diffraction method.⁹⁹ However, the structure of this compounds remained unknown. In 1979, structural studies demonstrated¹²⁹ that this sulfide as well as the rubidium analogue $Rb_3Cu_8S_6$ have layered structures analogous to that of KCu_3S_2 . The structures of three sulfides, *viz.*, KCu_3S_2 ($K_3Cu_9S_6$), $K_3Cu_8S_6$ and KCu_4S_3 ($K_2Cu_8S_6$), are shown in Fig. 26 *a–c*. This comparison, which is not just formal, confirms that $K_3Cu_8S_6$ is intermediate between sulfides KCu_3S_2 and KCu_4S_3 . It was demonstrated¹³⁰ that KCu_4S_3 occurs as a low-temperature phase, which is stable up to 820 °C. At higher temperatures, the KCu_3S_2 phase is stable. Sulfide $K_3Cu_8S_6$ occurs as a metastable phase. The optimum conditions for the synthesis of the latter consist in annealing at 875 °C for 1–2 h.

As can be seen from Fig. 26 *a*, the low-temperature KCu_4S_3 phase contains close-packed layers in which all copper atoms are tetrahedrally coordinated. In the high-temperature KCu_3S_2 phase (Fig. 26 *c*), the layers are corrugated because the copper atoms adopt both the tetrahedral and trigonal coordinations. The structure of $K_3Cu_8S_6$ is intermediate between the above-described structures. The $[Cu_4S_4]^{n-}$ chains are linked in layers *via* shared edges of the tetrahedra so that the semisegment of the double layer, which is observed in KCu_4S_3 , is formed. The $Rb_3Cu_8S_6$ salt has the analogous structure.¹²⁹

In the same year, selenides $Rb_3Cu_8Se_6$ and $Cs_3Cu_8Se_6$ were synthesised by the carbonate procedure from powdered copper and selenium sulfide.¹³¹ After annealing at 900–1050 °C (3–4 h), the melt was slowly cooled and washed with water and alcohol to obtain dark anthracite-like crystals. The structure of $Rb_3Cu_8Se_6$ is similar to those of sulfides $K_3Cu_8S_6$ and $Rb_3Cu_8S_6$. Apparently, the cesium salt crystallises in two modifications one of which is analogous to $Rb_3Cu_8Se_6$, whereas the second modification was not identified. The results of electrophysical measurements for selenides are unavailable in the literature. However, based on their compositions and on the shortest Cu–Cu distances (0.2488–0.2893 nm) in these compounds, it can be said with assurance that these compounds are metals.

The electrophysical and magnetic studies of the crystals of $K_3Cu_8S_6$ were performed.¹³⁰ The magnetic susceptibility depends only slightly on the temperature at $T > 180 \text{ K}$. However, this dependence becomes pronounced at temperatures lower than 180 K, which is indicative of a phase transition of the second kind. This transition is reversible. The transition temperature can be determined more accurately from the temperature dependence of the $(\partial\chi/\partial T)$ derivative (150 K). At approximately 50 K, the second transition (of the first kind) with the noticeable hysteresis was observed.

The electrical resistance of single crystals of $K_3Cu_8S_6$ is $5 \times 10^{-4} \Omega \text{ cm}$; the $\rho(T)$ dependence was measured in the range of 350–5 K.¹³¹ The resistance decreases linearly as the temperature decreases, which is indicative of the metallic behaviour of

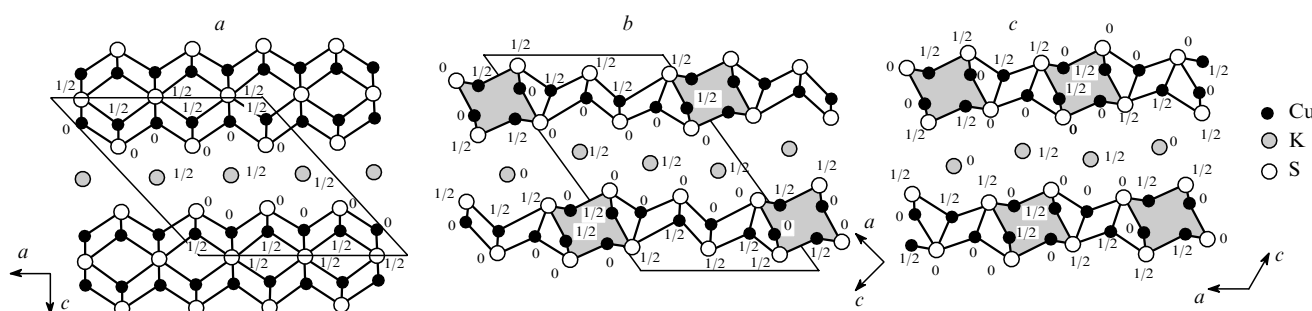


Figure 26. Structures of sulfides KCu_4S_3 (a), $K_3Cu_8S_6$ (b) and KCu_3S_2 (c).¹³⁰ In all the structures, the K^+ ions separate layers.

single crystals of $\text{K}_3\text{Cu}_8\text{S}_6$ down to 160 K. At about 150 K, a reversible phase transition occurs, which is manifested in an increase in the resistance in the course of subsequent cooling to 63 K. At this temperature, the resistance decreases sharply and from this point on the $\rho(T)$ dependence again corresponds to the metallic behaviour in the region of 50–5 K. The anomaly at about 160 K is also present in the temperature dependence of the thermoelectromotive force. Its plus sign confirms that $\text{K}_3\text{Cu}_8\text{S}_6$ is a metal with hole conductivity. In a study,¹³¹ all these anomalies were attributed to the occurrence of the state with CDWs, which is typical of low-dimensional metals, *viz.*, of quasi-one-dimensional salts {for example, of $\text{K}_2[\text{Pt}(\text{CN})_4]\text{Cl}_{0.3} \cdot x\text{H}_2\text{O}$ and NbSe_3 } and of quasi-two-dimensional salts (TaSe_2). However, this state can also occur in three-dimensional metals (for example, in CuV_2S_4). Sulfide $\text{K}_3\text{Cu}_8\text{S}_6$ can be considered (as is evident from its structure) as a quasi-two-dimensional metal. However, unlike quasi-two-dimensional metals, such as, for example, NbSe_2 or TaS_2 , the layers in $\text{K}_3\text{Cu}_8\text{S}_6$ are noticeably anisotropic, as is evident from the mode of linkage of the Cu_4S_4 columns in layers. The fact that the metallic properties are retained at temperatures lower than the phase transition temperature indicates that this anisotropy is yet inadequate to consider the crystals of $\text{K}_3\text{Cu}_8\text{S}_6$ as quasi-one-dimensional. An analogous anisotropy of the layers occurs, for example, in molybdenum bronze $\text{K}_{0.3}\text{MoO}_3$, which is a structurally two-dimensional metal with a essentially monomeric CDWs.

X-Ray scattering was studied at different temperatures¹³² and it was found that the phase transition at 153 K generates states, which are incommensurate with the lattice period, with the wave vector

$$q = \frac{(1 - \delta)b^*}{2},$$

where δ is the temperature-dependent variable ($\delta \approx 0.1$ at 150 K) and b^* is the reciprocal lattice vector. At 55 K, the wave vector of CDW becomes commensurate with the lattice period, which leads to a structural phase transition resulting in the superstructure with the commensurate period at $q = (\frac{1}{5}, \frac{1}{5}, 0)$. Sulfide $\text{K}_3\text{Cu}_8\text{S}_6$ is the first example of a metal with the hole conductivity in which CDWs with pronounced p character appear.

In conclusion, let us consider a few available examples of tellurides of Group IB elements containing discrete Te^{2-} or Te_2^{2-} ions.

Thus, ternary copper tellurides with compositions MCuTe^{97} and MCu_3Te_2 ^{104, 133} ($\text{M} = \text{Na}$ or K) satisfying Zintl's criterion were described. In 1976, telluride TiCu_2Te_2 was synthesised from the elements (600 °C, 48 h).¹³⁴ This telluride can be assigned to the series of $\text{MCu}_{2n}\text{X}_{n+1}$ chalcogenides. According to the data of X-ray diffraction analysis, this telluride is isostructural to selenide TiCu_2Se_2 . The electrophysical properties of the telluride under consideration were studied in Ref. 90. The electrical resistance (293 K) of single crystals of TiCu_2Te_2 is $2.3 \times 10^{-5} \Omega \text{ cm}$. The $\rho(T)$ dependence is analogous to that corresponding to metals, *viz.*, the resistance decreases linearly (by a factor of 3.5) as the temperature decreases and reaches $6.5 \times 10^{-6} \Omega \text{ cm}$ at 77 K. Holes act as charge carriers (the results of measurements of the Hall effect). Although the electrical resistance decreases as the samples are cooled, the ρ_{300}/ρ_{77} ratio is rather small. This is attributable to the fact that the concentration of the carriers in the sample decreases substantially (by a factor of 21) in the range of 300–77 K simultaneously with an increase (by a factor of 76) in the carrier mobility (from $34 \text{ cm}^2 \text{ V}^{-1}$ at 300 K to $2600 \text{ cm}^2 \text{ V}^{-1}$ at 77 K), *i.e.*, the effect of an increase in the carrier mobility is more pronounced than the effect of a decrease in their concentration. This leads to an increase in the conductivity upon cooling. To put it differently, TiCu_2Te_2 would be more properly characterised as a semimetal.

Layered mixed-valence telluride $\text{K}_2\text{Cu}_5\text{Te}_5$ was synthesised¹³⁵ by heating the telluride K_2Te with copper and tellurium in an evacuated tube (350 °C, 3 days). The telluride was obtained as black parallelepiped-shaped crystals. The structure of this salt

consists of the corrugated $[\text{Cu}_5\text{Te}_5]_n^{2n-}$ layers alternating with the layers of the potassium ions. The $[\text{Cu}_5\text{Te}_5]_n^{2n-}$ layers are formed by the Cu_2Te_2 rhombi linked *via* shared edges so that their structure corresponds to the distorted *anti*- PbO type. A comparison with the structure of CuTe demonstrates that the addition of 0.4 e per CuTe molecule leads to the cleavage of some of $\text{Te}-\text{Te}$ bonds in $\text{K}_2\text{Cu}_5\text{Te}_5$, whereas the addition of one electron (as in NaCuTe) leads to the cleavage of all $\text{Te}-\text{Te}$ bonds and generates the ideal structure of the *anti*- PbO type. Therefore, $\text{K}_2\text{Cu}_5\text{Te}_5$ is intermediate between CuTe and NaCuTe .

The electrical resistance and the thermoelectromotive force were measured for $\text{K}_2\text{Cu}_5\text{Te}_5$ and it was revealed that this telluride is a p -type metal in the range of 300–5 K. The electrical resistance is $6.67 \times 10^{-5} \Omega \text{ cm}$ at 293 K and reaches $3.1 \times 10^{-6} \Omega \text{ cm}$ at 5 K. The telluride possesses temperature-independent paramagnetism ($2.56 \times 10^{-4} \text{ emu mol}^{-1}$).¹³⁵

The electronic structure of the $\text{K}_2\text{Cu}_5\text{Te}_5$ salt was studied by quantum-chemical calculations using the extended Hückel method.¹³⁶ Since the conductivity increases only insignificantly as the temperature decreases in the range of 293–5 K, the nature of the ground state remains unclear, *i.e.*, the question of whether this telluride is a metal or a semimetal remains open. Another problem studied in Ref. 136 is associated with the possibility of the synthesis of tellurides $\text{K}_3\text{Cu}_5\text{Te}_5$ and KCu_5Te_5 . In particular, the question was studied of whether the addition of one electron to the $[\text{Cu}_5\text{Te}_5]_n^{2n-}$ layer or removal of one electron from this layer can lead to the metal–nonmetal transition.

According to the data obtained, the pre-Fermi region ($\varepsilon_F = -10.5 \text{ eV}$) from -10.1 to -12.6 eV is formed predominantly by the $5p$ orbitals of tellurium atoms, whereas the region from -12.6 to -16 eV is formed by the $3d$ orbitals of copper atoms. A broad gap extends from -10.1 to -7.5 eV . However, a narrow peak corresponding to σ^* antibonding orbitals of the $\text{Te}(2)-\text{Te}(2)$ bond is present at -8.3 eV (Fig. 27). The scheme of the structure of the $[\text{Cu}_5\text{Te}_5]_n^{2n-}$ layer is shown in Fig. 27. It can be seen that this layer contains three types of tellurium atoms. Only the $\text{Te}(2)$ atoms are involved in formation of the $\text{Te}-\text{Te}$ bonds. The populations of the $5p_y$ states of the tellurium atoms are approximately equal [1.43, 1.45 and 1.49 e for $\text{Te}(1)$, $\text{Te}(2)$ and $\text{Te}(3)$, respectively], *i.e.*, holes are to a large extent delocalised in the layer. This fact as well as the approximately equal $\text{Cu}(2)-\text{Te}(1)$ and $\text{Cu}(3)-\text{Te}(3)$ distances allows one to consider $\text{K}_2\text{Cu}_5\text{Te}_5$ as a metal. From the results of calculations it follows that the crystals of this telluride should exhibit the noticeable anisotropic conductivity. Unfortunately, it was impossible to measure this anisotropy because of small dimensions of the crystals.

The addition of one electron to the $[\text{Cu}_5\text{Te}_5]_n^{2n-}$ layer, which corresponds to the transformation to $\text{K}_3\text{Cu}_5\text{Te}_5$, leads to filling of the p band formed by the $5p$ orbitals of the tellurium atoms. One would expect that this will result in the metal–nonmetal transition. However, it was demonstrated¹³⁶ that the insertion of potassium leads not only to an increase in the degree of filling of the p band but also to structural changes. The structure of $\text{K}_2\text{Cu}_5\text{Te}_5$ contains vacancies sufficient for location of potassium ions above the $\text{Te}(2)-\text{Te}(2)$ bonds. The insertion of potassium leads to the cleavage of the bonds. In this case, the peak localised at -8.3 eV is broadened and merges with the p band. As a result, $\text{K}_3\text{Cu}_5\text{Te}_5$ retains the metallic properties, possesses two holes per formula unit and is a structural analogue of the NaCuTe salt.

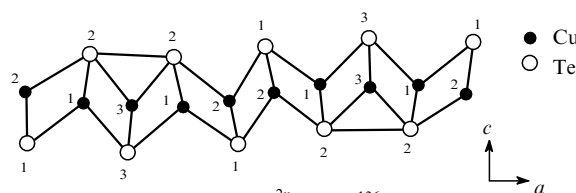


Figure 27. Scheme of the $[\text{Cu}_5\text{Te}_5]_n^{2n-}$ layer.¹³⁶

Upon the removal of one electron, which corresponds to the transformation to KCu_5Te_5 , the $\text{Te}(1)–\text{Te}(3)$ bond could be formed, *i.e.*, the Te_2^{2-} ion could be formed if the potassium atoms located above this bond are removed. This would result in the formation of the energy gap, *i.e.*, in the metal–nonmetal transition. However, according to the results of the study,¹³⁶ the metallic state is retained in this case because there are three $\text{Te}–\text{Te}$ bonds per two holes with respect to $\text{K}_2\text{Cu}_{10}\text{Te}_{10}$.

As part of continuing studies of reactions proceeding in melts of polytellurides, Zhang *et al.*¹³⁷ prepared a new class of polytellurides containing dodecahedral $[\text{Cu}_8\text{Te}_{12}]$ clusters, *viz.*, $\text{K}_4\text{Cu}_8\text{Te}_{11}$, $\text{M}_3\text{Cu}_8\text{Te}_{10}$ ($\text{M} = \text{Rb}$ or Cs), $\text{M}_1\text{M}'_2\text{Cu}_8\text{Te}_{10}$ ($\text{M}, \text{M}' = \text{K}, \text{Rb}$ or Cs) and $\text{M}_2\text{BaCu}_8\text{Te}_{10}$ ($\text{M} = \text{K}, \text{Rb}$ or Cs). Telluride $\text{K}_4\text{Cu}_8\text{Te}_{11}$ has a three-dimensional framework structure formed by the $[\text{Cu}_8\text{Te}_{12}]$ clusters linked to each other. Each layer contains an encapsulated K^+ ion (Fig. 28). The structure contains channels parallel to the b axis. These channels are occupied by potassium ions. The $[\text{KCu}_8\text{Te}_{12}]^{3-}$ clusters are ideal platonic bodies (the point symmetry group T_h) formed by the Cu_2Te_3 planar pentagons linked to each other. Each tellurium atom belongs to a Te_2^{2-} ion so that the clusters are in fact formed by the copper and ditelluride ions $[\text{Cu}_8(\text{Te}_2)_6]$.

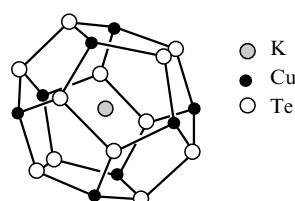


Figure 28. Structure of the $[\text{Cu}_8\text{Te}_{12}]$ cluster inside which the K^+ ion is located.¹³⁷

Unlike the $\text{K}_4\text{Cu}_8\text{Te}_{11}$ salt containing three-dimensional networks of the clusters, the $\text{Rb}_3\text{Cu}_8\text{Te}_{10}$ and $\text{Cs}_3\text{Cu}_8\text{Te}_{10}$ compounds have layered structures. The $\text{Rb}_3\text{Cu}_8\text{Te}_{10}$ salt consists of $[\text{RbCu}_8\text{Te}_{10}]_n^{2n-}$ layers alternating with the layers of Rb^+ ions. In spite of a substantial structural difference, the major structural blocks in the latter salt are identical to those observed in $\text{K}_4\text{Cu}_8\text{Te}_{11}$. The layers are formed by the $[\text{Cu}_8\text{Te}_{12}]$ pentagonal dodecahedra linked to each other. The Rb^+ ions are encapsulated into these layers. The structure of the cesium salt is analogous to that of the rubidium salt.

The structural studies of the salts with the mixed composition demonstrated that encapsulation is favourable for ions of smaller radii. Thus, in the $\text{KCs}_2\text{Cu}_8\text{Te}_{10}$ and $\text{KRb}_2\text{Cu}_8\text{Te}_{10}$ salts, the potassium ions are located inside the dodecahedra.

The $\text{K}_2\text{BaCu}_8\text{Te}_{10}$ and $\text{Rb}_2\text{BaCu}_8\text{Te}_{10}$ salts are isomorphous with the $\text{Rb}_3\text{Cu}_8\text{Te}_{10}$ salt. The centre of the dodecahedral cavity is occupied by the Ba^{2+} ion, whose ionic radius is close to that of the K^+ ion. In the case of the potassium salt, the K^+ ions are located between the layers, which implies that encapsulation of the ion with the larger charge is more favourable in the case of the equal ionic radii.

Zhang *et al.*¹³⁷ studied the electrophysical and optical properties of the tellurides synthesised. According to the structural data, the formula of the $\text{K}_4\text{Cu}_8\text{Te}_{11}$ salt can be written as $\text{K}_4\text{Cu}_8(\text{Te}_2)_5\text{Te}$. Taking the charges of the ditelluride and telluride ions to be equal to -2 and the charge of the copper ions to be equal to $+1$, it can be concluded that this salt satisfies Zintl's criterion and, consequently, should exhibit semiconducting properties. This suggestion is also confirmed by the fact that the electrical resistance of the crystals of $\text{K}_4\text{Cu}_8\text{Te}_{11}$ (293 K) is rather small ($6.25 \times 10^{-3} \Omega \text{ cm}$) but it increases according to the activation law as the temperature decreases.

The $\text{M}_3\text{Cu}_8\text{Te}_{10}$ and $\text{MM}'_2\text{Cu}_8\text{Te}_{10}$ salts (which do not meet Zintl's criterion) contain the $[\text{Cu}_8(\text{Te}_2)_4\text{Te}_2]^{3-}$ anions and, consequently, these salts are mixed-valence compounds. According to

the results of quantum-chemical calculations,¹³⁷ the degree of oxidation of copper in these compounds is equal to $+1$ (the $3d$ orbitals of the copper atoms are located substantially lower than the $5p$ orbitals of the tellurium atoms). Therefore, the p band formed by the orbitals of the tellurium atoms contains one hole per formula unit. It is believed that these salts exhibit metallic properties. The data of electrophysical measurements confirmed that the $\text{Rb}_3\text{Cu}_8\text{Te}_{10}$, $\text{Cs}_3\text{Cu}_8\text{Te}_{10}$ and $\text{KRb}_2\text{Cu}_8\text{Te}_{10}$ salts exhibit metallic properties in the range of $5–300 \text{ K}$. Thus, the specific resistance of the samples of $\text{Cs}_3\text{Cu}_8\text{Te}_{10}$ decreases by almost three orders of magnitude from $1.1 \times 10^{-3} \Omega \text{ cm}$ at 293 K to $1.2 \times 10^{-6} \Omega \text{ cm}$ at 5 K . The ρ_5 value for this salt is the smallest among all chalcogenides based on copper.

The thermoelectromotive forces of the $\text{M}_3\text{Cu}_8\text{Te}_{10}$ salts are positive and increase linearly with temperature in the range of $90–300 \text{ K}$, which indicates that these compounds are metals with hole conductivity. The magnetic properties of these salts are also typical of metals. These salts exhibit temperature-independent paramagnetism.

The $\text{M}_2\text{BaCu}_8\text{Te}_{10}$ salts satisfying Zintl's criterion should be analogous to $\text{K}_4\text{Cu}_8\text{Te}_{11}$. It was found that $\text{K}_2\text{BaCu}_8\text{Te}_{10}$ and $\text{Rb}_2\text{BaCu}_8\text{Te}_{10}$ possess the low electrical resistances at 293 K . Their resistances increase only slightly as the temperature decreases down to $\sim 150 \text{ K}$. Below 150 K , the electrical resistance increases more rapidly. This means that either these salts are degenerate semiconductors or they have a very narrow forbidden band. The optical measurements in the visible and UV regions revealed no gaps. However, the gap is observed in the IR region and it corresponds to 0.1 eV for the $\text{Rb}_2\text{BaCu}_8\text{Te}_{10}$ salt. The barium salts exhibit the temperature-independent paramagnetism typical of dielectrics.

The scarce data on copper tellurides allow one to make definite conclusions. Thus, the $\text{Te}\cdots\text{Te}$ contacts, which are shortened compared to the sum of the van der Waals radii, were found in tellurides $\text{Na}_6\text{Te}(\text{Te}_5)$, Na_2Te_6 , M_2Te_3 ($\text{M} = \text{K}, \text{Rb}$ or Cs), M_2Te_5 ($\text{M} = \text{Rb}$ or Cs) and CsTe_4 .¹³⁸ However, these contacts are absent in tellurides containing bulky cations, for example, in $(\text{Ph}_4\text{P})_2\text{Te}_4 \cdot 2\text{MeOH}$ and Me_4NMTe_4 ($\text{M} = \text{Cu}$ or Ag). Apparently, cations characterised by a high charge to radius ratio assist in decreasing Coulomb repulsions between polytelluride ions and in reducing the possibility of $\text{Te}\cdots\text{Te}$ interactions. In this connection, melts of polytellurides containing barium ions along with alkali metal cations were studied further. Thus, isomorphous polytellurides $\text{NaBa}_6\text{Cu}_3\text{Te}_{14}$ and $(\text{K}_{0.60}\text{Ba}_{0.40}) \cdot \text{Ba}_6\text{Cu}_{2.58}\text{Te}_{14}$ were isolated.¹³⁸ The structure of the $\text{NaBa}_6\text{Cu}_3\text{Te}_{14}$ salt is based on the $[\text{Cu}_3\text{Te}_3(\text{Te}_3)_3]^{9-}$ clusters of a new type. These clusters are six-membered rings formed by three copper atoms and three tellurium atoms. Each copper atom is coordinated in a bidentate fashion to the Te_3^{2-} ion, thus acquiring trigonal coordination (Fig. 29). Hence, the cluster ions each contain one six-membered ring and three four-membered rings. The $[\text{Cu}_3\text{Te}_3(\text{Te}_3)_3]^{9-}$ clusters are packed in stacks. The Na^+ ions are encapsulated into the cavities between these stacks. The composition of the stacks can be represented by the formula $[\text{NaCu}_3\text{Te}_3(\text{Te}_3)_3]_n^{8n-}$. Each stack is surrounded by six stacks formed by the Ba^{2+} ions. Each telluride ion is surrounded by six Ba^{2+} ions, thus adopting a trigonal-prismatic coordination environment. Therefore, the structure of this telluride is best described by the formula $\text{Ba}_6[\text{NaCu}_3\text{Te}_3(\text{Te}_3)_3]\text{Te}_2$, which satisfies Zintl's criterion. Because of this and taking into account the existence of ionic $\text{Te}\cdots\text{Te}$ contacts, which are shortened compared to the sum of the van der Waals radii, this telluride would be expected to be a narrow-band semiconductor or a semimetal.

This conclusion was confirmed by both electrophysical and optical measurements. Thus, ρ_{RT} is $\sim 10 \Omega \text{ cm}$, increases according to the activation law as the temperature decreases and reaches $2.5 \times 10^3 \Omega \text{ cm}$ at 20 K , which corresponds to the width of the forbidden band of about 0.01 eV and to the absorption in the far-IR region (at about 40 cm^{-1}). According to the data of measure-

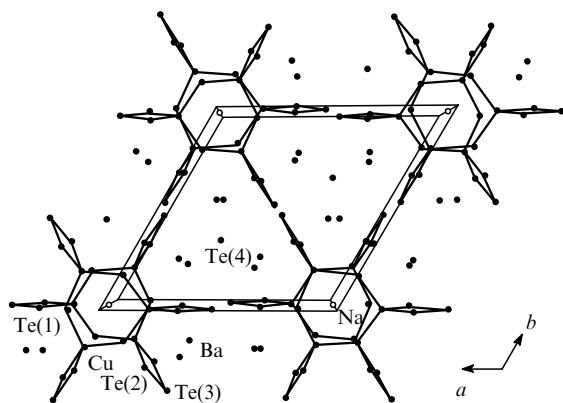


Figure 29. Packing of $\text{NaBa}_6\text{Cu}_3\text{Te}_{14}$ along the c axis.

ments of the thermoelectromotive force, telluride $\text{NaBa}_6\text{Cu}_3\text{Te}_{14}$ is a p -type semimetal (the Seebeck coefficient is $\sim 100 \mu\text{V K}^{-1}$).

The structure of telluride $(\text{K}_{0.60}\text{Ba}_{0.40})\text{Ba}_6\text{Cu}_{2.58}\text{Te}_{14}$ is very similar to that described above, with the difference that the cavities in the $[\text{Cu}_3\text{Te}_3(\text{Te}_3)_3]^{9-}$ stacks are statistically occupied by the K^+ and Ba^{2+} ions. The retention of the electroneutrality is provided by the presence of an equivalent number of vacancies in positions occupied by the copper atoms. This telluride is a p -type semiconductor. Its ρ_{RT} is $10^5 \Omega \text{ cm}$, increases as the temperature decreases and reaches $10^{12} \Omega \text{ cm}$ at 130 K, which corresponds to the width of the forbidden band of 0.69 eV. Both tellurides possess diamagnetic properties.

Telluride $\text{K}_{0.33}\text{Ba}_{0.67}\text{AgTe}_2$ was described.¹³⁹ Unlike analogous tellurides based on copper, this telluride has a layered structure (Fig. 30), which is characterised by the presence of two type of monolayers separated by the K^+ and Ba^{2+} ions. One of the monolayers is a corrugated $[\text{Ag}_2\text{Te}_2]^{2-}$ layer and the second monolayer is a planar-square layer formed by the tellurium atoms. The degree of oxidation of the tellurium ions in the $[\text{Te}_2]^{4/3-}$ monolayer is $-2/3$ on the assumption that the degrees of oxidation of the silver and tellurium ions in the $[\text{Ag}_2\text{Te}_2]^{2-}$ layer are $+1$ and -2 , respectively.

It should be noted that the existence of the ideal planar-square layers formed only by the tellurium atoms is the unique peculiarity of telluride $\text{KBa}_2[\text{Ag}_3\text{Te}_3]\text{Te}_3$. The crystals of the RbTe_6 and $\text{Cs}_3\text{Te}_{22}$ salts¹⁴⁰ also contain planar layers of tellurium atoms. However, these layers can be considered as derivatives of the structure shown in Fig. 30 in which $2/5$ of all tellurium atoms are removed. The double planar layers of tellurium atoms were found in the unusual $(\text{Te}_2)_2(\text{I}_2)$ compound,¹⁴¹ which can be considered as a product of intercalation of tellurium by iodine.

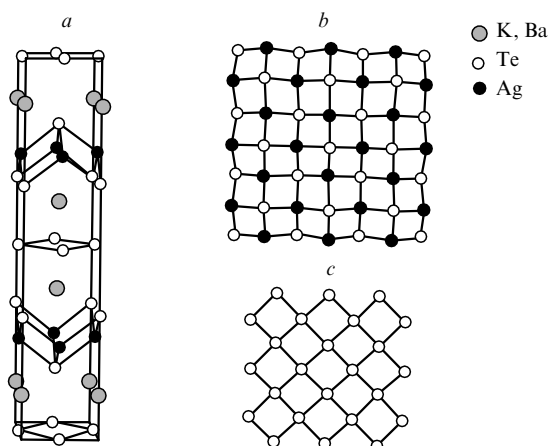


Figure 30. Structure of $\text{K}_{0.33}\text{Ba}_{0.67}\text{AgTe}_2$; (a) the unit cell; (b) the $[\text{Ag}_2\text{Te}_2]^{2n-}$ layers; (c) the $[\text{Te}_2]^{4n-/3}$ layers.¹³⁹

The covalent interactions between the $[\text{Ag}_2\text{Te}_2]$ and $[\text{Te}_2]$ layers are negligible. According to the quantum-chemical calculations within the framework of the extended Hückel method, the Fermi level is located within the band formed by atomic orbitals of the tellurium atoms of the $[\text{Te}_2]$ layer. This corresponds to a gap in the band structure of the $[\text{Ag}_2\text{Te}_2]$ layers. Consequently, this compound can exhibit metallic properties due to the planar-square $[\text{Te}_2]$ layers.

The measurements of the electrical resistance and the thermoelectromotive force demonstrated that this telluride exhibits semiconducting properties. Thus, ρ_{RT} is $\sim 5 \Omega \text{ cm}$ and increases according to the activation law as the temperature decreases. The width of the forbidden band, which was determined from the temperature dependence of ρ , is 0.06 eV to which the optical absorption at energies lower than 0.15 eV corresponds. The semiconducting properties of $\text{K}_{0.33}\text{Ba}_{0.67}\text{AgTe}_2$ are also confirmed by the results of measurements of the thermoelectromotive force. It has a positive value and the Seebeck coefficient is $200 - 300 \mu\text{V K}^{-1}$.

This discrepancy between theory and experiment may be accounted for by different reasons. Thus, it is quite apparent that nonrelativistic calculations for a salt containing the heavy atom, such as tellurium, are inadequate. Another possible reason is that the mixed-valence state of the silver ions in the telluride is absent because silver, unlike copper, obviously cannot exist in chalcogenides in the form of Ag^{2+} . The structural distortion of the $[\text{Te}_2]^{4/3-}$ layers due to the appearance of CDWs may be also responsible for the manifestation of semiconducting properties. The latter possibility was considered in Ref. 139. Since X-ray diffraction studies did not reveal structural distortions resulting in the deviation from the ideal I_4/mmm symmetry, the authors used the electron diffraction method, which is more sensitive to weak structural distortions of the $[\text{Te}_2]^{4/3-}$ layers. The electron diffraction data are unambiguously indicative of the presence of two superlattices. In one type of domain, distortions generate an incommensurate superlattice with $a_{\text{super}}^* = 0.352a_{\text{sub}}^*$; $b_{\text{super}}^* = b_{\text{sub}}^*$, $c_{\text{super}}^* = c_{\text{sub}}^*$. The domains of the second type contain a commensurate superstructure with $a_{\text{super}} = 3a_{\text{sub}}$; $b_{\text{super}} = 3b_{\text{sub}}$, $c_{\text{super}} = c_{\text{sub}}$. The results obtained confirm the suggestion that CDWs are responsible for localisation of electrons in the $[\text{Te}_2]^{4/3-}$ layers. The formal charge of the tellurium ions in the layers is equal to $-2/3$. Hence, the appearance of CDWs is associated with the formation of the Te_3^{2-} ions in the $[\text{Te}_2]$ layers in the case of the occurrence of the superstructures 3×3 and 3×1 because the charge, which fluctuates in the ideal square lattice, is localised on going to the tritelluride ion.

However, the available data on mixed copper tellurides, while rather scarce, demonstrate that tellurides differ substantially from sulfides and selenides. Although simple tellurides with compositions identical to those of sulfides and selenides exist, the majority of tellurides have no analogues among the corresponding sulfides and selenides. The same is true for their structures. Thus, the structures of CuS and CuSe are identical, whereas the CuTe structure is quite different. Unlike the widespread copper polysulfides, examples of the presence of polytelluride ions in copper salts are few in number. Thus, the isostructural $\alpha\text{-KCuX}_4$ and $\text{M}_3\text{Cu}_8\text{X}_6$ salts ($\text{X} = \text{S}$ or Se) are known, whereas the corresponding tellurides do not exist. At the same time, there are no sulfide analogues of $\text{K}_2\text{Cu}_5\text{Te}_5$ or $\text{K}_4\text{Cu}_8\text{Te}_{11}$.

As was mentioned in Chapter III, attempts to prepare mixed sulfide–telluride copper complexes from a melt of $\text{M}_2\text{S}_x\text{Te}_{1-x}$ afforded salts containing sulfide and trithiotelluride ions. Later on, the $\text{MM}'\text{TeS}_3$ salts ($\text{M} = \text{K}, \text{Rb}$ or Cs ; $\text{M}' = \text{Cu}$ or Ag) containing only TeS_3^{2-} ions, viz., CsCuTeS_3 , α - and β - KAgTeS_3 , RbCuTeS_3 , RbAgTeS_3 and CsAgTeS_3 , were isolated.¹⁴² The last-mentioned four salts are quasi-two-dimensional and isomorphous. These salts contain the anionic $[\text{M}'\text{TeS}_3]^{2-}$ layers between which the alkali metal ions are located (Fig. 31). The Cu^+ ions are coordinated by four sulfur atoms of the TeS_3^{2-} ions, thus adopting a distorted tetrahedral coordination. Each TeS_3^{2-} ion acts as a

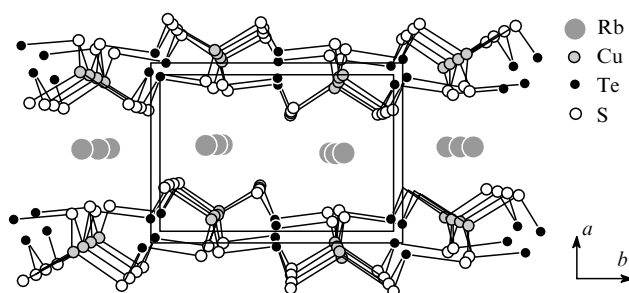


Figure 31. Two-dimensional structure of RbCuTeS_3 along the c axis. The rubidium ions form monoatomic layers between the $[\text{CuTeS}_3]_n^-$ layers.¹⁴²

bridge and links four Cu^+ ions. Two sulfur atoms each link one Cu^+ ion and the third sulfur atom acts as a bridge between two Cu^+ ions.

The α - KAgTeS_3 compound has a centrosymmetrical layered structure. The most substantial difference in the structures of the α and β phases consists in the difference in the arrangement of the pyramidal TeS_3^{2-} ions. In the structure of α - KAgTeS_3 , the tellurium atoms are located on the surface of the layers so that their lone electron pairs are directed away from the layer. Neither silver ions nor alkali metals interact with these lone pairs. On the contrary, the K^+ ions are surrounded by seven sulfur atoms.

The crystals of CsCuTeS_3 belong to the cubic system. In the crystal structure, the CuTeS_3^- ions are linked to each other to form a three-dimensional non-centrosymmetrical chain. The Cu^+ ions have a planar-trigonal coordination. Each CuS_3 triangle is linked to three adjacent TeS_3^{2-} pyramids *via* shared vertices and *vice versa*. The crystallographically equivalent sulfur atoms are linked through the copper and tellurium atoms at an angle of $\sim 90^\circ$.

All compounds of the trithiotellurides series satisfy Zintl's criterion, which accounts for their dielectric properties. The optical measurements revealed the presence of the forbidden band in the region from 1.95 eV (RbCuTeS_3) to 2.2 eV (α - KAgTeS_3).

Kanatzidis¹⁴⁰ summarised a rare experience in the field of inorganic chemistry of tellurium and noted that this division of synthetic and structural chemistry of chalcogenides is characterised by the fact that both the compositions and structures of tellurides are unpredictable. However, even from the available data it is clear that ternary copper and silver tellurides are very promising material because they show diverse physical properties (from dielectric to semiconducting), possess interesting magnetic properties and exhibit transitions to states with CDWs. These transitions, which attracted the attention of chemists only early in the 1970s, comprise a new exciting field of solid-state chemistry because they are closely associated with the problem of the variable valence and charge ordering in crystals. The detailed consideration of this problem is beyond the scope of this review. Let us only mention the small but rather informative review devoted to this problem.¹⁴³

V. Conclusion

As is evident from the present review, the chemistry of ternary copper chalcogenides, which has progressed in the last decade, shows promise from the viewpoint of the development of new materials with a broad spectrum of electrophysical properties, including new high-temperature superconductors. In essence, only ternary copper and silver chalcogenides containing ions of alkali or alkaline-earth metals as well as thallium have been systematically studied. Data on physicochemical properties of ternary $\text{Ln}-\text{Cu}-\text{X}$ chalcogenides (Ln is a rare-earth element), which are analogues of high-temperature superconductors, are scarce. This field of research is in its infancy. In 1994, the first mixed copper chalcogenides containing cerium, *viz.*, KCuCe_2S_6 and

KCu_2CeS_4 , were synthesised.^{144, 145} Both sulfides were prepared from $\text{K}_2\text{S}-\text{Cu}-\text{Ce}-\text{S}$ melts and have layered structures. Their compositions do not satisfy Zintl's criterion (it is highly improbable that cerium in sulfides has the degree of oxidation of +4). However, both salts exhibit dielectric properties; the width of the forbidden band in KCuCe_2S_6 is 1.8 eV. In $\text{K}_2\text{Cu}_2\text{CeS}_4$, the gap was not found in the range of 250–2500 nm. The conductivity of this salt at 293 K ($\sigma_{RT} \sim 10^{-3} \Omega^{-1} \text{cm}^{-1}$) is five orders of magnitude larger than that of the KCuCe_2S_6 salt. However, the temperature dependence of the electrical resistance is typical of semiconductors. The thermoelectromotive force of crystals of the $\text{K}_2\text{Cu}_2\text{CeS}_4$ salt has a plus sign and the thermoelectromotive force decreases as the temperature decreases, which may be indicative of the metallic state. However, the thermoelectromotive force is much larger than the expected value for a metal.

Based on these facts as well as on the results of magnetic measurements, the authors¹⁴⁴ proposed the following formulas for mixed sulfides: $\text{K}^+\text{Cu}^+(\text{Ce}^{3+})_2(\text{S}^{2-})_2(\text{S}_2^{2-})_2$ for KCuCe_2S_6 and $\text{K}_2^+(\text{Cu}^+)_2\text{Ce}^{3+}(\text{S}^{2-})_3(\text{S}^-)$ for $\text{K}_2\text{Cu}_2\text{CeS}_4$. The magnetic susceptibility of the KCuCe_2S_6 salt obeys the Curie–Weiss law (the Weiss constant $\theta = -67 \text{ K}$), $\mu_{\text{eff}} = 3.1 \mu_B$, which is close to the purely spin value of $2.83 \mu_B$ for two unpaired electrons (one electron from each Ce^{3+} ions). A more complex situation arises with sulfide $\text{K}_2\text{Cu}_2\text{CeS}_4$. For this compound, either the $\text{K}_2^+\text{Cu}^+\text{Cu}^{2+}\text{Ce}^{3+}\text{S}_4^{2-}$ structure with the mixed-valence state for copper or the above-mentioned structure containing 'holes' in the p band formed by the $3p$ orbitals of the sulfur atoms has to be postulated. According to the approach accepted in our works, the mixed-valence states both of sulfur and copper atoms should be considered, as in the case of the above-considered chalcogenides, taking into account substantially covalent interactions between copper and sulfur atoms.

However, the absence of metallic properties in sulfide $\text{K}_2\text{Cu}_2\text{CeS}_4$ seems to be strange. Sutorik *et al.*¹⁴⁴ attributed this situation to the fact that the peculiarities of the crystal structure of this compound lead to the formation of a very narrow band, which, in turn, results in the formation of low-lability polarons in the presence of highly charged ions, such as Ce^{3+} ions in the case under consideration.

In the case of sulfides KCuCe_2S_6 and $\text{K}_2\text{Cu}_2\text{CeS}_4$, the combination of rare-earth elements and the alkali metal does not lead to an increase in the degree of oxidation of copper, unlike high-temperature superconductors. The reason is that the electronegativity decreases in going from oxygen to sulfur. Besides, as is evident from the present review, no copper sulfides (neither binary nor mixed) containing only Cu^{2+} ions are known.

Two years later,¹⁴⁶ sulfide KCuEu_2S_6 was synthesised. This salt contains double layers formed by the EuS_8 polyhedra (bicapped trigonal prisms) and the CuS_4 polyhedra (tetrahedra) linked to each other. The authors did not perform electrophysical measurements. However, judging from the dark-brown colour of the crystals, it is believed that this sulfide is a narrow-band semiconductor.

The manifestation of the effect of the chalcogen content on the physical properties of mixed copper oxides and sulfides is also different. It is known¹⁰ that in oxides, such as, for example, $\text{La}_2\text{CuO}_{4-x}$ or $\text{YBa}_2\text{Cu}_3\text{O}_{6.5+x}$, the degree of oxidation of copper increases as the oxygen content increases. Sulfide analogues of oxides $\text{La}_2\text{CuO}_{4-x}$ and $\text{Y}_2\text{Cu}_2\text{O}_5$ were synthesised¹⁴⁷ with the aim of elucidating the effect of the anionic subsystem on the electrophysical properties of chalcogenides based on copper. Sulfides $\text{La}_2\text{CuS}_{4+x}$ and $\text{Y}_2\text{Cu}_2\text{S}_{5+x}$ were prepared by fusing a mixture of Ln_2S_3 , CuS and S at 800–900 °C. Their individuality was confirmed by X-ray diffraction studies. The X-ray photoelectron spectra have doublets in the region of the $ES(2p)$ values. One of these doublets at 161.8 eV corresponds to the S^{2-} ions⁸² and the second doublet at 162.8 eV can be assigned to the S_2^{2-} ions. In the $ECu(2p_{3/2})$ region, the lines at 932.6 eV correspond to the Cu^+ ions. According to the data of X-ray photoelectron spectroscopy, a decrease in the sulfur content in samples upon annealing

in vacuo occurs as follows: lines at 934.5 eV, which correspond to the Cu^{2+} ions, appear and intensities of the lines corresponding to the disulfide ions decrease.

Samples of $\text{La}_2\text{CuS}_{4+x}$ saturated with sulfur have the composition La_2CuS_5 . Based on the results of X-ray photoelectron spectroscopy, their structures can be represented by the formula $\text{La}_2^{3+}\text{Cu}^+(\text{S}_2^{2-})_{1.5}(\text{S}_2^{2-})_2$. Sulfide La_2CuS_5 exhibits dielectric properties. When sulfur is removed until the sample acquires the composition La_2CuS_4 , the degree of oxidation of copper increases and the content of disulfide ions decreases. The appearance of the mixed-valence state of copper leads to the nonmetal–metal transition. The temperature dependence of the electrical resistance of samples of La_2CuS_4 is typical of metals. Below 100 K, the temperature dependence of the resistance is nonlinear.

Sulfide $\text{Y}_2\text{Cu}_2\text{S}_{5+x}$, which is maximum saturated with sulfur, has the composition $\text{Y}_2\text{Cu}_2\text{S}_5$. Its X-ray photoelectron spectrum has lines at 932.8 and 934.5 eV belonging to the Cu^+ and Cu^{2+} ions.⁸² Sulfur is present as the S^{2-} and S_2^{2-} ions [$ES(2p) = 161.8$ and 162.8 eV, respectively]. The $\rho(T)$ dependence is typical of metals (Fig. 32). When sulfur is removed until the compound acquires the composition $\text{Y}_2\text{Cu}_2\text{S}_4$, this dependence becomes more complex and goes through a weak maximum at $T \sim 240$ K. According to the results of X-ray photoelectron spectroscopy, this sample contains sulfur only as sulfide ions and the $\text{Cu}^+:\text{Cu}^{2+}$ ratio decreases from 3:1 in the initial sample to 1:1 in the final product.¹⁴⁸

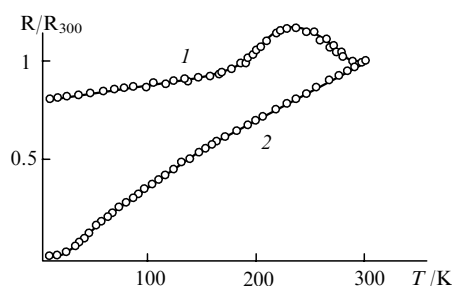
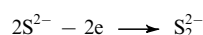
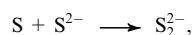


Figure 32. Temperature dependence of the electrical resistance of samples of $\text{Y}_2\text{Cu}_2\text{S}_4$ (1) and $\text{Y}_2\text{Cu}_2\text{S}_5$ (2).¹⁴⁸

Hence, in the case of sulfides, the situation is opposite to that observed in oxides. The possible reasons for this fact are the lower electronegativity of sulfur responsible for reducing properties of the sulfide ion,



as well as the reaction



in the course of which excess sulfur is bound by sulfide ions rather than oxidises Cu^+ ions.

Apparently, these processes are hindered when the sulfur content is decreased and, as a consequence, the degree of oxidation of sulfur decreases as its content decreases.

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^b — *Russ. J. Phys. Chem. (Engl. Transl.)*

Ferroelectricity of polymers based on vinylidene fluoride

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- VIII. Ferroelectricity of ultrathin films
- IX. Conclusion

Abstract. Characteristics of the ferroelectricity in polyvinylidene fluoride (PVDF) and copolymers based on vinylidene fluoride (VDF) with different previous thermomechanical histories are analysed. Switching of polarisation and the fluctuation mechanism of formation of new nuclei upon the appearance of conformation defects such as kink bonds are considered. The role of the space charge, which stabilises the new polarisation position, is noted. It is shown that the Curie transition can be either a first- or second-order phase transition depending on the copolymer composition. The influence of the morphology of PVDF on some ferroelectric characteristics is found. In particular, the morphology of thick lamellar crystals is favourable for enhanced spontaneous polarisation. It is shown that a ferroelectric structure approaching the texture of an ideal single crystal can be created in Langmuir–Blodgett films. As the number of unimolecular layers decreases, the concentration of conformational defects in these films increases and the crystallographic order in the lattice is violated. This intensifies the low-temperature Curie transition. The bibliography includes 247 references.

I. Introduction

Poly(vinylidene fluoride) (PVDF) and copolymers based on vinylidene fluoride (VDF) present interest for both fundamental science and applied research. This is due to the fact that these materials were found to exhibit ferroelectric properties normally atypical of polymers. Owing to the high piezo- and pyro-electric activities found in PVDF films,¹ this polymer has been recommended in some cases as a competitive material for energy converters of various types.^{2,3} The results of experimental and theoretical studies in this field need to be surveyed at intervals for two reasons. Firstly, this could prompt the ways for optimisation of characteristics of the materials studied, which is significant for the solution of applied problems. Secondly, this would help to

elucidate the influence of the polymeric state of substance on its electrophysical characteristics and would thus provide the understanding of the fundamental features of the formation of ferroelectricity and piezo- and pyroelectric properties in other polymers, for example, in poly(vinylidene cyanide),^{4–13} odd nylons,^{4–16} polyacrylonitrile,^{17,18} polyurethanes,^{19,20} liquid-crystal polymers^{21–26} and biopolymers.²⁷

PVDF is known to exhibit clear-cut polymorphism.²⁸ Three of the four crystallographic modifications of PVDF usually have non-zero cell dipole moments; therefore, there are prerequisites for the formation of a ferroelectric structure. Crystallites (or their sections) can be compared with domains characterised by a particular value of spontaneous polarisation.

II. General characteristics

The ferroelectric character of PVDF and VDF copolymers is confirmed, among other facts, by the occurrence of dielectric hysteresis for these materials. Figure 1 presents the variation of the electric displacement (D) as a function of the electric field strength E for a uniaxially stretched PVDF film.²⁹ It can be seen that hysteresis is displayed only in fields with a strength greater

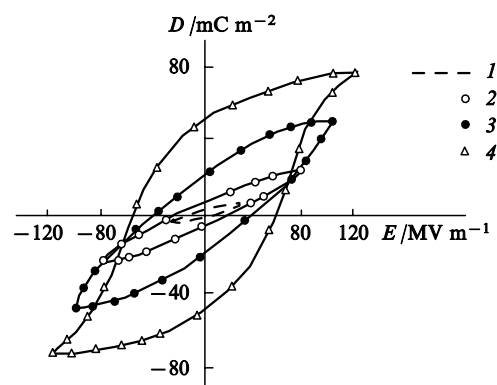


Figure 1. Electric displacement in a uniaxially stretched PVDF film at 20 °C vs strength of the external electric field.²⁹ Frequency of the electric field 10^{-3} Hz; strength / MV m $^{-1}$: (1) 40, (2) 80, (3) 100, (4) 120.

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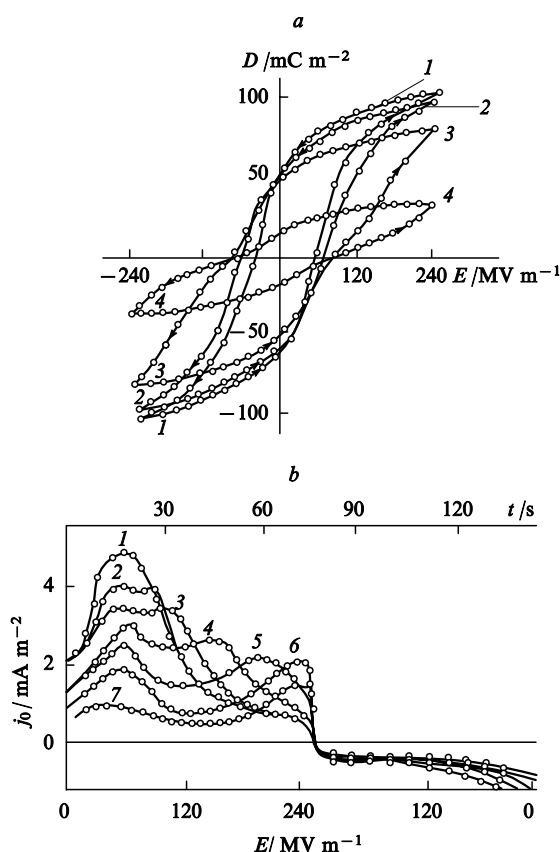


Figure 2. Temperature dependences of the electric displacement (a) and the polarisation current density (b) vs the electric field strength in the initial non-polarised PVDF film.²⁹

T /°C: 20 (1), -20 (2), -60 (3), -100 (4) (a); 20 (1), 0 (2), -20 (3), -40 (4), -60 (5), -80 (6), -100 (7) (b); t is the current time.

than 40 MV m^{-1} and that an increase in the field strength results in an increase in both the remanent (for $E = 0$) and spontaneous polarisation, P_r and P_s , respectively. In relatively low fields (80 MV m^{-1}), the curve shows double hysteresis. This can be seen in more detail in Fig. 2, which shows the variation of properties of a non-polarised film placed in a 240 MV m^{-1} field for temperatures varying over wide limits.

Temperature plays an important role for the manifestation of ferroelectricity in PVDF and in crystallisable VDF copolymers. Only a fraction of the sample bulk is occupied by crystals; the rest (which makes 50% to 60% in PVDF) is filled by a disordered phase. The role of this phase in the formation of ferroelectricity is not entirely clear. The dynamics of chains in the disordered phase can have a substantial influence on the characteristics of the electric hysteresis (see Fig. 2). In temperature regions below the glass transition temperature of PVDF ($T_g \approx -40$ °C), large-amplitude motions of chain sections are frozen. Some researchers (e.g., Tamura *et al.*³⁰) have observed even the disappearance of the hysteresis in low fields. However, in high fields, disappearance was not noted but the $D-E$ dependences were characterised by double hysteresis (see Fig. 2a). This can be seen more clearly in the field dependences of the polarisation current density (see Fig. 2b), which have two peaks at low temperatures. The position of one (lower-field) peak remains virtually unchanged, while the other peak shifts to lower fields as the temperature rises. The low-field peak may be related to the response of polar crystals to the application of the field and the peak at higher fields may be due to the response of dipoles in the disordered phase. Evidently, an increase in the temperature is favourable for the activation of the latter process because the second peak markedly shifts to lower fields. In the region below -40 °C, this shift can occur due to a

decrease in the relaxation times of the local forms of mobility upon an increase in temperature; above -40 °C, this can be due to the generation of cooperative forms of mobility with high amplitudes.²⁸

Thus, the amorphous phase makes a certain contribution to the formation of ferroelectricity and cannot be regarded as an 'inert matrix'. This conclusion appears sufficiently justified because the double hysteresis has been noted both for PVDF³¹ and for VDF copolymers with tetrafluoroethylene (TFE)^{32,33} or trifluoroethylene (TrFE).³⁴ It has been shown for the latter copolymer³⁴ that the probability of double hysteresis depends on the method used to prepare the sample. In particular, double hysteresis in the VDF copolymer with TrFE of the 52.8/47.2 composition is manifested only for samples crystallised by slow cooling of the melt. In the several initial polarisation cycles, these samples exhibit a typical double hysteresis, which is transformed into a single hysteresis in the subsequent cycles (Fig. 3). A similar result has been obtained for uniaxially stretched PVDF samples (Fig. 4a); no double hysteresis is observed for polarised samples at any temperature. This transformation in the pattern of the $D-E$ hysteresis should point to fundamental changes in the material structure after the generation of non-zero remanent polarisation.

One process which might result in structural changes is the irreversible increase in the degree of crystallinity after polarisation.³⁵ The kinetics of transition of the film subjected to polarisation into a new structural state depends on the frequency of the electric field applied. Thus at room temperature and a frequency of $\sim 10^{-3}$ Hz, this requires several poling cycles;^{29,34} when the frequency is 50 Hz, the double hysteresis passes into single hysteresis in one cycle of the increase in the intensity of the polarising field.^{31,32} Analysis of the time dependences of the polarisation current and thermodepolarisation curves for the 75/25 VDF/TrFE copolymer suggests that polarisation involves two types of dipoles (in the crystal and in the amorphous phase).³⁶

It can be seen from comparison of Figs. 2 and 4 that the structural changes in the film induced by poling have a substantial effect on the temperature dependences of both the coercive field and the remanent polarisation. Whereas in the initial sample, E_c changes slightly with the temperature, in the polarised state, this value markedly increases as the temperature diminishes. The state of chain dynamics in the disordered phase affects precisely the magnitude of the coercive field; it can be seen that the E_c-T plot is broken at about the glass transition temperature (see Fig. 4b). The sharper growth in the E_c in the region of T_g indicates that freezing of the high-amplitude cooperative motion of chain segments retards substantially the processes of polarisation switching. The remanent polarisation depends on the temperature to a lesser extent, although an increase in P_r has been noted below 50 °C.

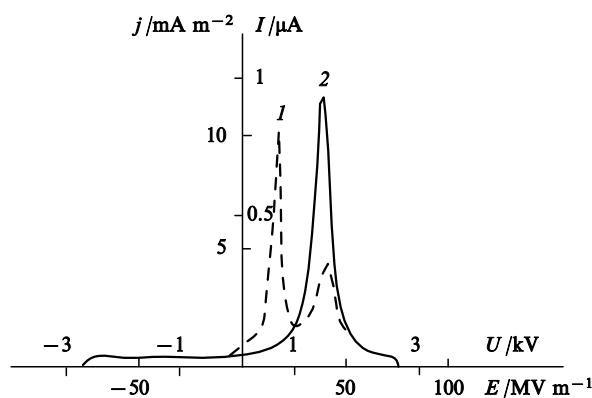


Figure 3. Reversible polarisation current vs the intensity and voltage (U) of the electric field (5×10^{-3} Hz/ 27 °C) in the several initial (1) and subsequent (2) cycles of poling of VDF/TrFE samples.³⁴

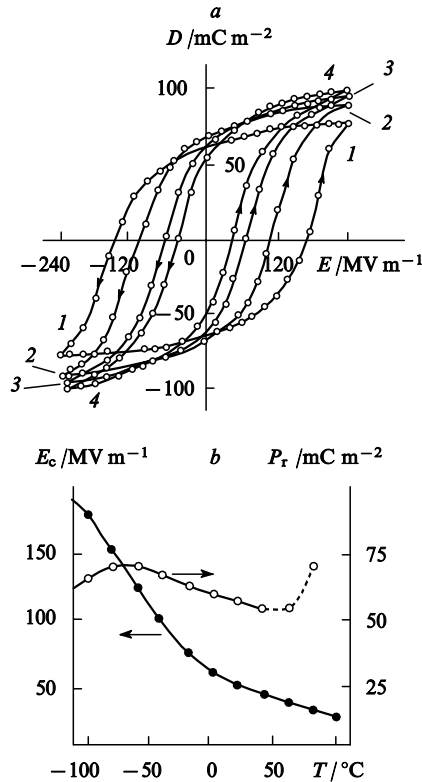


Figure 4. Influence of the temperature on the D – E hysteresis curves (a) and on the hysteresis parameters (coercive field E_c and the remanent polarisation P_r) (b) in uniaxially stretched polarised PVDF films.²⁹ T / °C: –100 (1), –60 (2), –20 (3), 20 (4).

Measurements of the hysteresis during the variation of the polarising field frequency from 10^{-2} to 10^{-4} Hz demonstrated that neither P_r nor the piezoelectric constant e_{31} depend on the frequency. This finding permitted the conclusion²⁹ that the ferroelectricity in PVDF has a purely dipole origin. A similar conclusion has been drawn for the 73/27 VDF/TFE copolymer, for which experimental P_r and P_s values are in good agreement with those calculated using a simple dipole model.³⁷

It has been assumed³⁸ that free charge carriers in the polymer get frozen in deep traps and this compensates to an extent the intrinsic polarisation of crystals. This hypothesis was confirmed³⁸ by the data on the influence of annealing of a polarised PVDF film on the shape of the D – E hysteresis curve. The curve obtained in the first cycle of measurements after annealing was distorted. This was explained by assuming that immediately after the annealing, the charge carriers are characterised by a non-equilibrium distribution, which changes during the subsequent poling cycles.

The dipole nature of the ferroelectricity is also confirmed by the hysteresis type of variation of the intensities of some absorption bands in the IR spectra.^{28, 39, 40} This conclusion is also supported by the qualitatively consistent results of studies^{41, 42} devoted to X-ray recording of the change in the distribution of the b axes (direction of the dipole moment) of the β -phase lattice after polarisation. It was shown that the intensity of the 110, 200 reflections of the crystalline β -phase changes by more than 20% following polarisation along particular directions. When developing the model of polarisation switching, Kepler and Andersen⁴² proceeded from the fact that the orthorhombic cell of the β -phase can be transformed into a hexagonal cell upon 1% distortion. The chains in the planar zigzag conformation can occupy one of six equivalent positions (Fig. 5). When a field E is applied, the b axis of the cell occupies one of these positions with the probability⁴²

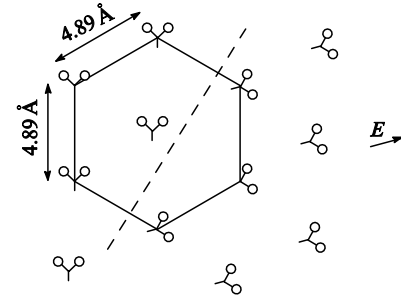


Figure 5. Packing of the PVDF chains in the crystal lattice of the β -phase. The dashed line denotes the boundary between the domains.⁴³

$$f(\psi) = \exp(a \cos \psi) \left[\sum_{i=1}^6 \exp(a \cos \psi_i) \right]^{-1}, \quad (1)$$

where ψ is the angle between the domain dipole moment (μ) and the direction of the field (E); in addition, $\psi_i = \psi + (1/3)(i-1)\pi$; $a = \mu E/kT$.

After polarisation, the orientation of the dipole moments can be described by the normalised distribution function

$$\begin{aligned} \frac{n(\psi)}{n_0} &= f(\psi) \left[\int_0^{2\pi} f(\psi) d\psi \right]^{-1} = \\ &= \frac{3}{\pi} \left[\exp(a \cos \psi) \right] \left[\sum_{i=1}^6 \exp(a \cos \psi_i) \right]^{-1} \end{aligned} \quad (2)$$

(n is the number of oriented axes, n_0 is the total number of axes), and polarisation is described by the equation

$$P = \frac{3P_0}{\pi} \int_0^{2\pi} \left[\exp(a \cos \psi) \cos \psi \right] \left[\sum_{i=1}^6 \exp(a \cos \psi_i) \right]^{-1} d\psi, \quad (3)$$

where P_0 is the overall polarisation under the assumption that all dipoles are completely oriented.

The intensity of X-ray diffraction for the case of variation of the angle between the direction of incidence of the beam and the perpendicular to the film surface has been calculated.⁴² The intensity curves for various values of the parameter $\exp(2\mu E/kT)$ were constructed. The experimental points obtained by averaging over seven samples are in the best agreement with the calculation based on the assumption that $\exp(2\mu E/kT) \simeq 10^3$.

Similar experiments have been carried out in another study.⁴⁴ The researchers monitored the variation in the intensity of the 110, 200 reflections after poling of a PVDF film shaped like a cylinder rotating around its axis, which coincided with the stretching direction. These experiments also confirmed the hypothesis that the dipole orientation can change by 60° steps during polarisation (see Fig. 5). This polarisation model is also confirmed by calculations of the potential energy for the chain rotation, which show that two neighbouring equilibrium positions of the CF_2 group are separated by 60°.⁴² Finally, the data on the hysteresis of the IR bands upon application of a field also point to 60-degree reorientations. Indeed, in terms of the model assuming 180-degree steps of rotation, no changes in the IR absorption intensity should be expected because the intensity is proportional to $\cos^2\theta$ (see Ref. 40).

The values of polarisation calculated from Eqn (3) are presented in Table 1. The most probable $\exp(2\mu E/kT)$ value for PVDF amounts to 10^3 ; it is matched by $P \simeq 111 \text{ mC m}^{-2}$. The crystallinity of the sample is normally $\sim 50\%$; hence, polarisation should be 50 mC m^{-2} , which is consistent with the PVDF remanent polarisation found experimentally. The known $\exp(2\mu E/kT)$ value can be used to determine the dipole moment of the domain.⁴² For the field $E = 600 \text{ kV cm}^{-1}$ at 100°C , it amounts to $3 \times 10^{-28} \text{ C m}$. If the dipole moment of a monomer

Table 1. Polarisation of crystalline PVDF calculated for various magnitudes of the $\mu E/kT$ parameter.⁴²

$\mu E/kT$	$\exp(2\mu E/kT)$	$P/\text{mC m}^{-2}$
0.00	1	0
1.15	10	66
2.30	10^2	98
3.45	10^3	111
4.61	10^4	116
5.76	10^5	120
6.91	10^6	121

unit in a planar zigzag chain is taken to be $\mu_0 = 7 \times 10^{-30}$ C m, then a domain should comprise ~ 40 monomer units. The polar β -phase crystals with normal sizes (~ 100 Å) contain many more monomer units. This means that field-induced orientation occurs in an area the size of which is much smaller than the size of the β -phase crystal. This conclusion is probably confirmed by the data of analysis of the ferroelectric and pyroelectric characteristics of thin films of the 70/30 VDF/TrFE copolymer prepared by the Langmuir–Blodgett method.⁴⁵ In the films containing several monolayers, the formation of a domain structure was noted; hysteresis of the pyroelectric current and a first-order Curie transition of the ferroelectric–paraelectric type was clearly observed for these films.

The regions of spontaneous polarisation, typical of ferroelectrics, can be probed using the electrochromism of optical labels. The optical labels used are normally azo dyes that efficiently absorb in the visible region. For instance, 4-dimethyl-amino-4'-nitrostilbene (DANS), for which the dipole moment in the ground state and the difference between the dipole moments in the ground and excited states are known, has been used as the optical label for PVDF and systems based on it.^{46, 47} To estimate the strength of the local (internal) field E_l which had appeared in the sample after polarisation, the researchers made use of the fact that the absorption spectra of DANS in the perturbed ($E \neq 0$) and non-perturbed ($E = 0$) states differ in the absorbance and in the frequency of the main absorption band.⁴⁸

The local field strength in polarised samples of a blend of PVDF and poly(methyl methacrylate) (PMMA) proved to be more than twice as high as the strength of the external field during poling.⁴⁷ A similar result has been obtained for the VDF/TrFE copolymer.⁴⁶ Apparently, for these polymers, the influence of the charge carriers injected from the electrode material should be taken into account. This hypothesis is supported by the results of analysis of the polarisation profile in these samples by the thermal pulse method.^{49, 50} The polarisation profile is formed not only by dipoles but also by the space charge. The role of the latter is to stabilise the areas of oriented dipoles, which ensures the invariability of E_l in the temperature range of annealing (60–90 °C).⁴⁷ Some decrease in E_l near 60 °C (glass transition region) implies, apparently, that the fields of the disordered phase areas should also make a contribution to E_l . This contribution is relatively low because the most pronounced decrease in E_l occurs at about ~ 120 °C, where annealing is accompanied by depolarisation processes due to disorientation of the β -phase crystals.

Jimbo *et al.*⁵¹ have attempted to determine the above-noted substantial changes in the coercive field observed in the polarised PVDF upon the temperature variation (see Fig. 4) using a simple phenomenological relaxation theory. In accordance with this theory, they calculated the E_c values, which corresponded to the experimental data in the temperature range chosen.

As noted above, PVDF and VDF-based copolymers contain at least two phases (ordered crystalline phase and disordered amorphous phase) having substantially different electric parameters, in particular, dielectric permittivity. This is attributable to the fact that the disordered phase occurs at room temperature in the liquid-like state and its chains execute cooperative motion with

large amplitudes.²⁸ Therefore, depolarisation field E_d , the direction of which is opposite to that of the applied field E , can arise at the boundaries of ferroelectric crystals.

The field E_l which really acts on the crystal can be described by the equation⁵²

$$E_l = E - E_d = f \left[\left(E - \frac{L}{\varepsilon \varepsilon_0} \right) (P_c - P) \right] = f \left[\left(E - \frac{L}{\varepsilon \varepsilon_0} \right) \left(\frac{1}{\alpha f} - 1 \right) P \right], \quad (4)$$

where f is a parameter related to the depolarisation factor L and to the difference between the dielectric constant of the sample as a whole ε and that of the crystalline region ε_c (their polarisations are P and P_c , respectively), ε_0 is the vacuum dielectric constant and α is the degree of crystallinity.

The fact that E_l is lower than E means that the experimental hysteresis curves do not reflect characteristics of polar crystals. By processing experimental P – E curves, Ikeda *et al.*⁵² elucidated the dependences for the crystallites, *i.e.*, those in the P_c – E_l coordinates. The theoretical P_c – E_l curves were constructed for $L = 0.04$ and 0.08 ; provided that $\varepsilon = 12$ and $\varepsilon_c = 3$, this is matched by $f = 1.031$ and 1.064 and the draw ratios for an ellipsoidal crystal are 6.5 and 3.8. Since f differs insignificantly from unity, then, taking into account that $E_l = fE_c$ (see Ref. 51), the coercive field values for the calculated and experimental curves are virtually identical.

Spontaneous polarisation of the crystal P_{sc} and that for a sample with the degree of crystallinity α are related as follows:⁵¹

$$P_{sc} = \frac{P}{f\alpha}.$$

When $\alpha = 0.45$, spontaneous polarisation is substantially higher than the overall polarisation. The value $P_{sc} \simeq 170$ mC m^{−2} obtained by Ikeda *et al.*⁵² is consistent in order of magnitude with the spontaneous polarisation (130 mC m^{−2}) calculated for a perfect crystal of the β -phase.

III. Characteristic features of the polarisation switching processes

The analysis of the features of polarisation switching processes is conveniently started with the data on PVDF; this homopolymer has been studied in the uniaxially stretched state, in which the crystalline phase occurred in the ferroelectric β -modification. Switching experiments usually consist in the application to the film of a stepwise field and recording of the time dependence of the electric displacement or polarisation current. The latter operation is often replaced by differentiation of the $D(t)$ curve (t is the current time) with respect to time. These curves are shown in Fig. 6. It can be seen that, as the electric field strength increases, the inflection point in the $D(t)$ curve and, correspondingly, the

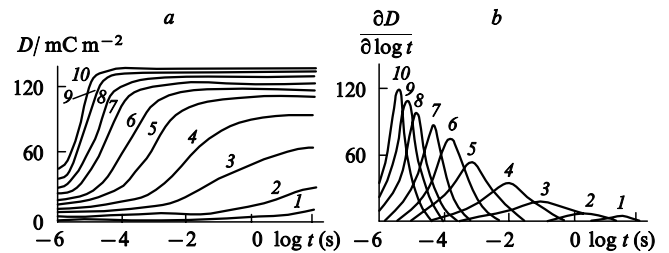


Figure 6. Time dependences of the electric displacement (a) and its derivative with respect to time (b) for the ferroelectric switching in a polarised PVDF film at 20 °C and at various external electric field strengths.⁵³ $E/\text{MV m}^{-1}$: 20 (1), 40 (2), 60 (3), 80 (4), 100 (5), 120 (6), 140 (7), 160 (8), 180 (9), 200 (10).

maximum of the derivative shift to shorter times. This type of behaviour has also been noted for classical inorganic ferroelectrics and is usually described by the relations

$$\tau_s = \tau_0 \exp\left(\frac{E_a}{E}\right) \quad (5)$$

or

$$\tau_s = \tau_0 \left(\frac{E}{E_0}\right)^{-n}, \quad (6)$$

where τ_s is the time of polarisation switching [corresponding to the maximum of the derivative of $D(t)$ or to the switching point], τ_0 is the pre-exponential factor, E_a is the activation field, and E_0 and n are constants. The $D(t)$ function can be represented as follows

$$D = D_0 + 2P_s \left[1 - \exp\left(-\frac{t}{\tau_s}\right)\right]^n, \quad (7)$$

where D_0 is the instant electric displacement and $2P_s$ is the reversible polarisation. The exponent n corresponds approximately to the half-width of the $\partial D/\partial \log t$ peak. When the field strength is 60 MV m^{-1} , the exponent n for the 65/35 VDF/TrFE copolymer is greater than 5.

It has been noted above that the specific character of the polymeric state is due, on the one hand, to the strong anisotropy of bonds along and across the chain and, on the other hand, to the presence of an amorphous phase in addition to the crystalline phase. The chain dynamics of the amorphous phase below and above glass transition temperature are substantially different;²⁸ therefore, to understand the mechanism of generation of ferroelectricity in polymers, it is important to find out how this can influence the switching characteristics. Furukawa *et al.*⁵³ have studied the processes of switching in a polarised PVDF film in which the amorphous phase occurred in the liquid-like or vitrified state (Fig. 7). It can be seen that, when the field is so high (200 MV m^{-1}), switching can also take place below T_g (-40°C). Below the glass transition temperature, the equilibrium electric displacement regularly decreases, the maximum switching rate D diminishes, and the peaks themselves become markedly broader as the temperature decreases. Figure 8 presents the field dependences of the switching times in a polarised PVDF film at various temperatures. These plots are linear both above and below the glass transition temperature, indicating that relations (5) and (6) hold. Transition of the amorphous phase into the glassy state noticeably changes the switching parameters (Table 2). In fact, as the temperature diminishes from room temperature to T_g , the exponent n and the constant τ_0 in Eqn (6) substantially increase (see Table 2). If the field dependences are represented as Eqn (5), then, in accordance with the results obtained by Furukawa and Johnson,⁵⁴ the transition of the disordered phase in the glassy state is also accompanied by a substantial increase in the activation field; E_a is 1.1 GV m^{-1} at 20°C and 1.9 GV m^{-1} at -60°C .

PVDF is characterised by higher activation fields and by higher exponents n in relations (6) or (7) than inorganic ferro-

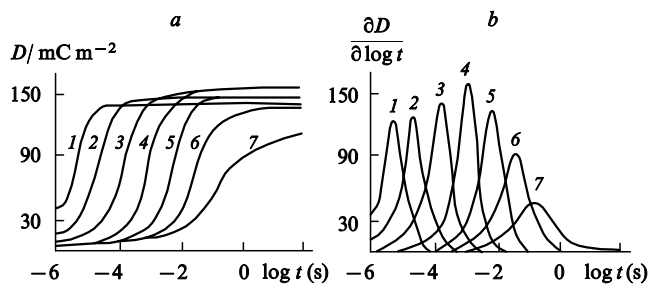


Figure 7. Time dependences of the electric displacement (a) and its derivative with respect to time (b) for the ferroelectric switching in a polarised PVDF film at $E = 200 \text{ MV m}^{-1}$ and various temperatures.⁵³ $T/^\circ\text{C}$: 20 (1), 0 (2), -20 (3), -40 (4), -60 (5), -80 (6), -100 (7).

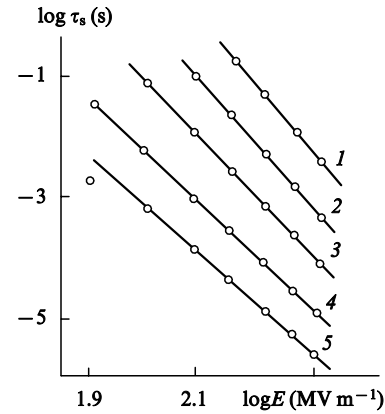


Figure 8. Field dependences of the switching times in a polarised PVDF film at various temperatures.⁵³ $T/^\circ\text{C}$: -60 (1), -40 (2), -20 (3), 0 (4), 20 (5).

Table 2. Values n and τ_0 for PVDF and the 73/27 VDF/TrFE copolymer determined in the switching experiments.

$T/^\circ\text{C}$	n	$\log \tau_0 (\text{s})$
PVDF ^{53, 54}		
20	7.6	12.02
0	8.0	13.63
-20	9.7	18.35
-40	10.7	21.19
-60	10.6	22.15
VDF/TrFE ⁵¹		
20	10.2	16.48

electrics. This fact was explained⁵³ in terms of the model of nucleation and growth of domains. Within the framework of this model, the switching curve $D(t)$ is described by the expression

$$D = 2P_s \left\{ 1 - \exp \left[- \int_0^t N_0 R e^{-Rs} F(v(t-s)^m) ds \right] \right\}, \quad (8)$$

where N_0 is the number of nucleation sites, R is the probability of nucleation, s is the current time, F is a factor depending on the shape of the growing domain, v is the growth rate, t is the total time, and m is the growth dimensionality. If switching is assumed to occur in very thin lamellae, consideration can be restricted to two-dimensional growth, *i.e.* $m = 2$. In this case, it follows from Eqn (8) that

$$D = 2P_s \left\{ 1 - \exp \left[- \frac{2FN_0v^2}{R^2} \left(\frac{R^2t^2}{2} - Rt + 1 - e^{-Rt} \right) \right] \right\}. \quad (9)$$

If $Rt \gg 1$, then

$$D = 2P_s [1 - \exp(FN_0v^2t^2)], \quad (10)$$

if $Rt \ll 1$, then

$$D = 2P_s \left[1 - \exp \left(- \frac{FN_0v^2R}{3} t^3 \right) \right]. \quad (11)$$

In both cases, the n values found by the calculations are smaller than those found experimentally. Agreement with experimental results can be attained by assuming that the domain growth is self-accelerated.

The influence of the state of the disordered phase on the switching parameters has also been studied by Matsushige *et al.*,⁵⁵ who derived switching characteristics from the time variation of the transpolarisation current at the same field strength

(200 MV m⁻¹). Three temperature regions of variation of τ_s characterised by different activation energies of the switching process can be distinguished. The first region lies below T_g and has an activation energy of 2.3 kcal mol⁻¹. Here, the dynamics of molecular motion is characterised by only local types of motion, which can occur in both the amorphous and crystalline phases.²⁸ The activation energy of switching increases somewhat when cooperative forms of motion are excited in the amorphous phase ($60^\circ\text{C} > T > T_g$). Finally, the third region falls to temperatures above 60°C , when motion in crystalline lamellae begins.²⁸ This motion decreases the activation barrier to switching.

Thus, switching is sensitive not only to crystalline domains but also to the surrounding disordered areas.

A complex pattern of the curves of reversible polarisation has also been found for the VDF/TrFE copolymer. Specific features of switching near the Curie point, in which a ferroelectric–paraelectric transition occurs, have been studied.⁵⁶ In the vicinity of this point (68°C), the plot for D at low fields has two steps (Fig. 9).

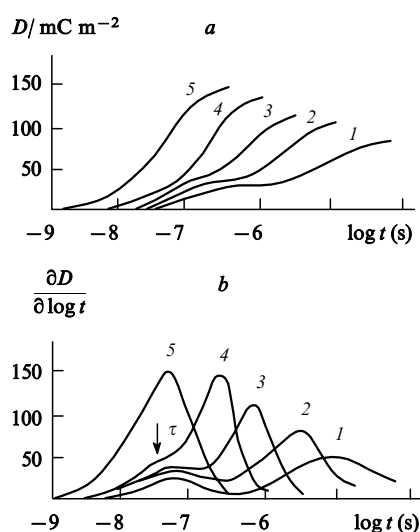


Figure 9. Time dependences of the electric displacement (a) and its derivative with respect to time (b) for polarisation switching in 65/35 VDF/TrFE at 63°C and various field strengths.⁵⁶ E /MV m⁻¹: 75 (1), 90 (2), 135 (3), 200 (4), 300 (5).

The shape of experimental curves is described adequately by an equation with two switching times, one (τ) being independent on the field intensity and the other (τ_s) depending on it according to the law normal for ferroelectrics (Fig. 10). The switching time (τ) varies in the same way as that for an ordinary relaxation process; therefore, the expression for D can be written as follows:⁵⁶

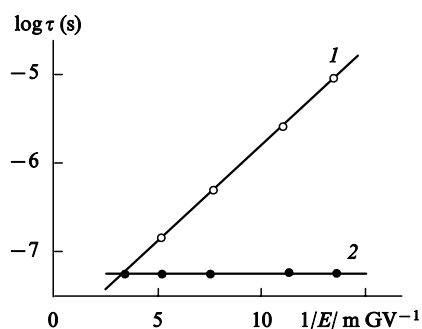


Figure 10. Field dependences of the switching times τ_s (1) and τ (2) in the 65/35 VDF/TrFE copolymers at 63°C .⁵⁶

$$D = \varepsilon_0 E + \Delta \varepsilon E \left[1 - \exp\left(-\frac{t}{\tau}\right)^\beta \right] + 2P_r \left[1 - \exp\left(-\frac{t}{\tau_s}\right)^n \right], \quad (12)$$

where $\Delta \varepsilon$ is the relaxation force, β is a parameter determining the distribution of the relaxation time, and n is a parameter determining the shape of the switching curve. This expression is suitable (provided that τ does not depend on E) for describing the experimental switching curves shown in Fig. 9. In particular, it also accounts for the shape of the curve at high fields. The straight lines shown in Fig. 10 intersect at a certain field strength. At the point of intersection, $\tau = \tau_s$; therefore, switching curves for such field strength attest to a one-step process.

The changes in the field dependence of τ_s with an increase in the temperature in the copolymer considered and in PVDF are similar. However, as the Curie point is approached, the slope of this plot markedly decreases. According to Eqn (5), this is equivalent to the decrease in the activation field E_a . Taking into account the probable generation of great fluctuations of the motion near the Curie point, a hypothetical mechanism for the nucleation of domains during polarisation switching was proposed.⁵⁶ The scheme of this mechanism is presented in Fig. 11. The authors proceeded from the real conformational structure found in the chains of PVDF and VDF copolymers.

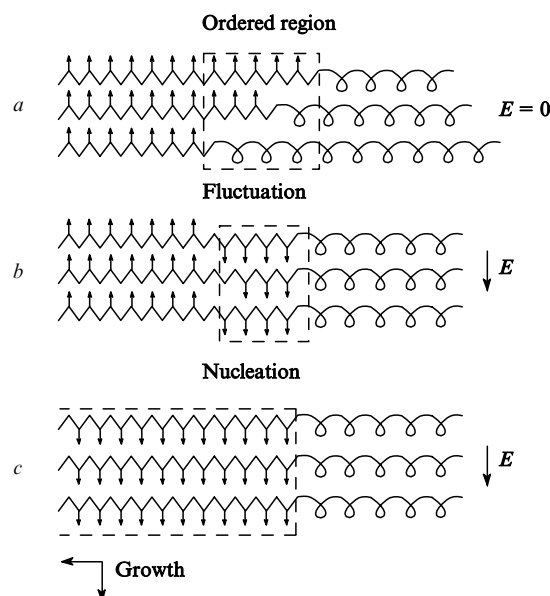


Figure 11. Scheme for the fluctuation motion (a), nucleation (b) and the growth of the nucleus (c) in the switching processes in 65/35 VDF/TrFE.⁵⁶

The ordered areas in the VDF copolymers with TrFE or TFE are known to crystallise as the ferroelectric β -phase with the planar zigzag conformation. The polarisation of a domain in a polarised film is stipulated by the external field. The results of X-ray and IR-spectroscopy studies demonstrate that, in addition to the planar zigzag conformation, chain sections occurring in a mixed conformation, TT, TG, or TG⁻, are also present.²⁸ They should be located either in the amorphous phase or in the crystals of the paraelectric phase, which can coexist with the ferroelectric phase. These sections should be the first to respond to a field because the relaxation times τ for them are shorter than τ_s (if the fields are not extremely high) (see Fig. 10). If the chains are mainly located in the film plane (this is the case for the uniaxially oriented state), a chain section having, for example, the TGTG⁻ conformation should pass into a different position upon the interaction of the field with the transverse component of the dipole moment. In a high field, a conformational transition of the TGTG⁻ $\rightarrow$ TTTT type is possible;²⁸ therefore, the second stage in the nucleation process is the appearance of chain sections in the

planar zigzag conformation with a new orientation of the dipole moment. Evidently, these processes involve simultaneously a certain rearranging region rather than individual sections of the chain because above T_g , the micro-Brownian motion in the amorphous phase is to some extent cooperative.²⁸ After a nucleus has formed by the above mechanism, it starts to grow in both the longitudinal and transverse directions.

Certainly, the mechanism described above merits attention because it is underlain by the real structure of the chains in PVDF and VDF copolymers. The validity of this mechanism is confirmed by the presence of tie chains, characteristic only of crystallisable polymers, in the compounds considered. As a result of spontaneous nucleation during crystallisation, the same chain can be incorporated in both the crystal and the neighbouring disordered phase. If the chain section adjacent to the crystal occurs in the TGTG⁻ conformation, the orientation and conformational changes described above would create internal stresses in the section of the same chain contained in the crystal because the direction of its dipole moment would be opposite to the new direction of the field. This fact as well as the influence of an external electric field are additional factors inducing transpolarisation of a region of the crystalline phase. The time τ (like the normal relaxation time) decreases as the temperature increases, which can also affect the temperature dependence of the switching time τ_s .⁵⁵

The above mechanism for the generation and development of domains in the switching processes does not take into account the effect of the space charge formed by both the inherent charge carriers and those injected from the electrodes during poling. However, experimental results imply that this effect cannot be neglected. For example, in a study⁵⁷ dealing with switching in the 73/27 VDF/TrFE copolymer on exposure to 1-second rectangular pulses, an unusual phenomenon was discovered, which can be described as follows. As the delay period t_0 between the preceding and the subsequent pulses (having opposite polarities) increases, the switching curves regularly shift to longer switching times. The same trend is observed if the strength of the external field decreases (see, for example, Figs. 6, 8). This correlation led the researchers to the conclusion that the decrease in the switching time following an increase in the duration of leaving the sample after a high-voltage pulse has been applied is due to field effects. Since the external field strength was maintained constant (80 MV m⁻¹), all the foregoing was explained by variation of the local field acting on the domain. The period the sample is left and the final concentration of charge carriers in the sample bulk create real prerequisites for the processes described above.

Free charge carriers are present both in non-polarised (remaining catalyst, ionic side products of the synthesis, *etc.*) and polarised PVDF. In the latter case, there are also charge carriers injected from the electrode. It is assumed that charge carriers are captured into deep traps located along the boundaries between the ordered and amorphous regions. If these regions occur in the liquid-like state, in which the segments execute cooperative motion with large amplitudes,²⁸ there are conditions for the charge to be liberated and re-captured by another trap. From energy reasons, it is more favourable for these carriers to be located on polar surfaces of crystallites, which should result in partial compensation of their polarisation. The local polarisation P_l would differ from the macroscopic value P ; in accordance with Eqn (4), this should change the field E_l acting on the crystal. These effects have been considered quantitatively.⁵⁸ The expression proposed for E_l has the form

$$E_l = -\frac{n'(1-\alpha)P_0}{\varepsilon_a - (\varepsilon_a - \varepsilon_c)n'(1-\alpha)} \exp\left(-\frac{t_0}{\tau}\right), \quad (13)$$

where n' is the depolarisation factor for ellipsoidal crystals with dielectric constant ε_c immersed in an amorphous matrix with dielectric constant ε_a , and α is the volume fraction of these crystals. The exponential term (kinetic factor) includes the characteristic

relaxation time of the space charge τ , which is related to the conductivity of the amorphous phase g by the equation

$$\tau = \frac{\varepsilon_a - (\varepsilon_a - \varepsilon_c)(1-\alpha)n'}{g[1 - (1-\alpha)n']}. \quad (14)$$

The overall expression for the polarisation switching time with allowance for the foregoing has the following form:

$$\log \tau_s = \log \tau_0 + \frac{0.4343E_a}{E + A \exp(-t_0/\tau) - E_l}, \quad (15)$$

where E_a and A are constants for a given polymer, E_l reflects the correction of the external field E due to the effect of the depolarising field.

Figure 12a shows experimental points for τ_s at various t_0 for samples of the 73/27 VDF/TrFE copolymer obtained by quenching and by slow cooling. It can be seen that τ_s increases with an increase in t_0 in accordance with Eqn (15). The τ_s value is always greater for a quenched sample, all other factors being the same. This can be explained qualitatively by the following fact, which has been confirmed experimentally. The volume fraction of the ferroelectric phase is always lower in a quenched sample; therefore, the conductivity of the amorphous phase g should be greater. In conformity with Eqn (14), this results in a lower τ and, according to relation (15), this increases τ_s . Yet another way for increasing the conductivity in the copolymer considered is an increase in the concentration of charge carriers by doping with, for example, iodine.⁵⁹ For a doped sample, the τ_s values are greater and the shape of the curves calculated from Eqn (15) is described adequately by experimental data (Fig. 12b).

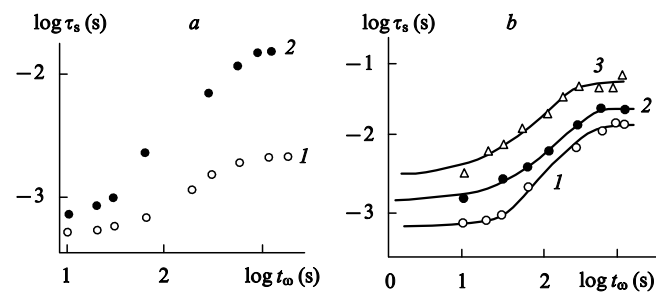


Figure 12. Plots for the polarisation switching time in 73/27 VDF/TrFE films prepared either by slow cooling or by quenching (a) and either non-doped or doped with iodine (b) in a 80 MV m⁻¹ field (see Refs 57–59); (a): (1) cooling, (2) quenching; (b): (1) without doping, (2) doping for a week, (3) doping for a month; the solid line corresponds to the calculation by Eqn (15).

The experiments carried out by Bihler *et al.*^{60,61} were devoted to the non-trivial role of the space charge in the polarisation switching in PVDF and VDF copolymers. In the study of polarisation of the initial films and transpolarisation of polarised films in pulsed electric fields, the attention was concentrated on the comparison of the time dependences of the electric displacement D and the resulting remanent polarisation P_r . The D value was measured using a capacity divider circuit and P_r was measured by generation of a pressure pulse in the short circuit mode. The investigation objects were PVDF films crystallised as mixtures of α - and β -phases⁶⁰ and 75/25 VDF/TrFE copolymer films.⁶¹ Figure 13 presents the time dependences of D and P_r for isotropic films of 75/25 VDF/TrFE to which a primary high-voltage pulse has been applied. Both characteristics vary according to similar patterns but the positions of the characteristic points on the $D(t)$ and $P_r(t)$ curves are substantially different. For example, the time it takes for P_r to reach half its equilibrium value (this is marked by the vertical line) in a 160 MV m⁻¹ field amounts to ~ 100 μ s, whereas the electric displacement virtually reaches its maximum over this period. More detailed data for this

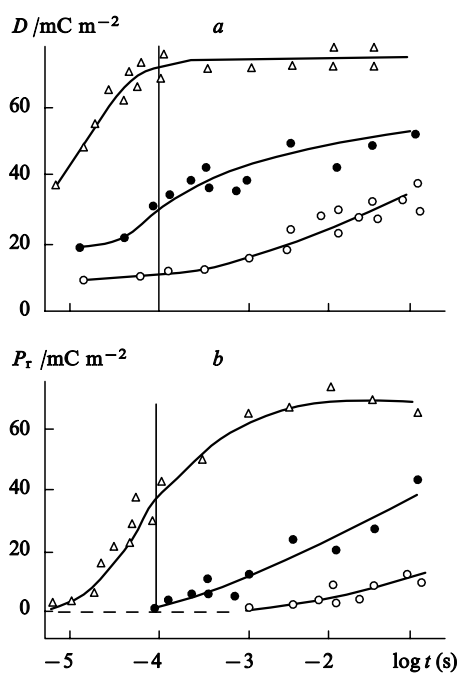


Figure 13. Time dependences of the electric displacement (*a*) and the remanent polarisation (*b*) upon application of a pulse electric field with various strengths in the initial non-polarised films of the 75/25 VDF/TrFE copolymer.⁶¹
E /MV m⁻¹: 80 (1), 120 (2), 160 (3).

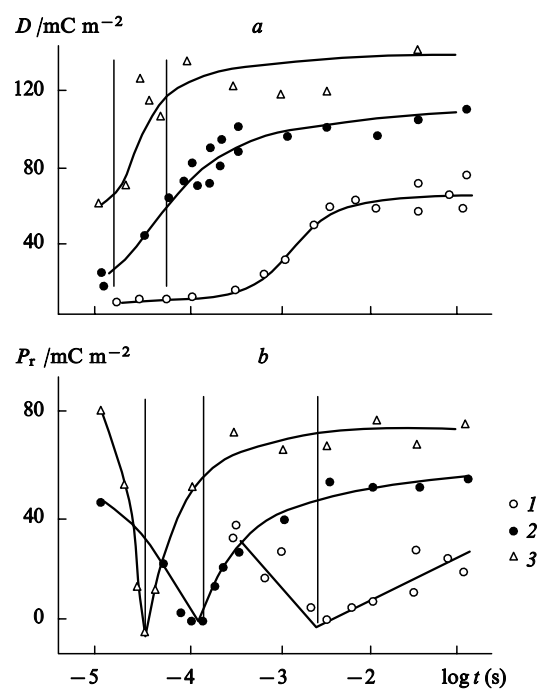


Figure 14. Time dependences of *D* (*a*) and *P_r* (*b*) for pulse transpolarisation in various fields of preliminarily polarised films of the 75/25 VDF/TrFE.⁶¹
E /MV m⁻¹: 80 (1), 120 (2), 160 (3).

copolymer and also for PVDF are presented in Table 3. It can be seen that for both compounds, the points where the slope begins and when half the equilibrium *P_r* value is attained on the *P_r*(*t*) curve are substantially displaced to longer times with respect to the corresponding points on the *D*(*t*) curves. Qualitatively similar data have also been obtained for preliminarily polarised films upon application of a high-voltage pulse with the opposite polarity (Fig. 14). The *D*(*t*) curves follow the same pattern as those for initial (non-polarised) films but the *P_r*(*t*) plots have a minimum which separates two branches reflecting antiparallel variation. The descending branch of *P_r* evidently corresponds to the removal of the polarisation which had existed before the pulse with the opposite polarity was applied. The increase in *P_r* is apparently due to the formation of a remanent polarisation in the new direction. As in the previous case, the time it takes for *D* to reach half its equilibrium value (marked by vertical lines) proves

even shorter than the time required for the initial polarisation to diminish to zero (a vertical line is also drawn through the minimum point). This led the researchers^{60,61} to the conclusion that the processes responsible for the increase in *D* and *P_r* are not equivalent. It is believed that an increase in *D* reflects the rotation of dipoles, which respond to a high field almost instantaneously. The delay of the formation of the remanent polarisation is due to the fact that this process involves the carriers forming the space charge. If dipoles of the ferroelectric β-phase have occupied a new position in the field, then, due to the finite mobility of charge carriers, the space charge would occupy a new equilibrium position within some period after the dipoles have rotated, which is actually observed in the experiment. The influence of the space charge is not limited to the retarded kinetics of equilibration of *P_r* with respect to *D*. The space charge also plays an important role in the stabilisation of the remanent polarisation, resulting in the retention of piezo- and pyro-electric properties in polarised films of PVDF and VDF copolymers over long periods of time.

Table 3. Parameters of the characteristic points in the time dependences for 75/25 VDF/TrFE and PVDF recorded during poling of films by high-voltage pulses of various durations.

<i>E</i> / MV m ⁻¹	Beginning of the slope /μs		The time it takes to reach half the maximum value /μs	
	I	II	I	II
VDF/TrFE ⁶¹				
80	400	3 000	1 000	17 000
120	30	100	50	2 000
200	1	10	< 10	80
PVDF ⁶⁰				
120	200	2 000	20 000	40 000
200	< 10	80	10	3 000

Note. I are characteristic points on the *D*(*t*) curves; II are characteristic points on the *P_r*(*t*) curves.

Thus, polarisation switching in PVDF films and films of VDF copolymers with a ferroelectric β-phase occurs most likely in two stages. The first (fast) stage involves reorientation of domains due to the rotation of dipoles *via* 60-degree rotations of the chains (see Fig. 5). This conclusion is confirmed by numerous structural data and also by calculations of the activation energy of switching in terms of this model.⁶² According to these calculations, the activation barrier should not exceed several tens of kilocalories per mole, which agrees with the experimental values. For example, it has been reported⁵⁵ that the activation barrier does not exceed 10 kcal mol⁻¹ and, according to another publication,⁶³ it is not higher than 18 kcal mol⁻¹. The latter value is much lower than would be required by the model which implies 180-degree rotations of the chain.⁶² The stage of formation (nucleation) of new domains is apparently a fluctuation type process.^{56,64} For this stage, it is necessary to take into account the possibility that the same chain can be incorporated both in the crystal and in the disordered phase adjacent to it. If the relaxation processes in the latter are taken into account in the nucleation of a new domain,

the chains in the crystal acquire an additional rotational moment, which facilitates the growth of new domains.⁶²

The structural heterogeneity of PVDF creates prerequisites for the influence of fine features of the phase boundary; the disordered phase is characterised by a higher dielectric constant, which may result in the appearance of a depolarising field.^{57,59,65} When free charge carriers are present, the structural heterogeneity induces the second stage of the resultant switching process. In this stage, due to the migration of the carriers over the disordered interfacial regions, the space charge relaxes to a state matching the newly formed domains.

IV. Curie transition

The ferroelectricity of the polymer systems in question should be described by general phenomenological relations. For example, in the absence of mechanical stress ($X = 0$), the variation of free energy G as a function of polarisation P is described by the expression

$$G = \frac{1}{2}\beta(T - T_0)P^2 + \frac{1}{4}\gamma P^4 + \frac{1}{6}\delta P^6, \quad (16)$$

where T_0 is the characteristic temperature; the β and δ constants are positive, and the sign of constant γ depends on the type of transition (it is negative for first-order transitions and positive for second-order transitions). The first derivative of G with respect to polarisation gives an equation which describes the electric field

$$E = \beta(T - T_0)P + \gamma P^3 + \delta P^5. \quad (17)$$

For a second-order phase transition, $\beta > 0$, $\gamma > 0$, and δ can be regarded as being equal to zero. In this case, the equation for the dielectric susceptibility χ has the form

$$\chi = [\beta(T - T_0) + 3\gamma P_s^2]^{-1}. \quad (18)$$

By differentiating this expression, one finds the second- (ϵ_2) and third-order (ϵ_3) dielectric constants⁶⁵

$$\epsilon_2 = -3\gamma P_s \chi^3, \quad (19)$$

$$\epsilon_3 = (-\gamma + 18\gamma^2 P_s^2 \chi) \chi^4. \quad (20)$$

At temperatures below the Curie point T_C ,

$$P_s^2 = \frac{\beta(T_0 - T)}{\gamma} \quad (21)$$

and

$$\epsilon_3 = 8\gamma \chi^4. \quad (22)$$

Since $\gamma > 0$, the ϵ_3 value is positive and ϵ_2 is negative. Above the Curie point, $P_s = 0$; hence, $\epsilon_2 = 0$. With allowance for Eqn (20), we have

$$\epsilon_3 = -\gamma \chi^4.$$

Thus, for a second-order phase transition, the second-order dielectric constant ϵ_2 is always negative below the Curie point and at T_C , it becomes equal to zero. The sign of the third-order dielectric constant ϵ_3 changes from positive to negative at the Curie point.

As noted above, for a first-order phase transition, $\gamma < 0$, and $\delta > 0$. In this case,

$$\chi = [\beta(T - T_0) + 3\gamma P_s^2 + 5\delta P_s^4]^{-1}, \quad (23)$$

$$\epsilon_2 = -(3\gamma + 10\delta P_s^2) P_s \chi^3, \quad (24)$$

$$\epsilon_3 = -[\gamma P_s^2(10\delta - 18\gamma^2 - 120\chi\gamma\delta P_s^2 - 200\chi\delta^2 P_s^4)] \chi^4. \quad (25)$$

The Curie point is determined by the temperature at which the energies of the polar and nonpolar phases become identical. This means [with allowance for Eqn (16)] that

$$T_C = T_0 + \frac{3\gamma^2}{16\beta\delta}. \quad (26)$$

During heating, the first-order phase transition ($\gamma < 0$) will be observed above T_C , whereas during cooling, it will occur below T_C . Thus, in practice, to determine the type of Curie transition, one should record the temperature dependences of ϵ_2 and ϵ_3 or establish the presence (or the absence) of a hysteresis of one or another characteristics during heating or cooling.

Strong piezoelectricity was first detected in a textured PVDF film;¹ therefore, it is this homopolymer that was used to verify the hypothesis about the ferroelectric nature of this phenomenon. However, the homopolymer is an inconvenient object for the study of the temperature anomalies which accompany the hypothetical ferroelectric–paraelectric transition. The temperature region of the Curie transition coincides in this case with the melting region; therefore, it is difficult to separate them in the experiment.

The presence of piezo- and pyro-electric properties in PVDF has stimulated the search for ways of modifying the chemical structure of this polymer. Copolymerisation of VDF with TFE and TrFE proved to be the most suitable method. The introduction of even small amounts of these co-monomers results in the formation of the polar (ferroelectric) β -phase directly during crystallisation from the melt, which is not characteristic of the homopolymer.²⁸ This type of chemical modification of PVDF also influences the parameters of the unit cell being formed. The tendency of variation of the interplanar spacings in VDF/TFE copolymers upon the variation of the proportion of TFE can be followed by looking at Table 4. It can be seen that an increase in the TFE proportion is accompanied by an increase in the interplanar spacing corresponding to the intermolecular 200, 110 reflections. Hence, the cell packing becomes less dense along the direction perpendicular to the c axis.

Table 4. Interplanar spacings ($\text{\AA}$) in oriented VDF/TFE copolymers with various co-monomer ratios.⁶⁶

[VDF] (mol.%)	Reflections		
	200, 110	001	201, 111
100	4.28	2.56	2.22
89	4.38	2.55	2.21
79	4.48	2.56	2.23
71	4.61	2.56	2.24
64	4.75 ^a	2.57	2.26
54	4.82 ^a	2.58	2.27

^a Non-resolved doublet.

This fact is, apparently, the main reason why the Curie transition and the melting point in these copolymers occur in different temperature ranges, which permits recording of the pure Curie transition by, for example, the X-ray diffraction method.⁶⁶ The influence of the temperature on the interplanar spacing and on the unit cell dimension along the a axis in the 76/24 VDF/TFE copolymer is illustrated by Fig. 15. It can be seen that hysteresis phenomena are observed not only for the reflection intensities but also for the interplanar spacings. The transition to the paraelectric phase is accompanied by a discontinuous increase in the unit cell parameter a . The temperature range in which both reflections coexist is attributed to the presence of both the ferroelectric and paraelectric phases. Yet another interpretation of this fact assumes the formation of some single phase with a symmetry lower than the hexagonal symmetry.^{67,68}

The changes in the 200 and 110 reflections for VDF/TFE copolymers with compositions 76/24 and 75/25 are qualitatively similar,⁶⁸ although the hysteresis phenomena are less pronounced

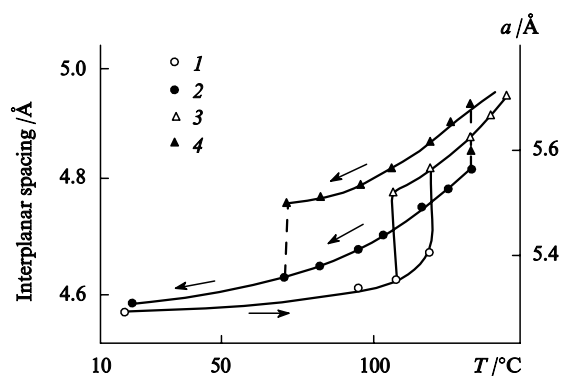


Figure 15. Temperature dependences of the interplanar spacings and the unit cell parameter a for the ferroelectric (1, 2) and paraelectric (3, 4) phases of the 76/24 VDF/TFE prepared in the heating (1, 3) and cooling (2, 4) regimes.⁶⁶

in the latter case. In view of the high information content of IR spectroscopy, it would be of interest to follow the variation of the conformational state of PVDF chains in the vicinity of the Curie transition by this method. These data are presented in Fig. 16 for the 75/25 VDF/TFE copolymer.⁶⁸ It can be seen that the bands at 842 and 1325 cm^{-1} , arising from the planar zigzag conformation in the chains of the VDF copolymer, become much less intense in the temperature region of this transition. Simultaneously, the proportion of chain units occurring in the helical *gauche*-conformation increases in the same temperature range. It is significant that the sharp decrease in the content of *trans*-conformers observed in the vicinity of the Curie transition involves not only VDF sections in the copolymer but also TFE sequences (a band at 620 cm^{-1}), a certain fraction of which (*e.g.*, for the 71/29 composition) can occur as dyads.⁶⁹

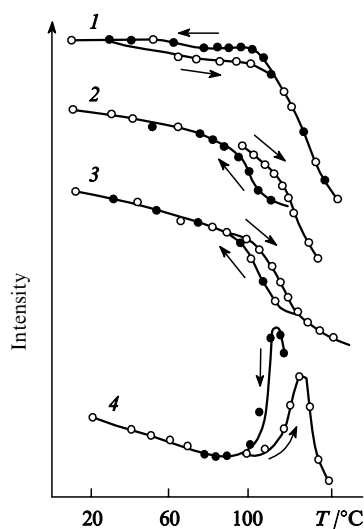


Figure 16. Temperature dependences of the relative variation of the intensities of the bands and 620 (1), 842 (2), 1325 (3), and 926 cm^{-1} (4) in the IR spectra of the ferroelectric 75/25 VDF/TFE copolymer.⁶⁸ (1) TFE groups in the *trans*-conformation, (2, 3) VDF groups in the *trans*-conformation, (4) VDF groups in the *gauche*-conformation.

Thus, the ferroelectric–paraelectric transition in VDF/TFE copolymers is accompanied, apart from the change in the lattice parameters, by the substantial change in the conformational state of the chains, the equilibrium of the *trans*- and *gauche*-isomers being displaced towards the latter.

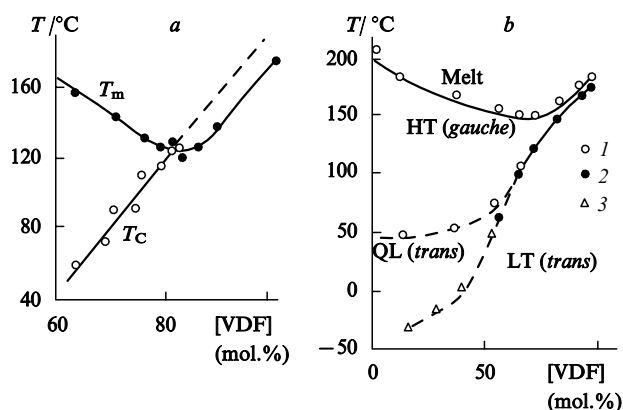


Figure 17. Melting and Curie points as functions of the VDF content in VDF/TFE copolymers⁷⁰ (a) and phase diagram of VDF/TrFE (b).⁶⁷ HT is the paraelectric phase, LT and QL are the ferroelectric phases; (1–3) are boundaries between the phases.

As the proportion of TFE in the copolymer increases, a regular decrease in the Curie point should be expected in addition to the monotonic ‘loosening’ of the crystal along the a axis of the unit cell. This is confirmed by the results of X-ray diffraction^{67, 70} and spectroscopic⁶⁸ studies. According to X-ray diffraction data,⁷⁰ an increase in the fraction of TFE to 40 mol.% is accompanied by a linear decrease in the Curie point (Fig. 17a). The dependence of the melting point on the monomer ratio has a minimum; when the VDF fraction in the copolymer is below 80 mol.%, the Curie transition and melting temperatures are different, and these processes can be observed separately. With the assumption that the linear dependence of T_c on the VDF fraction still holds when this fraction is above 80 mol.% (dashed line in Fig. 17a), the Curie point for pure PVDF (in the β -phase) should be 198 °C, which is higher than the melting point (175 °C).

Copolymers of VDF with TrFE, which possess higher piezoelectric characteristics, have been studied more comprehensively in this respect. In several studies of the thermal properties of these copolymers by differential scanning calorimetry (DSC), in addition to the melting endotherm, typical of crystallisable polymers, one more peak, attributed to the Curie transition, was observed at lower temperatures (Table 5).^{67, 71–73} As the proportion of TrFE in the copolymer increases, the Curie point is displaced to lower temperatures. The enthalpy of this transition in the heating regime is always greater than that in the cooling regime. When the content of VDF is more than 70 mol.%, the Curie point exhibits a clear-cut hysteresis, pointing to a first-order phase transition. However, for the copolymer with 52.8 mol.% of VDF, the temperature hysteresis is hardly visible, which indicates the possibility of a second-order phase transition. In this case, the enthalpy is much lower.

Structural studies of VDF/TrFE copolymers showed⁶⁷ that their unit cell parameters, like those of VDF/TFE copolymers (see Fig. 15), change in the region of the Curie transition, which is due to the rearrangement of the polar cell into a nonpolar one. However, this transition is not so unambiguous, as was first suggested. Detailed analysis of the line contour of the intermolecular reflection near the Curie transition showed that two types of ferroelectric phases, QL and LT, can, in principle, exist.^{28, 67} This conclusion has also been drawn in several other studies. For example, the presence of two heat evolution peaks below the melting region on the DSC curves has been explained⁷⁴ by the presence of two types of lattice of the ferroelectric phase differing in their degree of defectiveness. These peaks are matched by two maxima on thermal depolarisation curve for 75/25 and 70/30 VDF/TrFE copolymers. Experiments on the observance of dielectric hysteresis in these copolymers showed two peaks for the transpolarisation current, the characteristics of which depend on

Table 5. Temperatures and enthalpies of the Curie transition, melting and crystallisation for VDF/TrFE copolymers with various component ratios.⁷³

[VDF] (mol.%)	Heating				Cooling			
	$T_C/^\circ\text{C}$	$\Delta H_C/\text{J g}^{-1}$	$T_m/^\circ\text{C}$	$\Delta H_m/\text{J g}^{-1}$	$T_C/^\circ\text{C}$	$\Delta H_C/\text{J g}^{-1}$	$T_{cr}/^\circ\text{C}$	$\Delta H_{cr}/\text{J g}^{-1}$
0	—	—	190	19	—	—	173	20
52.8	60	5.9	125	29	62	3.0	142	27
64.6	70	14	150	28	64	11	137	25
73	116	20	145	24	75	13	133	23
75	120	24	143	24	77	13	132	24
78	129	29	149	23	85	18	133	24
100 (PVDF)	—	—	153	41	—	—	139	32

the previous thermal history³⁴ and poling conditions of the samples.⁷⁵

The appearance of dielectric anomalies points to the ferroelectric–paraelectric transition. Therefore, if there exist two types of ferroelectric phases with different degrees of crystallographic order, the temperature dependences for the real (ϵ') and imaginary (ϵ'') components of the complex dielectric constant should have two maxima. This is actually the case for the 65/35 VDF/TrFE copolymer (Fig. 18). The phase diagrams of VDF/TrFE copolymers show these two ferroelectric phases (see Fig. 17b, QL and LT

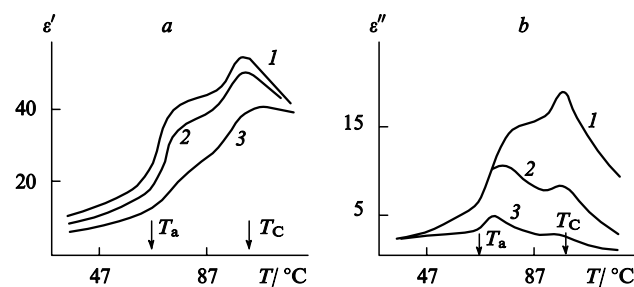


Figure 18. Temperature dependences of the real (a) and imaginary (b) components of the complex dielectric constant recorded during heating of the 65/35 VDF/TrFE copolymers.⁷⁶ Frequency /MHz: 0.5 (1), 2.5 (2), 10 (3).

phases). According to the diagram, the more defective ferroelectric phase QL is formed only in copolymers with low concentrations of VDF, whereas in copolymers enriched in VDF, the ferroelectric transition follows the LT → HT pattern. Having agreed with the qualitative character of this diagram, Ogura *et al.*⁷⁶ reported data that made it more precise. Figure 19 shows the diffraction curves in the region of the principal intermolecular reflection for the 65/35 VDF/TrFE copolymer. At room temperature (below the Curie point), the copolymer with this composition should contain only the LT type ferroelectric phase (see

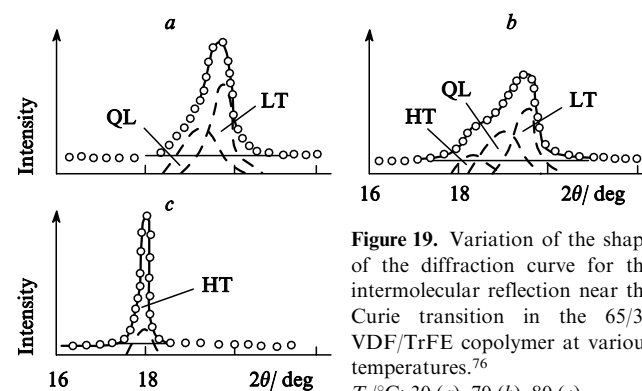


Figure 19. Variation of the shape of the diffraction curve for the intermolecular reflection near the Curie transition in the 65/35 VDF/TrFE copolymer at various temperatures.⁷⁶ $T/^\circ\text{C}$: 30 (a), 70 (b), 80 (c).

Fig. 17b). However, two components of the reflection (see Fig. 19a, b) point to the presence of both phases, QL and LT. In addition, as the temperature is raised, the LT → HT transition and then the HT → melt transition should occur. However, the paraelectric phase HT starts to appear in the presence of both the QL and LT phases (Fig. 20). In the vicinity of a certain temperature T_a , the proportions of the ferroelectric phases QL and LT start to decrease and the pattern of the temperature dependences of the corresponding interplanar spacings changes. In the same region, the paraelectric phase HT appears; in the range between T_a and T_C it coexists with the ferroelectric phases.

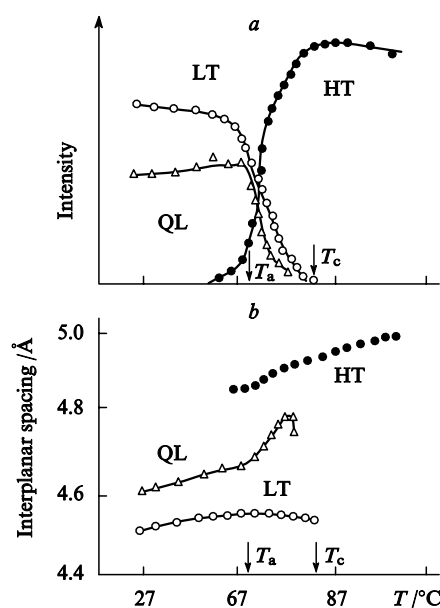


Figure 20. Temperature dependences of the reflection intensities (a) and interplanar spacings (b) for the paraelectric and ferroelectric phases in the region of the Curie transition for the 65/35 VDF/TrFE copolymer.⁷⁶

The QL phase has greater interplanar spacings than LT. According to Tashiro *et al.*,⁶⁷ the less dense packing of the QL phase can be described by two structure models (Fig. 21). The first model implies the formation of crystals in which chains with planar zigzag conformations arranged in the (130) planes are bent with respect to c axis through an angle of 18° (Fig. 21a). Bends of this type can also arise in the crystals of the LT phase but in this case, the angle is $\sim 3^\circ$. The other model assumes the occurrence of 60° domains (Fig. 21b). These defects preclude the possibility of a denser packing, as in the LT phase. For example, the LT phase is characterised by the following monoclinic unit cell parameters: $a = 9.12 \text{ \AA}$, $b = 5.25 \text{ \AA}$, c (chain axis) $= 2.55 \text{ \AA}$, $\beta = 93^\circ$. The QL phase has the same lattice symmetry but contains a portion ($\sim 30\%$) of crystals with the above-noted defects. The crystal parameters are as follows: $a = 9.16 \text{ \AA}$, $b = 5.43 \text{ \AA}$, c (chain

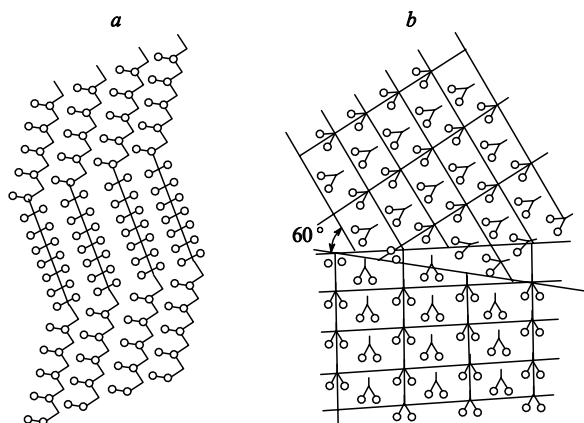


Figure 21. Schematic pattern of the disordered structure of the QL phase in the model of bent chains with the planar zigzag conformation (a) and in the model of the 60-degree domains (b).⁶⁷

axis) = 2.53 Å, $\beta = 93^\circ$. It can be seen that the lattice distortions arising on passing from the LT phase to the QL phase are accompanied by a noticeable decrease in the packing density in the polar direction (*b* axis).

As the Curie point is approached (in the rising temperature regime), conformational changes start to occur in the chains of the copolymers considered, as in the VDF/TFE copolymer (see Fig. 16). This is illustrated by Fig. 22 for 72/28 VDF/TrFE. It can be seen that near T_C , the intensity of the band at 1290 cm^{-1} , corresponding to the long sequences of VDF chains in the planar zigzag conformation (*trans*), sharply decreases.²⁸ Conversely, the intensity of the band at 612 cm^{-1} , due to the TGTG[−] conformation (*gauche*),²⁸ starts to increase substantially. Apparently, this is due to the fact that, as the Curie point is approached, bonds with 'defective' conformations, TG, T₃G, TG[−] and T₃G[−], begin to appear in the VDF chains in the planar zigzag conformation. This fact may account for the decrease in the intensities of reflections of the LT and QL phases and the increase in the intensity of the reflection due to the paraelectric HT phase (see Fig. 20a). The same assumption can explain the change in the interplanar spacing and the decrease in the intensity of the 001 reflection of the β -phase (see Fig. 22a,b). The pronounced hysteresis of the above-mentioned characteristics indicates that the Curie transition in this copolymer is a first-order phase transition.

In view of the appearance of conformations corresponding to the α - and γ -modifications in the PVDF chains,²⁸ a dense packing of chains in the paraelectric HT phase should not be expected. In fact, this phase is characterised by the following unit cell

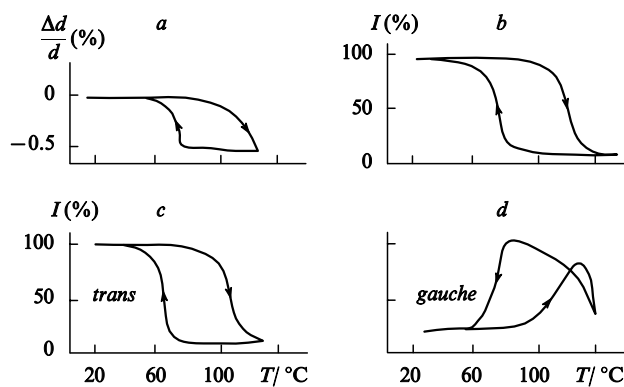


Figure 22. Temperature variations of the relative change in the interplanar spacing (a), the intensity of the 001 reflection (b), the intensity of the bands at 1290 (c) and 612 cm^{-1} (d) in the IR spectra of the 72/28 VDF/TrFE copolymer.⁸⁶

parameters: $a = 9.75$ Å, $b = 5.63$ Å, c (chain axis) = 4.60 Å and $a/b = \sqrt{3}$. Several questions concerning the structure of paraelectric phase remain to be solved because calculation of the statistical chain packing does not provide agreement with experimental results.⁶⁷ This was attributed to the intense thermal motion in the HT phase, which can be recorded by dielectric measurements^{77, 78} and NMR.^{79, 80}

It should be noted that the presence of the QL and LT phases can account for the appearance of the 'anomalous' double hysteresis patterns in VDF/TrFE copolymers with high contents of a second co-monomer.^{75, 81, 82}

The type of Curie transition in VDF copolymers is usually identified based on the presence or absence of hysteresis on the temperature dependence of one or another parameter sensitive to phase transformations. These parameters are found in the studies of thermal, electric and spectroscopic properties of objects. The NMR method and measurements of ultrasound⁸³ and crystal microhardness⁸⁴ are used more rarely for this purpose. Analysis of the temperature dependences of structural and spectroscopic characteristics of both VDF/TFE and VDF/TrFE containing more than 65 mol.% of VDF shows that temperature hysteresis is always observed in heating–cooling cycles (see Figs. 15, 16, 22). However, for VDF/TrFE copolymers of the compositions 60/40 and 52/48, this hysteresis becomes slightly visible.⁸⁵ This behaviour is typical of a second-order phase transition.

This conclusion was confirmed in another study⁶⁵ using a more appropriate method based on the measurement of non-linear dielectric properties, in particular, second- (ϵ_2) and third-order (ϵ_3) dielectric constants. These characteristics behave in different ways in first- and second-order phase transitions. Figure 23 shows the temperature variation of ϵ_2 and ϵ_3 for 52/48 and 73/27 VDF/TrFE copolymers. It can be seen that these characteristics behave differently for the two copolymers. Indeed, ϵ_2 and ϵ_3 of the 73/27 copolymer remain finite and positive over the whole temperature range up to the Curie point, whereas for 52/48 copolymer, ϵ_2 drops to zero, and ϵ_3 changes its sign at the Curie point. In accordance with relations (20) and (25), the criterion for a second-order phase transition is clearly fulfilled for the 52/48 copolymer (see Fig. 23a,c). Conversely, for the 73/27 composition (and for 65/35, which is not shown in the Figure), the condition for a first-order phase transition is complied with. Thus, the hypothesis that the character of phase transition in

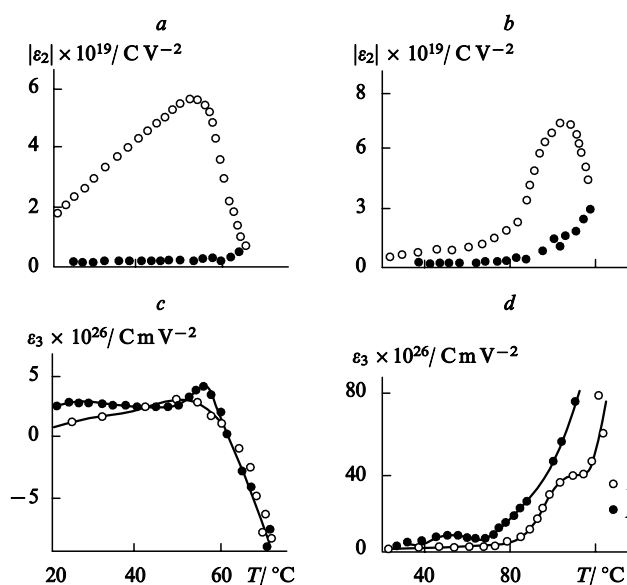


Figure 23. Temperature dependences of the second- and third-order dielectric constants in VDF/TrFE copolymers with compositions 52/48 (a, c), 73/27 (b, d) obtained in the heating (1) and cooling (2) regimes.⁶⁵

VDF/TrFE copolymers changes at a composition of 52/48 (or near it) is confirmed not only by the specific features of the temperature hysteresis.

The VDF/TrFE copolymers are convenient as model compounds for predicting the behaviour of the LT–HT phase boundary. If the copolymer is considered to be ideally statistical, *i.e.* containing no composition fluctuations, the T_C value should be proportional to the concentration of ferroelectric groups in VDF.⁸⁸ This, however, is not confirmed by experiments (see Fig. 17b). This inconsistency can be due to the following reasons. Firstly, the appearance of ferroelectricity in the blocks of TrFE chains cannot be ruled out.^{81,87} Secondly, the real copolymers cannot be regarded as ideally statistical. In fact, VDF/TrFE copolymers (as well as PVDF) contain a certain number of defects caused by the ‘head-to-head’ attachment.^{28,69} In addition, for instance, in VDF/TFE copolymers, about 5% of TFE units occur as dyads even when the TFE proportion is 29 mol.%.⁶⁹

Both reasons can, on the one hand, be responsible for the non-linear course for the LT–HT phase boundary (see Fig. 17b) and, on the other hand, account for the formation of two ferroelectric phase modifications, LT and QL. The question why the Curie point in VDF/TrFE copolymers corresponds to a first-order phase transition for VDF contents of more than 60 mol.% and to a second-order phase transition for lower VDF concentrations has been tackled by Odajima⁸⁷ from the viewpoint of statistical theory. For this purpose, the investigator analysed the dielectric anomalies near the transition, characterised by the inverted dielectric absorption $\Delta\epsilon$. Finite (non-zero) $1/\Delta\epsilon$ values at the Curie point are inconsistent with the classical views [see, for example, relation (18)]. Evidently, this is due to the specific character of crystallisable polymeric systems, namely, to the presence of disordered areas, which are taken into account by using a constant in the theoretical description of the temperature dependence of $1/\Delta\epsilon$ near the Curie transition.⁷⁷ The structural heterogeneity of VDF/TrFE copolymers and the possibility of composition fluctuations in their chains are responsible for the fact that the region of dielectric anomaly covers a fairly broad temperature range; the Curie transition can thus be attributed to diffuse phase transitions.⁸⁷ This is also confirmed by the fact that the Curie points found by DSC and NMR are lower than those found from dielectric measurements.^{89–91}

The types of the phase transition at the Curie point have been predicted using the temperature dependences of the absorbances at two wavelengths (850 and 610 cm^{-1}) in the paraelectric phase of the copolymers considered. The former band corresponds to the bonds in the *trans*-conformation and the latter corresponds to the bonds in the *gauche*-conformation.²⁸ The D_{850}/D_{610} ratio was regarded as being equivalent to the ratio of populations of these states. In the case of the 72/28 VDF/TrFE copolymer, the D_{850}/D_{610} ratio for the paraelectric phase was found to increase on raising the temperature, while for the composition 52/48 it was found to decrease.⁹² If the energies of the *trans*- and *gauche*-isomers are denoted by U_t and U_g , respectively, then for the 72/28 VDF/TrFE,

$$J = U_t - U_g < 0,$$

and for the composition 52/48,

$$J = U_t - U_g > 0.$$

In other words, *gauche*-isomers are found to be more stable in the former copolymer, and *trans*-isomers are more stable in the latter copolymer.

Resorting to these experimental facts, Odajima⁸⁷ developed a statistical theory of ferroelectric transitions in the copolymers in question for two models of pair interactions in the linear lattice formed by bonds in *trans*- and *gauche*-conformations with invoking combinatorial formulae.⁹³ The calculated reduced spontaneous polarisation as a function of reduced temperature in the region of ferroelectric transition is presented in Fig. 24a. Accord-

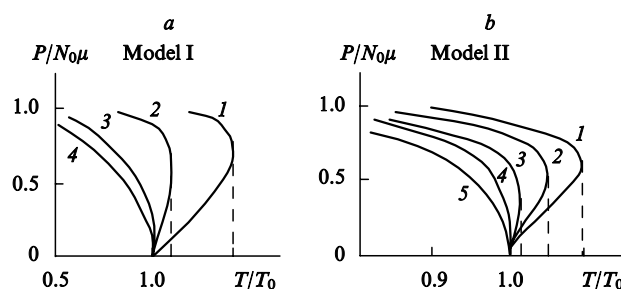


Figure 24. Temperature dependences of the reduced spontaneous polarisation in the region of the Curie transition for two models characterised by the parameter $B = J/kT_0$.⁸⁷

B : -2.0 (1), -1.0 (2), 0 (3), 2.0 (4) (a); -0.3 (1), -0.2 (2), 0 (3), 0.5 (4), 2.0 (5) (b). N_0 is the concentration of dipoles, μ is the dipole moment of the CF_2 group.

ing to both models, a first-order phase transition is manifested only for $J < 0$ because only in this case, do metastable states arise at temperatures $T > T_0$ (T_0 is the characteristic temperature). In the case where $J > 0$, a second-order phase transition occurs and no hysteresis is displayed. The latter situation ($J > 0$) occurs in 52/48 VDF/TrFE, for which almost no temperature hysteresis is observed in the region of transition.⁹²

Thus, the theory developed in the study cited⁸⁷ provides results which coincide qualitatively with experimental data. If a copolymer with a composition of 72/28 has $J < 0$,⁹² then $P \neq 0$ can also be fulfilled at $T > T_C$ (see Fig. 24), *i.e.* prerequisites for temperature hysteresis appear, which is consistent with the data of Table 5. For the 65/35 VDF/TrFE copolymer, hysteresis is also observed but the situation is more complicated. For this copolymer, $J \approx 0$ (see Ref. 92) and temperature hysteresis is possible only in terms of model II (Fig. 24b), which uses more complex combinatorics of bonds in the linear lattice than model I. It remains to be seen whether the calculated character of phase transition in 52/48 VDF/TrFE copolymer coincides with that observed in the experiment. The calculation⁸⁷ was based on the fact that free energy does not depend on lattice parameters. Practically, this could be the case only if the measurements are carried out in the ‘constricted’ state. The majority of experiments are carried out under free conditions under which the sample lattice should deform under the action of polarisation. Thus, the electrostriction effect can influence the free energy and, as a consequence, a second-order phase transition should be transformed into a first-order transition.⁹⁴

The 52/48 VDF/TrFE copolymer has a low Curie point; therefore, it can be used to monitor the influence of an external static field on the position of the Curie point. This task has been accomplished by Date.⁹⁵ The Curie transition was detected in the temperature dependences of the pyroelectric coefficient p_y based on the point where $p_y = 0$. This is exemplified in Fig. 25, which presents the experimental temperature dependences of the pyroelectric coefficient for this copolymer under the action of fields with various polarities. If the external field coincides in direction with the remanent polarisation, it shifts the Curie point to higher temperatures. If the field has the opposite sign, the Curie point shifts to lower temperatures. This shift is linear and has the slope

$$\frac{dT_C}{dE} = \Delta P \frac{T_C}{L}. \quad (27)$$

Here ΔP is the change in the polarisation near the Curie transition and L is the latent heat. By increasing the amplitude of the negative bias field, the Curie point can be appreciably decreased; in this particular copolymer, it can be brought close to room temperature. If the temperature in some region is raised (*e.g.*, by use of a laser), the direction of spontaneous polarisation in this region will be reversed due to the bias field. This enables optical

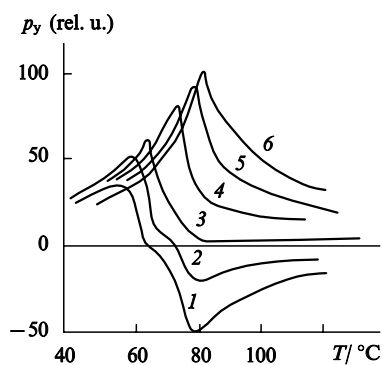


Figure 25. Temperature dependences of the pyroelectric constant in the 52/48 VDF/TrFE copolymer upon the application of electric fields with various strengths.⁹⁵

$E/\text{MV m}^{-1}$: -10 (1), -5 (2), 0 (3), 5 (4), 10 (5), 15 (6).

recording of information with the aid of ferroelectric polymer films, which was actually demonstrated in practice.⁹⁵

For recording, it is important to ensure efficient transfer of a thermal pulse to the ferroelectric matrix. Evidently, this can be attained by introduction into the films of dye molecules with an absorption band in the range of laser radiation. In this respect, studies of the behaviour of dyes carried out by Verkhovskaya *et al.*^{96–98} appear significant. In particular, it was found that doping of 70/30 VDF/TrFE copolymer by merocyanines makes it possible to observe photoelectric sensitivity in the visible and UV regions of the spectrum. Analysis of the fluorescence⁹⁸ and absorption⁹⁶ spectra showed intense interaction of the rhodamine 6G molecule with the ferroelectric phase of the copolymer. The appearance of temperature hysteresis in the region of the Curie transition indicates that it is a first-order phase transition. The so-called structure-chromic effect was established; this means that spectral characteristics of the dye molecules change depending on whether the crystalline phase occurs in the ferroelectric or in the paraelectric state. Thus, the principal band of merocyanines shifts to the blue region and becomes less intense above the Curie point.^{96,97} The optical recording in doped copolymers was performed using the dye spiropyran, which exhibits a photochromic effect. The possibility of observing the photorefractive effect using these systems has been demonstrated.⁹⁷

V. The mechanism of the generation of ferroelectricity based on NMR studies

The nature of ferroelectricity in the polymers in question can be elucidated more precisely on the basis of the molecular dynamics characteristics. Quasielastic neutron scattering is sometimes used for this purpose;⁹⁹ various modifications of NMR are employed more often. VDF/TrFE copolymers with various ratios of the components have served as the objects of NMR studies. For example, copolymer with the composition 70/30 has been studied.¹⁰⁰ The researchers attempted to answer a number of fundamental questions. In particular, they tried to find out whether or not passing from the low-temperature ferroelectric phase to the high-temperature paraelectric phase gives rise to specific mobility. If this mobility does appear, whether it results in a higher symmetry in the disordered phase. The point group of symmetry in this phase, which can vary from $6/mmm$ (centrosymmetrical lattice) to $6/2m$ (non-centrosymmetrical lattice), also presents interest.

The signal of free induction at temperatures above 80 °C can be represented as a superposition of two components.¹⁰¹ One component (for short times t) refers to the ^{19}F nuclei in the crystal and is described by the Gaussian function¹⁰⁰

$$M(t) = \Delta M(0) \exp\left(-\frac{M_{2c} t^2}{2}\right), \quad (28)$$

where M_{2c} is the second moment of the line for the crystalline phase.

The second component is associated with the amorphous phase: at $T > 80$ °C, this component is described by a Lorentzian dependence, typical of viscous liquids. The temperature dependence of the free induction signal from the NMR data can be used to estimate the change in the dynamic degree of crystallinity (in addition to the static degree of crystallinity, which can be estimated, for example, based on X-ray data). Figure 26 shows the temperature dependences of the dynamic degree of crystallinity and the rate of transverse relaxation as well as the DSC curves for 70/30 VDF/TrFE copolymer. In the region of the Curie transition, the dynamic degree of crystallinity markedly changes and hysteresis in the heating and cooling regimes is observed. The temperature plots for the transverse relaxation rate for the crystal also change markedly in the transition region and exhibit a clear-cut hysteresis. The chain dynamics in the amorphous phase also proves to be sensitive to the phase transition because the corresponding line in this region does not vary monotonically, although hysteresis is barely visible in this case.

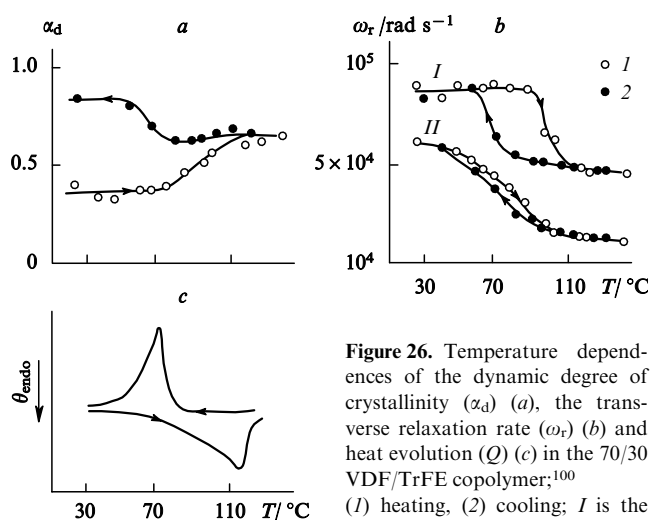


Figure 26. Temperature dependences of the dynamic degree of crystallinity (α_d) (a), the transverse relaxation rate (ω_r) (b) and heat evolution (Q) (c) in the 70/30 VDF/TrFE copolymer;¹⁰⁰ (I) heating, (2) cooling; I is the crystal, II is the amorphous phase.

Thus, the Curie transition in this copolymer is of dynamic origin and can be likened to the plastic phase transitions observed in some low-molecular-mass crystals.¹⁰⁰

By using different modulation frequencies (9.14 and 20 MHz), the researchers separated the contributions of the amorphous and crystalline phases to the spin–lattice relaxation times (T_1). The contribution of the amorphous phase (T_{1a}) varies nearly monotonically exhibiting no hysteresis in the transition region, whereas the contribution of the crystalline phase (T_{1c}) passes through a minimum in this region and exhibits a typical hysteresis in the heating–cooling cycles. Below the Curie point, the absolute values of T_{1a} and T_{1c} differ by more than an order of magnitude, whereas above the Curie point, they differ only by a factor of 2. Thus the parameters characterising the dynamics in the paraelectric phase are similar to those for the disordered phase. The chains forming the paraelectric phase can have several equilibrium positions, which should result in a higher symmetry compared to that in the ferroelectric phase.¹⁰²

The character of the Curie transitions in VDF/TrFE copolymers of various compositions can be judged from the data that are given in Table 6 and include results obtained by the NMR method. It can be seen that the Curie transition temperatures determined by different methods are somewhat different; however, in some cases, the tendency for hysteresis in the cooling and

Table 6. Temperatures T_C (°C) found by various methods for VDF/TrFE copolymers of various compositions in the heating (I) and cooling (II) regimes.^{104, 106}

Com-position	NMR ^a		NMR ^b		DSC		DM ^c	
	I	II	I	II	I	II	I	II
52/48	63	63	65	65	60	62	79	73
65/35	89	70	90	75	70	64	103	69
72/28	116	75	115	79	114	75	134	84

^a Based on the variation of the line width; ^b based on the variation of T_1 ; ^c dielectric method (measurement of $\Delta\epsilon^{-1}$).

heating regimes can be followed. It is confirmed once again that in 52/48 copolymers, a second-order phase transition occurs, which is replaced by a first-order phase transition for higher VDF concentrations.

Ishii and Odajima¹⁰³ used the Ising model^{104, 105} to calculate some parameters of the fluctuation transition, in particular, the effective distance (d) between the fluctuating ordered units connected by short-range forces and the correlation length of the fluctuation region of polarisation (ξ). The d and ξ values were found to be somewhat greater for 52/48 and 65/35 copolymers than for copolymers with other compositions. Apparently, the ferroelectric–paraelectric transformation in these copolymers is better interpreted as a second-order phase transition.

Later, the same researchers studied the molecular dynamics in the region of the Curie transition using a different NMR technique, namely, analysis of the shape of the absorption peaks.^{106–109} Textured films of the copolymers were used as the samples; the angle between the external field and the stretching direction was varied. At room temperature, the absorption line consists of three components, which are interpreted in terms of nonequivalence of the local fields for the fluorine nuclei occurring in the bulk of the ferroelectric phase, at its boundaries, and in the amorphous phase. For 52/48 copolymer, the absorption line at 30 °C contains only two components.^{106, 109} The temperatures of transition to the paraelectric phase, found from the narrowing of the widest component of the signal for various copolymers, are listed in Table 6. These temperatures are very close to the spin–lattice relaxation temperatures (T_1), their variation fitting in the general regularity of hysteresis in these copolymers. In fact, hysteresis is not displayed in the 52/48 copolymer but appears at higher VDF proportions.

Lovinger *et al.*¹¹⁰ used ¹H and ¹⁹F NMR spectroscopy to analyse the molecular dynamics in the VDF/TrFE copolymers containing 10 mol.% to 70 mol.% of VDF. When the composition was 70/30, the ¹H NMR free induction signal in the 15–60 °C temperature range consisted of three components. The narrowest and the medium components were attributed to the motion in the normal and ‘stressed’ amorphous phase, respectively. In the temperature range 60 °C < T < T_C , the medium component becomes more intense; this was interpreted as being due to the ferroelectric–paraelectric transition. The calculation of the second moment ΔH_2^2 for the medium and broad components, which are assigned to the paraelectric and ferroelectric phases, respectively, shows that these phases coexist in a broad temperature range, from 60 to 120 °C. The data on the second moment for the crystals of the paraelectric phase in the 70/30 VDF/TrFE copolymer indicate the possibility of substantial dynamic disorder in this phase. In fact, the ΔH_2^2 value for the rigid lattice of the paraelectric phase calculated based on the X-ray diffraction data should be 11.6 G², while the experimental value is only 2.5 G². This appreciable difference cannot be explained only by the changes in the type of packing in the crystal and in the chain conformations upon the Curie transition. Evidently, vigorous molecular motion, whose type is yet unknown, should be expected in the paraelectric phase. In particular, if the chains in the paraelectric phase are

assumed to rotate about the macromolecule axes, the calculated ΔH_2^2 value decreases to 3.5 G² (see Ref. 110).

The difference in the dynamic degree of crystallinity found from ¹H and ¹⁹F experiments for copolymers with VDF contents not higher than 70 mol.% is attributed to the difference in the compound compositions in the regions with slow and fast dynamics. The difference may be due to the segregation of phases enriched in VDF and TrFE groups; this is not at variance with the conclusion about the existence of two crystalline modifications in these copolymers¹¹¹ or with the conclusion concerning the presence of LT and QL phases. If segregation does occur, it should also influence characteristics of the disordered phase. Indeed, since the glass transition temperatures of PVDF and polytrifluoroethylene (PTrFE) are appreciably different (–40 and +40 °C, respectively), the regions enriched in VDF and TrFE should also be characterised by different glass transition temperatures. This can account for the specific features of the dynamics of these copolymers near 40 °C^{71, 112} and for the data of ultrasonic¹¹³ and NMR studies.¹¹⁴

A fairly unusual conclusion has been drawn¹¹⁴ in a study of copolymers with various previous thermal histories. In particular, samples obtained by quenching and isothermal crystallisation were studied, the perfection and the volume fraction of crystals being higher in the latter case. The Curie point for samples obtained by quenching was found to be higher than that for isothermally crystallised ones. Similar results were obtained by the DSC method.¹¹⁵ The second moment of the absorption line, ΔH_2^2 , scarcely changes above the Curie point.¹¹⁴ The interplanar spacing behaves in a similar way, while the intensities of the absorption bands corresponding to the planar zigzag conformation continue to change in the $T > T_C$ region.^{116, 117} This means that the conformational changes in the vicinity of the Curie transition ‘lag behind’ the changes in the lattice type.

Unlike ΔH_2^2 , the correlation time τ_c is determined by the movement of domain boundaries and, hence, the pattern of its temperature variation near T_C should be symmetrical. In reality, experiments showed slight asymmetry of this dependence.¹¹⁴ Rigamonti¹¹⁸ has attributed this asymmetry to the order–disorder transition.

Comparison of the anomalies in the temperature dependences of spin–lattice relaxation times in an ordinary and in a rotating system of coordinates near the Curie transition¹¹⁴ shows that they resemble most closely the dielectric anomalies considered, for example, by Davis *et al.*¹¹⁹ When comparing the spin–lattice relaxation times in copolymer samples obtained by quenching and isothermal crystallisation above the Curie point, the researchers noted that the samples are more perfect in the former case. This contradicts the known properties of crystallisable polymers. This contradiction can be explained by the presence in the copolymers of two crystalline phases, ferro- and paraelectric phases, which differ in both the lattice parameters and chain conformations. Crystallisation at $T > T_C$ should be accompanied by an increase in the proportion of chains in the helical conformations in the crystal; after cooling the sample to room temperature (*i.e.* below T_C), these chains will be perceived as conformational defects. This may be the reason for the lower Curie temperature observed for these samples. This hypothesis is confirmed by NMR data for samples of the 70/30 VDF/TrFE copolymer annealed above the Curie point.¹²⁰ Local mobility in the ferroelectric crystals was found; this can be attributed to the presence of the conformational defects mentioned above. These defects are ‘weak points’ in the ferroelectric phase (with chains in the planar zigzag conformation) but they can play an important role in the initiation of the Curie transition; specifically, they shift the transition to lower temperatures, which has been observed in a study.¹¹⁴

The chain dynamics in the disordered phase also influence the Curie transition. This phase has been reported¹²⁰ to have high-frequency mobility modes similar to those in the paraelectric phase. The parameters of these modes can also have an influence

on the characteristics of the ferroelectric transition because crystallisable polymers have no clear-cut phase boundaries.

At the crystal boundary, regions with tie-tough chains (TTC) are located, in which the same chains can be incorporated simultaneously in the disordered (in the strict crystallographic sense) phase and in the adjacent crystal. Since the neighbouring monomer units in a chain are linked by covalent bonds, the high-frequency motion modes in the disordered phase should at certain amplitudes generate conformational defects in the ferroelectric phase through the TTC sections. Evidently, this stage precedes the Curie transition. This is confirmed by the correlation between the variation of the interplanar spacing in the ferroelectric phase lattice and the intensity of the absorption band corresponding to the planar zigzag conformation. The change in the packing density of chains in the crystal is, apparently, the main reason for the generation of the high-frequency motion mode because high-frequency motions of the same nature were noted¹²⁰ in the amorphous phase below the Curie point and in the paraelectric crystal.

The views on the chain dynamics in the paraelectric phase have been detailed to a degree by varying the field frequency for resonance at the ¹H and ¹⁹F nuclei and analysing the data on the anisotropy of the second moment for textured samples.¹²¹ The researchers admit that rotation of the chain in the TGTG[−] conformation as a whole, which they proposed previously,¹¹⁰ appears unlikely, because a similar ΔH_2^2 value is found for this type of motion for chains in a planar zigzag conformation.¹²¹ The hypothesis of motion through propagation of kink bonds along the chain was also verified. For example, motion of the flip-flop type (a 180-degree kink) should result in the minimum of ΔH_2^2 being observed at an angle of 45° between the axis of tension and the direction of the magnetic field but this is not confirmed experimentally. This fact together with the fact that the calculated ΔH_2^2 value is several times greater than the experimental one prompted the researchers¹²¹ to conclude that this motion is impossible in the paraelectric phase. Motions as 120- or 60-degree kinks (between three or six symmetrical positions) are more probable because they provide reasonable agreement with experimental results. The possibility of the 'crankshaft' type motion involving three neighbouring bonds was also considered in the study cited.

VI. The influence of pressure on the characteristics of the ferroelectric transition

The mechanism of the formation of ferroelectricity in polymers can be elucidated more precisely by investigating the specific influence of various external factors, in particular, pressure and uniaxial stretching, on the ferroelectric–paraelectric transition parameters. The results of a study,¹²² dealing with the influence of pressure (up to ~1 GPa) on the components of the complex dielectric constant of PVDF and 70/30 VDF/TrFE can be considered as an example. The character of variation of the real dielectric constant ϵ' in the region of transitions upon variation of the external pressure can be followed from the temperature dependences shown in Fig. 27a. It can be seen that the $\epsilon'(T)$ curve for atmospheric pressure has two characteristic points. The low-temperature maximum is attributed to the dielectric anomalies in the vicinity of the Curie transition (T_C) and the inflection at higher temperatures is ascribed to the dynamic melting process (T_m). At higher pressures, both transitions are displaced to higher temperatures. This shift is non-linear (Fig. 27b). If the relative change in the volume ($\Delta V/V_0$) is taken as the variable, the temperature dependences for the Curie transition and for melting become straight lines (Fig. 27c). The slope regularly increases as the transition temperature rises; this also applies to the region of the transition associated with freezing of the micro-Brownian motion in the disordered phase.¹²²

In the case of the 52.8/47.2 VDF/TrFE copolymer, in which, as noted above, the Curie transition is a second-order phase

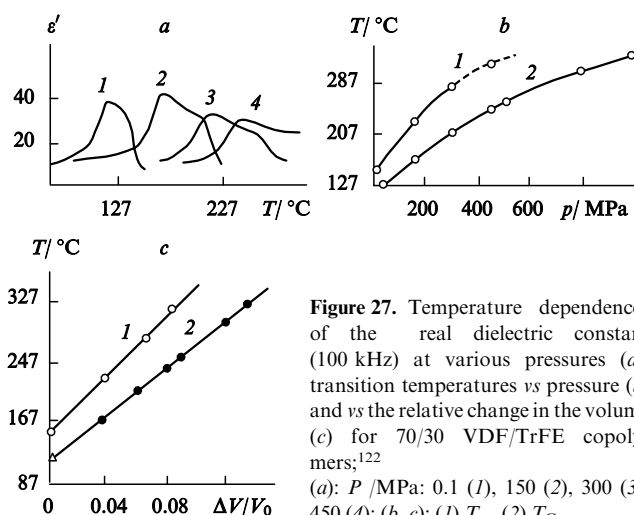


Figure 27. Temperature dependences of the real dielectric constant (100 kHz) at various pressures (a); transition temperatures vs pressure (b) and vs the relative change in the volume (c) for 70/30 VDF/TrFE copolymers;¹²² (a): P /MPa: 0.1 (1), 150 (2), 300 (3), 450 (4); (b, c): (1) T_m , (2) T_C .

transition, an increase in pressure influences the Curie transition temperature in a similar way.⁷³ If the Curie point is characterised by a maximum of ϵ' , the Curie–Weiss equations for this copolymer have the following form:

for $T < T_C$,

$$\frac{1}{\epsilon'} \approx \frac{T_C - T}{C_1}, \quad (29)$$

and for $T > T_C$,

$$\frac{1}{\epsilon'} \approx \frac{T - T_C}{C_2}. \quad (30)$$

The C_1 and C_2 constants for the standard pressure are 123 and 140 °C and $T_C = 67$ °C.

Similar relations have been obtained for the dependence of ϵ' on the pressure p for $p < p_C$,

$$\frac{1}{\epsilon'} \approx \frac{p_C - p}{C_3}, \quad (31)$$

and for $p > p_C$,

$$\frac{1}{\epsilon'} \approx \frac{p - p_C}{C_4}, \quad (32)$$

where $C_3 = 10.8$ GPa, $C_4 = 2.37$ GPa, and $p_C = 134$ MPa at 110 °C.

The displacement of the transition point under the action of external pressure for the copolymer with the 52.8/47.2 composition can be described by the following relation:⁷³

$$T_C = 76 \text{ °C} + 0.314p. \quad (33)$$

When the VDF content in the copolymer is 64.6 mol.%, two equations are needed to describe these dependences due to the hysteresis phenomena:

for heating,

$$T_C = 80 \text{ °C} + 0.383p \quad (34)$$

and for cooling,

$$T_C = 60 \text{ °C} + 0.401p. \quad (35)$$

The influence of pressure on the ferroelectric transition in these two copolymers can be followed from the data presented in Table 7. The experimental coefficients for the displacement of the Curie point as a function of pressure found by dielectric measurements and by the thermal expansion method are in good agreement with one another. The theoretical values of these coefficients were calculated using the Clausius–Clapeyron equation

Table 7. Curie temperatures, experimental and calculated coefficients of the displacement of the Curie temperatures (dT_C/dp /deg MPa), relative volume changes ($\Delta V/V_0$) and enthalpies (ΔH) for VDF/TrFE copolymers.^{73, 123}

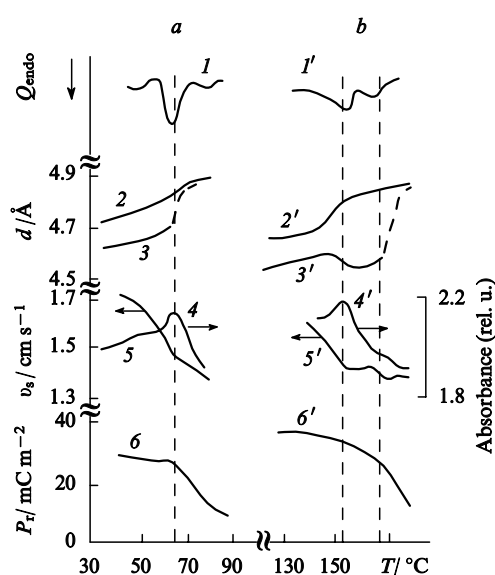
Regime	$T_C / ^\circ\text{C}$	dT_C/dp		$\frac{\Delta V}{V_0} \times 10^2$	$\frac{\Delta H \times 10^{-7}}{\text{J m}^{-3}}$
		experiment	calculation		
Composition 52.8/47.2					
Heating	67	0.314 ^a 0.318 ^b	0.487	1.56	1.09
Composition 64.6/35.4					
Heating	86	0.383 ^a 0.381 ^b	0.206	1.51	2.63
Cooling	60	0.401 ^a 0.394 ^b	0.170	−1.05	−2.06

^a Dielectric measurements; ^b thermal expansion.

$$\frac{dT_C}{dp} = \frac{T_C(\Delta V/V_0)}{\Delta H} \quad (36)$$

It can be seen from the Table that the experimental and theoretical coefficients for the transition displacement can differ by a factor of more than two. Comparison of the presented dT_C/dp values with those for a similar copolymer containing 70 mol.% of VDF shows¹²² that the previous thermal history of samples can affect substantially the pattern of the influence of pressure on the transition considered.

The effect of pressure on the 54/46 VDF/TrFE copolymer has been studied.^{124, 125} This was done using a set of methods including DSC, X-ray diffraction, $D-E$ hysteresis, and ultrasonic studies. The temperature dependences of a number of parameters determined by these methods are shown in Fig. 28. It can be seen that at a pressure of 350 MPa the Curie transition becomes a two-stage process. In fact, according to DSC, two endotherms appear instead of one. The interplanar spacings for the 110 and 200 reflections also change in two stages. Two characteristic points are present in the temperature dependences

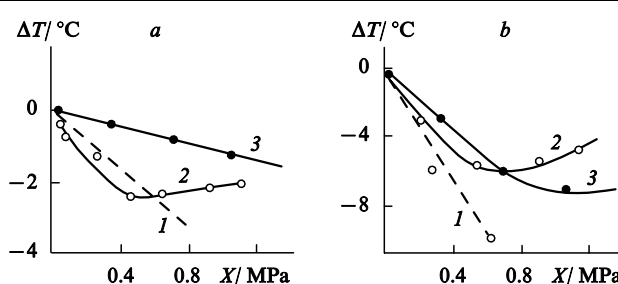
**Figure 28.** Temperature dependences of heat evolution (I , I'), interplanar spacing (2 , $2'$, 3 , $3'$), absorbance (4 , $4'$), sound velocity (5 , $5'$) and remanent polarisation (6 , $6'$) at a pressure of 0.1 (a) and 350 MPa (b) for the 54/46 VDF/TrFE copolymer.¹²⁴

of the absorbance, the sound velocity and the remanent polarisation.

This unusual phenomenon can be interpreted based on the above hypothesis concerning the formation of two types of ferroelectric phase, LT and QL, in the copolymers considered.^{124, 126} It is assumed that under normal pressure, crystallisation proceeds in the QL phase, whereas at the Curie point, the QL phase transforms in one step into the paraelectric phase. As the pressure increases to 350 MPa at room temperature, the QL ferroelectric phase transforms into a more perfect phase, LT. This can be judged from the decrease in the interplanar spacings for the 110 and 200 reflections (see Fig. 28, curves 2, 2' and 3, 3'). Heating under increased pressure is accompanied by transformation of the LT phase into the less perfect QL phase, which is subsequently transformed into the paraelectric phase. This scheme is consistent with a two-stage mechanism of the Curie transition, which is confirmed experimentally.

The influence of mechanical loading on the characteristics of the ferroelectric transition will be considered separately. Studies have been performed with textured films of VDF/TrFE copolymers to which mechanical stress X has been applied along¹²⁵ or across¹²⁷ the axis of tension. The Curie transition was monitored based on the characteristics of thermal shrinkage on heating (cooling) of uniaxially stretched films. It was found that the relative decrease in the size of the film (x) is most pronounced near the Curie transition. This characteristic temperature range was found to be well correlated with the range of specific changes in the structural parameters determined by X-ray diffraction and IR spectroscopy.¹²⁶

Figure 29 presents the displacement of the Curie point as a function of external stress. These plots allow one to follow the shift of the Curie transition. (The negative ΔT values imply displacement of T_C to lower temperatures). It can be seen that slight stress both along and across the axis of tension shifts the transition in both the heating and cooling regimes to lower temperatures. Thus, the shifts in the Curie temperature induced in the copolymers studied by an increase in the external stress are opposite to the pressure-induced shifts.

**Figure 29.** Influence of the external mechanical stress in isotropic (I) and uniaxially stretched (2 , 3) films of the 65/35 VDF/TrFE copolymer on the displacement of the Curie point during cooling (a) and heating (b).¹²⁷ The stress was applied along (2) and across (3) the stretching axis.

If we assume that the free energies of the ferroelectric (LT) and paraelectric (HT) phases are equal at the Curie point, then the shift of the Curie point caused by transverse stress X is described by the equation¹²⁷

$$\frac{dT_C}{dX} = -\frac{k' \Delta x_C}{\Delta S} \quad (37)$$

where k' is a constant, Δx_C is the change in the transverse dimension of the crystallite at the transition point, and ΔS is the difference between the entropies of the LT and HT phases. The sign of dT_C/dX in relation (37) is determined only by the sign of the constant k' . The negative sign is mainly due to high Poisson coefficient ($\mu_P = 4.5$), which is typical of textured crystallisable polymers.

It is very important to find out whether characteristics of the amorphous phase remain invariate during mechanical loading in the above experiments. Unfortunately, this point has been considered only in passing,^{125, 127, 128} although it deserves more comprehensive study. In fact, it has been found^{28, 129, 130} that loading of textured films of crystallisable polymers may bring about complex conformational transitions in amorphous regions (especially in those adjacent to the crystal).

This is confirmed by a study¹³¹ dealing with the variation of the longitudinal velocity of sound v_s and birefringence upon loading along the axis of tension of textured films of VDF/TFE. The increase in these values (for films with relatively low texturing temperatures T_d) points to conformational rearrangements, $TGTG^- \rightarrow (TT)_n$ and $T_3GT_3G^- \rightarrow (TT)_n$, for chain sections in disordered regions, which are highly pliable. The probability of these rearrangements depends substantially on the temperature of texturing (uniaxial stretching), which influences the number of conformational defects. Indeed, in the case of high T_d , the v_s and birefringence values change only slightly. The data of low-angle X-ray scattering indicate that the structure formed at these T_d is characterised by a greater difference between the densities (in the draw direction) of the crystal and the amorphous phase.^{131, 132}

External mechanical stress should apparently influence yet another ferroelectric characteristic of textured films — the time of polarisation switching τ_s in an electric field. For uniaxially stretched films, it would be pertinent to consider the influence of mechanical stress in the film plane applied at an angle normal to the axis of tension. This problem was solved in terms of the 60-degree switching model, according to which the nuclei of the new (switched) phase are formed at the crystal–amorphous phase boundary.¹³³ This model was substantiated by experimental facts pointing to a special role of the boundaries between the crystal and the amorphous phase and the TTC sections in them, which can act as the nuclei for new domains. Proceeding from this model, Jishi¹³⁴ considered the influence of the external stress X on τ_s with allowance for the Gaussian shape of stress distribution at the crystal–amorphous phase interface. By specifying particular values for the characteristic effective stress found from the experimental plots for the piezoelectric constant d_{32} vs mechanical stress,¹³⁵ the researcher cited showed that τ_s should diminish substantially under the action of stress. For example, at room temperature, the mechanical stress $X = 12$ MPa for a field with a strength of 200 MV m^{-1} should decrease τ_s by more than three orders of magnitude.¹³⁴ Unfortunately, this was not confirmed experimentally.

The role of pressure in the switching processes has been studied experimentally.¹³⁶ Figure 30 shows the characteristics of the switching process in PVDF with the ferroelectric β -phase as a function of the applied pressure. It can be seen that an increase in pressure increases the average switching time (τ_s) and regularly decreases the maximum current (Fig. 30a). The full transpolarisation charge, found by integrating the experimental curves, changes almost linearly starting from 200–300 MPa (Fig. 30b). The maximum current and τ_s vary nonlinearly as functions of pressure. To interpret the data obtained, the changes in the volume of the films with various degrees of crystallinity have been studied. This made it possible to estimate the compressibility of the crystalline and amorphous phases in a bulk sample.

The crystal was found to be the least compressible and the disordered phase was the most compressible; the real bulk specimen was found to have a medium compressibility. Since τ_s increases with pressure (when the specific volume decreases), it was assumed that the switching time should depend on the fraction of free volume f . This relationship can be described by an equation of the type of the Doolittle equation,¹³⁷ which is often used when studying the relaxation processes in polymers

$$\tau \approx \exp\left(\frac{1}{f}\right). \quad (38)$$

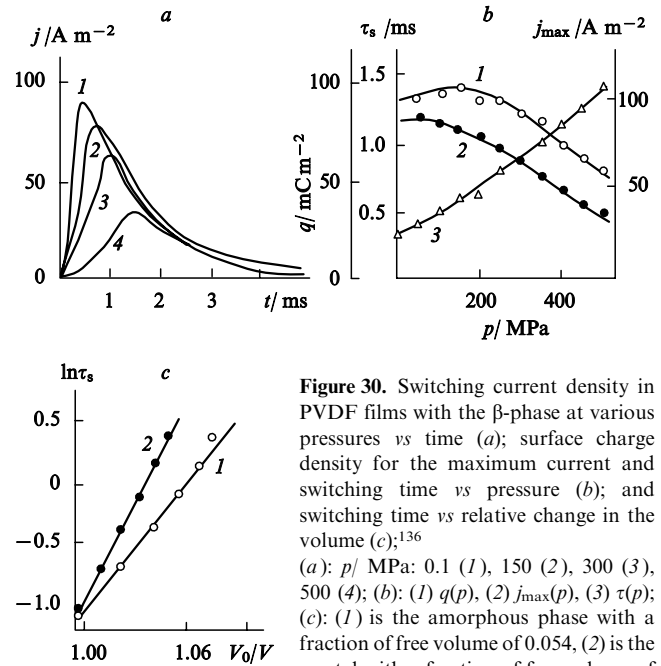


Figure 30. Switching current density in PVDF films with the β -phase at various pressures vs time (a); surface charge density for the maximum current and switching time vs pressure (b); and switching time vs relative change in the volume (c).¹³⁶ (a): p /MPa: 0.1 (1), 150 (2), 300 (3), 500 (4); (b): (1) $q(p)$, (2) $j_{\text{max}}(p)$, (3) $\tau(p)$; (c): (1) is the amorphous phase with a fraction of free volume of 0.054, (2) is the crystal with a fraction of free volume of 0.034.

The f value is expressed via the relative change of the volume¹³⁶

$$f(p) = \frac{f_0 V(p)}{V_0}, \quad (39)$$

where f_0 is the relative free volume at atmospheric pressure and room temperature, i.e. when $V(p) = V_0$. It follows from relations (38) and (39) that

$$\ln \tau(p) = \frac{A + V_0}{f_0}. \quad (40)$$

If this concept is valid, the variation of $\tau(p)$ as a function of $V_0/V(p)$ should follow a linear pattern in semilogarithmic coordinates (Fig. 30c). The slope of the plots for $\ln \tau_s$ vs V_0/V determines the f_0 value. The f_0 values were calculated for both the crystalline and amorphous phases based on the data on compressibility of samples with various crystallinity degrees. It was found that for the amorphous phase, $f_0 = 0.054$, which is close to the values 0.05–0.07, typical of standard amorphous polymers.¹³⁸

Thus, experimental plots for the switching time vs pressure imply that the state of the amorphous phase plays a very important role in the mechanism of polarisation switching in crystallites. This is consistent with the above-stated hypothesis that nuclei of new domains can arise in the amorphous phase (or at its boundary with the crystal), TTC sections playing a special role. Evidently, the dynamic characteristics of TTC should be the first to be taken into account, which is confirmed by the parameters of switching in samples with various previous thermal history and in samples exposed to γ -rays.¹³⁶

VII. The influence of the structural features of polymers on their ferroelectric characteristics

As the crystalline phase becomes more perfect, the ferroelectric parameters in crystallisable polymers are improved. An original method for decreasing the imperfection of the crystal lattice has been found.¹³⁹ A deuterated PVDF sample with the crystals of the β -phase was compared with a similar non-deuterated sample. The degree of perfection of the crystal lattice was estimated indirectly relying on the parameters of the D – E hysteresis dependences, obtained under the same poling conditions. For the non-deuterated sample (field strength $> 200 \text{ MV m}^{-1}$), the remanent

polarisation was 56 mC m^{-2} , which is consistent with the results of other researchers. The P_r value for the deuterated film proved to be almost twice as great ($\sim 100 \text{ mC m}^{-2}$), which was explained by a more perfect structure of the ordered regions. The reasons for this phenomenon are still not entirely clear, because a mere increase in the degree of crystallinity α could cause a similar increase in P_r .

The influence of the parameter α on P_r has been specially studied for 80/20 VDF/TFE samples with different previous thermal histories.¹⁴⁰ Three modes of crystallisation from the melt were considered, namely: quenching, crystallisation at 120°C and a pressure of 0.1 MPa , and crystallisation at 250°C and a pressure of 500 MPa . The melting points T_m were estimated from DSC data, and the degrees of crystallinity α were calculated from the density (Table 8). The α values varied from 43% to 80%. An increase in α was accompanied by an increase in not only the melting point but also the piezoelectric constant e (upon poling for 30 min in a field of 20 MV m^{-1}). The electrostriction constant k changed especially sharply (by an order of magnitude). The changes in the dielectric constant ϵ' confirmed the character of the variation of α (the crystalline phase has lower ϵ').

Table 8. Physical properties of the 80/20 VDF/TFE copolymer samples crystallised under various conditions.¹⁴⁰

ϵ' (10 Hz)	k (10 Hz)	$e \times 10^{-3}/\text{C m}^{-2}$	$T_m/^\circ\text{C}$	α (%)
10.3	-0.2	3.7	128	43
9.5	-1.0	4.6	140	60
7.6	-2.0	10.2	142	80

Figure 31a shows the curves for the polarisation current in the samples studied. It can be seen that, as α increases, the curve narrows down and shifts to lower fields. This points to a decrease in the coercive field. These curves were used to calculate the remanent polarisation. Both values are presented as functions of the degree of crystallinity in Fig. 31b. It can be seen that the plots are linear but variations of the two values are antiparallel; as α increases, P_r increases and E_c decreases. The former finding appears quite natural if ferroelectric properties are considered to originate from the crystalline phase. By extrapolating $P_r(\alpha)$ to $\alpha = 1$, one can find the P_r value for the crystals. It is equal to 84 mC m^{-2} . The relationship between P_r and the spontaneous polarisation P_s for isotropic samples can be represented as^{140, 141}

$$P_r = P_s[1 - \langle \cos^2\theta \rangle], \quad (41)$$

where θ is the angle between the field direction and the chain axis. In this particular case, $\langle \cos^2\theta \rangle = 1/3$; hence, the P_s value for the crystal is 126 mC m^{-2} . This is close to the value (140 mC m^{-2}) calculated from the relation¹⁴⁰

$$P_s = \left(\frac{\epsilon + 2}{3} \right) \langle \mu \rangle N \alpha F, \quad (42)$$

where $\epsilon = 3$ is the dielectric constant of the crystal, $\langle \mu \rangle = 2.1 \text{ D}$ is the dipole moment of the CF_2 group, $N = 1.4 \times 10^{28} \text{ m}^{-3}$ is the concentration of dipoles calculated based on the lattice parameters, $F = 0.9$ is the fraction of bonds formed in the normal ('head-to-tail'²⁸) fashion.

The decrease in the coercive field with an increase in the degree of crystallinity can be accounted for qualitatively by the high dielectric constant of the amorphous phase. This diminishes the field which really acts on the crystals, if they are assumed to be immersed into a disordered phase matrix. As the degree of crystallinity increases, the matrix should be reversed; thus, the crystals become located in an external field, which decreases the observed E_c .

A relationship has been found between the E_c value and some characteristics of the morphology of crystals of the ferroelectric phase.¹⁴⁰ It was found by scanning electron microscopy that in samples crystallised at 500 MPa , $150\text{--}250\text{-nm}$ thick lamellae, typical of extended-chain crystals (ECC), are formed. The low-angle X-ray scattering technique showed that the values for the long period L are also correlated with the α values; for samples with $\alpha = 0.43$ and 0.60 , the L values are $8\text{--}12$ and 30 nm , respectively. The variation of E_c as a function of $1/L$ was found to be linear (Fig. 31c); therefore, the magnitude of the coercive field for a hypothetical sample with an infinitely thick lamella can be calculated. This correlation can also be helpful in elucidating the role of specific defects of polymeric crystal folds in the mechanism of generation of ferroelectricity. It is assumed that the proportion of the folded areas in the crystal decreases as the large period increases; this creates more favourable conditions for the rearrangement of the dipole structure under the influence of an external field. This assumption is substantiated because near folds, the directions of the bond dipole moments vary continuously. This fact, together with the fact that specific defects of the 'entanglement' type can arise in these regions, hamper cooperative rearrangements in an electric field.

The dependence of the remanent polarisation on the volume fraction of crystals and the details of morphology can be followed by examining the data on the influence of annealing on the structural and ferroelectric characteristics of PVDF films.^{142, 143} For this purpose, uniaxially stretched films were used in which crystals occurred in the ferroelectric β -phase. The annealing was carried out under isometric conditions in order to prevent film shrinkage and crystal disorientation. Annealing at a temperature above 100°C causes substantial changes in the crystal structure. The decrease in the half-width ($\beta_{0.5}$) of the principal intermolecular reflections of the β -phase, 200 and 110, indicates a substantial increase in the transverse dimension of the crystal and/or its perfection. The shift of these reflections to greater angles points to an increased density of packing of the chains in the crystal. The remanent polarisation virtually does not depend on the above structural parameters because it does not change up to $T_0 = 160^\circ\text{C}$. A sharp increase in P_r (from 56 to 85 mC m^{-2}) is observed only upon annealing in the temperature range $170\text{--}180^\circ\text{C}$, i.e. in the range of pre-melting of the PVDF crystals. The appreciable increase in P_r observed under these conditions can be attributed to an increase in the degree of crystallinity (from 45 to 68%).¹⁴² Unfortunately, this has not been verified by direct methods. It can only be noted that the observed increase in P_r does not contradict the hypothesis¹⁴⁰ concerning the role of crystal folds. In fact, high-temperature annealing should be accompanied by melting of small (imperfect)

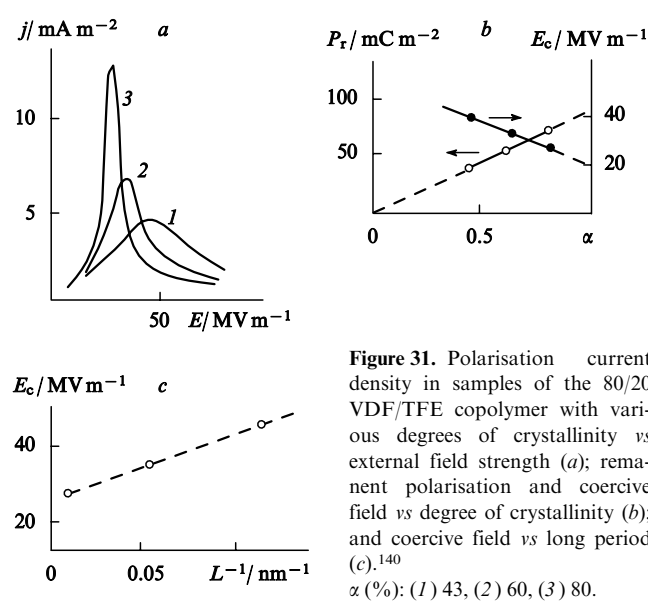


Figure 31. Polarisation current density in samples of the 80/20 VDF/TFE copolymer with various degrees of crystallinity vs external field strength (a); remanent polarisation and coercive field vs degree of crystallinity (b); and coercive field vs long period (c).¹⁴⁰ α (%): (1) 43, (2) 60, (3) 80.

crystals. Since annealing proceeds under conditions of external stress, recrystallisation processes can be accompanied by the formation of new crystals including extended-chain crystals, *i.e.* the concentration of specific defects of lamellar crystal folds can diminish, which is favourable for the P_r values.

The increase in the perfection of the crystal structure upon annealing at 100–160 °C, established by the X-ray diffraction method,¹⁴² does not influence the P_r value but limits the dynamics of the polarisation switching process. Thus the time of switching τ_s at –20 °C (in a field of 200 MV m^{–1}) amounts to 67.0 μ s for the initial sample and becomes 52.4 or 41.3 μ s after annealing at 120 or 160 °C, respectively.¹⁴³ A more detailed analysis shows that better packing of chains in the crystal results mainly in an increase in the rate of growth of the domain boundaries.¹⁴³

One of the approaches used to modify the polymer structure and molecular dynamics is plasticisation of polymers.^{144–146} In the case of crystallisable polymers, the introduced plasticiser (low-molecular-mass compound) is accumulated in amorphous regions, *i.e.* in sites characterised by an increased fraction of the free volume and decreased intermolecular interaction. It is of interest to follow the role of a plasticiser in the variation of the ferroelectricity characteristics. Tricresyl phosphate (TCP) was used as the plasticiser; it was introduced into a finished PVDF film at 130 °C in an amount of 5.5 mass % (see Ref. 145) or 1 mass % (see Ref. 146). The former study was devoted to the influence of the plasticiser on the field-induced $\alpha \rightarrow \beta$ transformation in isotropic PVDF films crystallised in a nonpolar α -phase.²⁸ The proportion of the polar β -modification arising was found to be much higher in the plasticised films under the same poling conditions.¹⁴⁵ The variation of the chain packing density in the ferroelectric phase was followed in relation to textured films with the β -phase oriented after treatment in a strong field. Comparison of the data on plasticised and non-plasticised films showed that in the former case, the polarisation-induced shifts of the principal intermolecular reflections, 200 and 110, of the β -phase to higher angles proved to be greater than those for the non-plasticised film. This was unambiguously attributed to the presence of the plasticiser because an increase in its concentration caused a regular shift of this reflection.¹⁴⁵

The effect of the same plasticiser on the remanent polarisation has been studied using characteristics of D – E hysteresis and thermodepolarisation currents. Even upon slight doping of PVDF films (the TCP content was 1 mass %), an increase in P_r was noted. This influence was more pronounced at low polarisation fields; at 60 mV m^{–1} and 20 °C, the addition of TCP resulted in an increase in P_r from 1 to 6 mC m^{–2}. The role of the plasticiser at high fields is less significant: at 200 MV m^{–1}, the P_r value increases upon doping from 57 to 66 mC m^{–2}.¹⁴⁶ These data demonstrate that the disordered phase plays a special role in the mechanism of formation of ferroelectricity in PVDF. The plasticiser most probably affects characteristics of the chain dynamics in the amorphous phase, especially at the boundaries with the crystals. The weakening of the interchain interaction in the sections with TTC should enhance the micro-Brownian mobility of chain segments. In this case, the crystal growth can be completed by some of the chains from the disordered phase; this must occur by an epitaxial mechanism. The increase in the proportion of the crystalline phase results in higher P_r values.

When considering the important role of the degree of crystallinity in the formation of ferroelectric characteristics of PVDF and VDF copolymers, one should not ignore other, equally significant, structural factors. When P_s remains constant, P_r can increase due to variation of $\langle \cos^2\theta \rangle$ [see relation (41)]. An increase in P_s can formally be attained by texturing an isotropic sample ($\langle \cos^2\theta \rangle = 1/3$) by uniaxial or biaxial stretching. According to X-ray diffraction data, the axes of macromolecules are arranged predominantly along the axis of tension within the plane of the film. The field is always directed at a right angle to the film plane, which implies a decrease in $\langle \cos^2\theta \rangle$ and an increase in P_r .

The validity of the foregoing is confirmed, for example, by comparing the characteristics of the D – E hysteresis in isotropic and textured films of VDF/TFE and VDF/TrFE copolymers, which always crystallise from the melt as the ferroelectric β -phase. The transition from the isotropic state to the textured state should be accompanied only by variation of the θ angle and should not be complicated by polymorphic transitions of the $\alpha \rightarrow \beta$ type as in the homopolymer.²⁸ This idea was verified for 94/6³² and 71/29 VDF/TFE.²⁸ It was found that the texturing process is really accompanied by an increase in P_r and also by a decrease in the coercive field.²⁸ The parameters of the D – E hysteresis in the films of VDF/TrFE copolymers with compositions 52/48, 65/35 and 73/27 have been compared.¹⁴⁷ The films were obtained by extrusion followed by rolling. The extruded films are characterised by slight crystal orientation; therefore, $\langle \cos^2\theta \rangle$ for these films would be close to that for isotropic samples. Rolling of the films between rolls is equivalent to a sort of uniaxial or biaxial stretching and brings about a clear-cut texture, which should substantially change the $\langle \cos^2\theta \rangle$ value. The ferroelectric characteristics of these films are listed in Table 9.

Table 9. Remanent polarisation, coercive field and piezoelectric constant e_{31} in rolled (I) and extruded (II) films of VDF/TrFE copolymers with a crystalline phase fraction of 41%.¹⁴⁷

Compo- sition	P_r /mC m ^{–2} (see ^a)		E_c /MV m ^{–1}		P_r /mC m ^{–2} (see ^b)		e_{31} /mC m ^{–2} (see ^b)	
	I	II	I	II	I	II	I	II
52/48	76	57	32	36	102	66	51	25
65/35	44	81	39	47	—	—	—	—
73/24	25	62	34	43	—	—	—	—

Note. The P_r and E_c values were found from characteristics of the D – E hysteresis.

^a Poling in the corona discharge at room temperature.

^b Contact poling at elevated temperatures.

It can be seen that the behaviour of the 52/48 copolymer is qualitatively similar to that of VDF/TFE copolymers, *i.e.* rolling results in higher P_r values and somewhat lower coercive fields compared to those before rolling. This is manifested especially clearly in the case of films prepared by contact poling at elevated temperatures, for which P_r (and, consequently, e_{31}) differ by a factor of ~ 2 . The data obtained for copolymers with higher VDF contents are contradictory; on passing from an extruded film to a rolled film, E_c changes as in the previous case but the variation of P_r shows an abnormal pattern. Unfortunately, the researchers cited¹⁴⁷ offer no explanation for this finding. This abnormal variation is surprising because the influence of the degree of crystallinity on P_r should not work in this case (the samples had equal proportions of the crystalline phase).

The relationship between the type of texture in the materials in question and the parameters of ferroelectricity has not been adequately studied. This can be illustrated, for example, by the data on D – E hysteresis of biaxially and uniaxially stretched PVDF films.¹⁴⁸ The former film contained crystals of both polar (β) and nonpolar (α) phases and the latter film contained only crystals of the ferroelectric phase. An increase in the number of cycles of D – E hysteresis for the former film was accompanied by an increase in both P_r and P_s , which is observed most frequently for polarisation of PVDF films. This can be caused to some extent by field-induced polymorphic transformations of the $\alpha \rightarrow \alpha_p$ and $\alpha \rightarrow \beta$ types.²⁸ The P_r and P_s values of the latter film decreased as the number of polarisation cycles increased. This finding was explained¹⁴⁸ by the somewhat speculative assumption that the field induces additional crystallisation of chains of the amorphous phase and this changes the ratio of the characteristic sizes of crystals and, hence, also changes the depolarisation factor.

The previous thermal history of texturing is a very important circumstance influencing the ferroelectric characteristics.¹⁴⁹ An increase in the temperature of uniaxial stretching is accompanied by a regular increase in the large period. The interlamellar layers are packed less densely due to a higher content of defective conformations, TGTG[−] and T₃GT₃G[−].^{28, 131, 149} The remanent polarisation in these films is several times lower.³³ The important role of the amorphous phase in the generation of ferroelectricity in VDF/TrFE copolymers has been pointed out in a series of studies,^{150–153} in which the Curie transition has been studied by Brillouin^{150, 151} and non-coherent neutron scattering.¹⁵² The attention is focussed on the dynamics of chains in this phase because near the Curie transition, the cooperative mobility with great amplitudes is characterised by reorientation frequencies of more than 10⁵ Hz.^{28, 153} It has been shown in relation to the 65/35 VDF/TrFE copolymers¹⁵⁴ that it is in oriented films that the parameters of several reflections of the ferroelectric crystals change markedly in the switching processes, whereas no changes are observed in isotropic films. Orientation is known to increase substantially the probability of formation of TTC.¹⁵⁵ The dynamics of the latter should be characterised by low relaxation times. As a consequence, the response of polar segments in such chains to an external electric field should initiate switching of the dipole moments of domains in the crystal. Therefore, the microstructure of the amorphous regions, especially at the boundaries with the crystal, should be taken into account in the mechanism of formation of ferroelectricity.

Identification of defects in ferroelectric crystals and elucidation of their influence on the ferroelectric characteristics of the polymers studied is an important problem. Some of the defects are entirely due to the character of macromolecules and generally cannot be eliminated. These defects can be represented, for example, by chain ends, which are located inside the crystal, and folds, typical of lamellar crystals of polymers. Some features of polymerisation of the compounds in question account for the appearance of the chemical defect caused by the 'head-to-head' attachment, which can be incorporated in the crystal bulk.²⁸ For crystals of the nonpolar α -phase, specific defects are also possible, consisting in different arrangements of chains in the lattice according to the 'up' and 'down' type.²⁸ In the interchain interactions, this can result in conformational rearrangements according to the TGTG[−] → GTG[−]T pattern. When the temperature increases, the equilibrium between these isomers shifts and, hence, the ordered phase passes into the 'condis' crystal state.¹⁵⁶ This transition is detected in the 47–77 °C range as a weak endothermic peak (with an enthalpy of 150–200 J mol^{−1}) in the heating cycle in DSC experiments.¹⁵⁶ This type of interaction is believed to be also responsible for dielectric relaxation,²⁸ which occurs in the crystalline phase of PVDF with α -modification.¹⁵⁷ At higher temperatures, this type of defect initiates conformational transitions of the TGTG[−] → T₃GT₃G[−] type and promotes the high-temperature α → γ phase transition.^{28, 158, 159} On exposure to strong electric fields of PVDF films crystallised as the α -phase, several new reflections were found,¹⁶⁰ which could not be assigned to any of the known polymorphic modifications (α , β , γ or α_p).²⁸ The appearance of a new superlattice for a conformationally non-commensurate form of PVDF is attributed to the interaction of the field with conformational defects of the type considered above.¹⁶⁰

Some details of the ferroelectric–paraelectric transition can be followed by comparing X-ray and spectroscopy data. In the case of oriented PVDF crystallised as the ferroelectric β -phase, the appearance of an additional blurred reflection near the identified 001 reflection is interpreted as being due to the conformational defect of the kink-bond type,¹⁶¹ i.e. local bonds in the TGTG[−] conformation appear in the crystal, while the majority of chains occur in the planar zigzag conformation.¹⁶² Defects of this type can be found in both VDF/TFE^{131, 163, 164} and VDF/TrFE copolymers.⁶⁷ These defects can be especially significant for the Curie transition, which is really confirmed by the temperature

Table 10. Values of the long period L , the transverse dimension of the crystal l_c , the size of amorphous layers l_a and the degree of crystallinity α for 70/30 VDF/TrFE films at various temperatures.¹⁶⁵

$T/^\circ\text{C}$	L/nm	l_c/nm	l_a/nm	$\alpha(\%)$
115	26.9	13.4	13.5	50
117	27.2	13.7	13.3	51
120	27.2	14.4	12.8	53
125	29.0	16.0	13.0	55
130	31.0	18.0	13.0	58
135	35.0	20.0	15.0	58

dependences shown in Fig. 16 and in Table 10. It can be seen that the transverse dimension of the crystal l_c remains virtually unchanged up to a temperature of 120 °C. However, the decrease in the concentration of bonds occurring in the *trans*-conformation starts well before 120 °C.

Thus, the lattice rearrangement at the Curie point ($\sim 120^\circ\text{C}$) is preceded by smooth accumulation of conformational defects, which occurs most likely as a thermally induced fluctuation process. The smooth changes in the microhardness of this copolymer can be due to the same process.¹⁶⁵ The rearrangement of the polar phase lattice into the lattice of the nonpolar phase might take place at a certain critical concentration of kink bonds (conformational defects) in the ferroelectric crystal. Above the Curie point, the crystals of the paraelectric phase start to grow noticeably and, simultaneously, the degree of crystallinity increases (see Table 10). The latter is due to the fact that some chains of the disordered phase are incorporated in the crystal by the mechanism of diffusion movement of defective bonds, which are laid on the surface of a new crystal. This process is expected to be facilitated by the similarity of the conformations in the amorphous phase and in the paraelectric crystal.

The 'memory' effects have been studied in relation to the 75/25 VDF/TrFE copolymer in the vicinity of the Curie transition.^{166–168} Analysis of the plots presented in Fig. 32 helps us to understand the essence of this effect. It can be seen that the ferroelectric phase (the reflection on the side of greater angles) and the paraelectric phase (the reflection on the side of smaller angles) coexist near the Curie point.

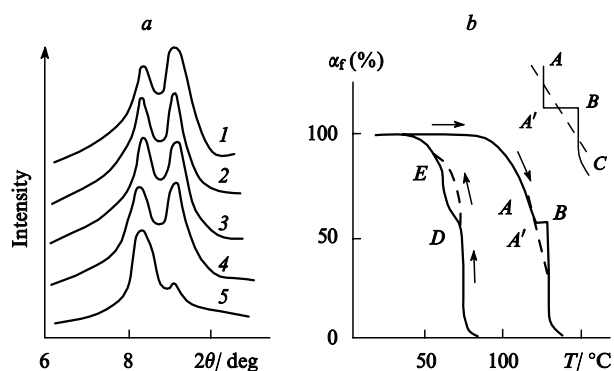


Figure 32. Character of the variation of the diffraction maxima in the vicinity of the Curie transition (a) and temperature dependences of the degree of the ferroelectric transition (α_f) (b) in 75/25 VDF/TrFE films.¹⁶⁸ $T/^\circ\text{C}$: (1) 120 (point A), (2) 120 (point A'), (3) 123, (4) 126, (5) 129.

Isotropic films prepared by quenching from the melt were studied. The rate of heating in the experiment was 2 K min^{−1}, the isothermal maintenance at each point was 30 min, and the maintenance at 120 °C (annealing) was carried out for 19 h and after that, the X-ray diffraction patterns were recorded. The annealing was accompanied by a marked decrease in the intensity of the reflection for the ferroelectric phase (see Fig. 32a). The

fraction of the ferroelectric phase remaining near the transition can be estimated from the intensity ratio of the two reflections (Fig. 32b). The change in the content of the ferroelectric phase upon annealing is marked by points *A* and *A'*. It can be seen that prolonged storage at 120 °C is accompanied by a change in the shape of the phase diagram curve; point *A* passes into *A'* instead of the movement along the trajectory shown by the dashed line. The subsequent temperature variation does not change the fraction of the ferroelectric phase (*A'B* section). Only at point *C*, is the character of the phase diagram restored. When the curve is recorded in the cooling regime, in addition to the hysteresis noted previously, the shape of the curve changes at point *D* (which corresponds to point *A'* regarding the phase ratio). The initial shape is restored at point *E*, reflecting the 'memory' effect in the system. Similar effects are also observed in inorganic ferroelectrics with incommensurate crystal structures; they are explained by interaction of mobile defects with the domain walls.¹⁶⁹

In the case of the polymer systems considered here, the incommensurability is determined by different chain conformations in the two phases; therefore, there are prerequisites for the memory effect. Judging by sections *AA'* and *BC* of the phase diagram, some relaxation processes occur in the crystalline phase and ensure transition of the system into an equilibrium state. These processes (which are described, in all probability, by an exponential law¹⁶⁸) might also be responsible for the unusual influence of the heating rate on the temperature of the Curie transition in VDF/TrFE copolymers.^{170, 171} The presence of these processes is confirmed by the study of the longitudinal acoustic mode (LAM), discovered in the crystals of VDF/TrFE copolymers in the frequency region of 10–20 cm⁻¹ (see Ref. 172). The characteristics of the LAM show that, as the proportion of TrFE in its copolymers with VDF increases, the libration frequency in the ferroelectric crystal decreases virtually linearly as a function of the average interchain distance.

The LAM bands for the copolymers considered here are poorly observable compared, for example, to those for polyethylene (PE).¹⁷³ This was attributed to the low degree of orientation in the copolymers, where the draw ratio was only 4, whereas in PE it reached 20. The poor orientation accounts for a broad distribution of the lamellae over thicknesses, resulting in appreciably broadened LAM bands.

The LAM characteristics were used to determine the sound velocity and the elastic constant c_{33} for a ferroelectric PVDF crystal. This polymer contains ~50 Å-thick lamellae; hence, based on the LAM frequency found and with the assumption of the half-wave resonance, the sound velocity in the crystal of the PVDF β -phase is $v_c = 7500$ m s⁻¹. If we assume that the crystal density $\rho_c = 1.97$ g cm⁻³ (see Ref. 28), then $c_{33} = \rho v_s^2 = 110$ GPa, which is comparable with this constant for the polyethylene crystal.

The elastic constants of the disordered phase have been estimated in terms of the two-phase model.¹⁷² They were 3.6 and 2.6 GPa for temperatures 27 and 87 °C; these values correspond to sound velocities of 1450 (27 °C) and 1250 m s⁻¹ (87 °C).

As the Curie point is approached, both phases (crystalline and amorphous) are 'softened' in similar ways: $\Delta v_{s\text{cr}}/v_{s\text{cr}} = -22\%$ and $\Delta v_{s\text{a}}/v_{s\text{a}} = -14\%$. This can serve as one more piece of evidence supporting the hypothesis of the strong connection between the chain dynamics in the disordered phase and characteristics of the Curie transition in the crystal.

The higher the temperature of crystallisation, the larger and the more perfect the crystals formed. When the crystals are formed in the paraelectric phase, they are less perfect. If crystallisation occurs at temperatures below T_C , the resulting ferroelectric crystals should be smaller and more perfect than those formed in the paraelectric phase. Hence T_C is determined by two factors acting in the opposite directions. A study has been devoted to verification of this hypothesis.¹⁷¹ It was shown that an increase in the crystallisation temperature is accompanied by an increase in the melting point (indicating the formation of larger crystals) but

in this case, the Curie point in the cooling regime decreases abnormally.

Similar conclusions have been drawn from the analysis of the Curie transition characteristics in the heating regime. The DSC curves for two copolymer samples obtained by fast quenching and by slow cooling of the melt were compared. The latter crystallisation mode in polymers is normally accompanied by a decrease in the fraction of the disordered phase and by crystal growth. Simultaneously, the melting point regularly shifts to higher temperatures. However, the Curie transition (in the heating regime) again shifts abnormally to lower temperatures. It was shown¹⁷¹ that crystals of the ferroelectric phase in samples with different previous thermal history are almost identical in size. This means that displacement of the Curie point in these samples cannot be explained by the change in the crystal geometry alone.

A similar variation of T_C observed for VDF/TrFE films prepared by crystallisation from solutions in solvents having different affinities to the TrFE groups is due to different concentrations of these groups in ferroelectric crystals.¹⁷⁴ The same might be responsible for this phenomenon observed in the above experiments. The co-monomer TrFE can be regarded as a defect in the PVDF chain. It is known that 'head-to-head' type defects can occur in PVDF crystals;²⁸ therefore, TrFE sections should also be incorporated in the ferroelectric phase. Since the thermodynamic flexibility of TrFE chains is lower than that of PVDF chains, it takes a long period of time for the former to be incorporated in the crystal. When the cooling rate is high (or the crystallisation temperature is low), it may happen that diffusion processes do not ensure, for kinetic reasons, the equilibrium number of TrFE groups in the crystal. Therefore, their concentration in the crystal may prove to be lower than the average concentration along the chain. Thus, the crystal becomes enriched in the VDF groups, which are responsible for the ferroelectricity. A decrease in the proportion of TrFE in the copolymer is known to result in all cases in higher Curie points. Thus, the Curie transition in the ferroelectric crystals obtained by fast quenching (or by crystallisation at lower temperatures), which are depleted of the TrFE groups, should be shifted to higher temperatures, which is actually observed in the experiments.

To understand the mechanism of ferroelectricity, it is significant to elucidate the role of crystal defectiveness. This problem was considered in relation to the 65/35 VDF/TrFE copolymer.¹⁵⁴ The data listed in Table 11 demonstrate how the transverse dimension and the second-kind defectiveness of the crystal, estimated from known relations (see, for example, Ref. 175), change upon polarisation. An increase in the polarising field leads mainly to an increase in the coherence length of the crystal and to a slight increase in the degree of its perfection.

Table 11. Coherence length of the crystal (l_{110}) in the ferroelectric (LT) and paraelectric (HT) phases and the second-kind defectiveness (g) in the LT phase upon polarisation of 65/35 VDF/TrFE films.¹⁵⁴

$E/\text{MV m}^{-1}$	l_{110}/nm		g
	LT phase	HT phase	
0	13	57	—
60	19	—	0.034
90	33	—	0.032
200	39	—	0.030

These processes are equivalent to an increase in the degree of crystallinity. The mechanism of this phenomenon assumes conformational rearrangements of the TGTG⁻ → (TT)_n and T₃GT₃G⁻ → (TT)_n types in the amorphous phase of the polymer. The additional incorporation in the crystal of sections with the planar zigzag conformation can be responsible for the increase in the coherence length after polarisation noted above.

This is confirmed to a degree by the results of a study by Latour and Moreira,¹⁷⁶ who found that polarisation of similar VDF/TrFE copolymers results in an increase in the intensity of the libration mode ($\sim 70 \text{ cm}^{-1}$) for the crystal in which the chains occur in a planar zigzag conformation.

Structural changes occurring during polarisation switching have also been studied for non-oriented films of the same copolymers.¹⁵⁴ The researchers noted that the extreme points are located in the regions where electric induction D reaches a virtually equilibrium value rather than in the regions characterised by the maximum rate of its variation. In experiments, an increase in the polarising field shifts the $D(t)$ curve to shorter times. The position of the minimum on the time dependence of the peak intensity varied in a similar way; however, in all cases, the minimum fell within the final stage of the switching process.²⁸ The resulting correlations were interpreted taking account of various ways of formation of new (switched) domains. If the old and the switched domains are coherent (and the fraction of switched domains is χ), the intensity of a reflection is determined by the expression

$$I = (1 - \chi)|F|^2 + \chi|F^*|^2 \approx |F|^2,$$

where F and F^* are structural factors of the old and new domains, respectively, which should be close because the type of the lattice remains the same. If the domains are non-coherent, then

$$I = |(17w)F + wF^*|^2 \leq |F|^2.$$

Thus, the assumption that the originating domain is not coherent with respect to the old one accounts for the decrease in the intensity of the 110 reflection observed experimentally. This decrease takes place if the new domain is rotated with respect to the old one (see Fig. 5). In all probability, the model with 120- or 180-degree rotation of the chain is realised. The latter is preferable because it requires that the boundary between the domains be located at the 100 planes, whereas for the 120-degree rotation, the 310 planes should be involved.¹⁵⁵

When the chain rotates through 180° , the hydrogen atoms go into the places of fluorines. The stress arising in the lattice can be diminished if the chain is translated by $c/2$ along the axis. Nevertheless, the 001 and 002 planes are distorted at the site of contact of the old and new domains. If the chains in two adjacent nascent domains are translated by $c/2$ in the opposite directions, the distortions are appreciably diminished. Thus, joining of two domains does not require translational motion of the chain in the arising new lattice with a new position with respect to the field.

It has been noted above that polarisation results in a threefold increase in the transverse dimension of the β -phase crystal in the VDF/TrFE copolymer (see Table 11). For a similar copolymer with the composition 75/25, this fact has also been confirmed by DSC.¹⁷⁷ The intensity of the low-temperature peak, which is attributed to the Curie transition, increases markedly after polarisation. Upon annealing at a temperature above 128°C after polarisation, the intensity of this peak decreases. The electron diffraction and IR spectroscopy data¹⁷⁸ do not show any changes in the lattice parameters or chain conformations, while changes in the domains do occur. After repeated annealing, a disproportion occurs in the narrow temperature range, $127\text{--}129^\circ\text{C}$, namely the remanent polarisation or electromechanical coupling coefficient (K_t) is already equal to zero,¹⁷⁹ whereas ferroelectric crystals are still present (the enthalpy of the Curie transition, $\Delta H \neq 0$). To eliminate this contradiction, it has been assumed¹⁷⁷ that rearrangements take place in ferroelectric crystals in this narrow temperature range (before transition to the paraelectric phase). As a result of chain rotation, in some domains, sub-domains are formed (without changes in the lattice parameters and chain conformations), in which spontaneous polarisation points to the opposite direction. Generally, this gives a zero remanent polarisation when ferroelectric crystals are still retained.

It has been shown in relation to the VDF/TFE copolymer¹⁴⁰ that crystallisation at elevated pressures is accompanied by the

formation of thick ($150\text{--}250 \text{ nm}$) lamellar crystals. These samples are also characterised by high remanent polarisation. Thus, it is clear that the P_r value is correlated with the morphology of the ferroelectric crystals formed. These correlations for VDF/TrFE copolymers have been considered in a series of studies.^{180–186} In one study,¹⁸¹ the problem of structuring in copolymers with high VDF contents, 86.88 mol.% and 94 mol.%, has been considered. These objects are of interest because, on the one hand, high temperatures of the Curie transition should be expected for these VDF proportions (this is important for the practical implementation of energy converters), and, on the other hand, crystallisation as the nonpolar α -phase is possible in this case.²⁸ This brought about the need to establish the details of the structuring of the copolymers in question and to identify their role in the variation of ferroelectric characteristics.

The films were prepared from a solution in dimethylformamide and annealed at a temperature (T_h) somewhat below the melting point. The structural characteristics were analysed using X-ray diffraction methods, IR spectroscopy, and electron diffraction. The morphology of the resulting crystals was studied by optical and electron microscopy. The copolymers under study can be described by the general formula $(\text{VDF})_x(\text{TrFE})_{1-x}$; the type of the morphology depends substantially on the x value. For $0.82 \leq x \leq 0.9$, this preparation technique always yielded thick lamellar crystals with dimensions $\sim 0.1 \mu\text{m}$, which has been noted previously for copolymers with $0.6 \leq x \leq 0.82$.¹⁷⁸ In the case of copolymers with $x = 0.94$, thick lamellae are formed only upon high-pressure crystallisation ($\sim 100\text{--}500 \text{ MPa}$); crystallisation under standard conditions results in spherulite morphology, typical of the PVDF α -phase.²⁸ Analysis of X-ray diffraction data shows that thick lamellae are formed by crystals of the α -, β - and, perhaps, even γ -phase. For copolymers with $x \geq 0.9$, the

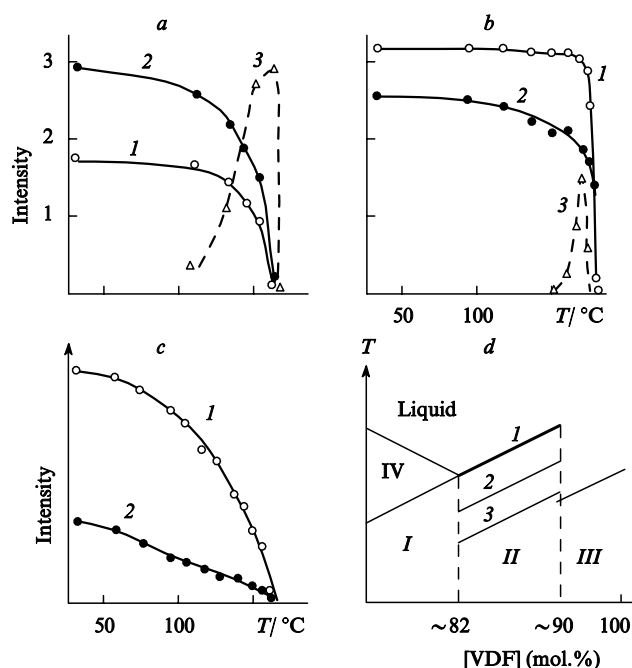


Figure 33. Temperature dependences of the X-ray reflection intensities for isotropic (a, b) and uniaxially stretched (c) films of the 88/12 VDF/TrFE copolymer before (a) and after (b, c) polarisation and the phase diagram for copolymers with high VDF fractions (d);¹⁸¹

(a): (1) β -phase, the coinciding 200 and 110 reflections; (2) α -phase, the 101 reflection; (3) rotator phase; (b, c): (1) β -phase, the 200 and 110 reflections; (2) β -phase, 001, 310, 020; (3) rotator phase; (d): transitions: (1) β -phase $\rightarrow$ liquid, rotator phase $\rightarrow$ liquid; (2) γ -phase $\rightarrow$ rotator phase; (3) α -phase $\rightarrow$ rotator phase; I — β -phase, thick lamellae; II — a mixture of α -, β -, and γ -phases, thick lamellae; III — α -phase, spherulites; IV — rotator phase.

spherulites are formed by the crystals of the α -phase (Fig. 33). The morphology is very significant for the stability of the crystals formed from copolymers of the same composition. This is demonstrated by the comparison of the temperature dependences of the intensities of the X-ray reflections of films incorporating lamellar crystals and thin fibrils, obtained by annealing and uniaxial stretching (Fig. 33a, b). It can be seen that in the former case, noticeable decrease in the intensity of the principal intermolecular reflections of the β -phase, 200 and 110, starts only at $\sim 100^\circ\text{C}$, while in the latter case (oriented films), it starts nearly at room temperature. A special role in this stability is played by film polarisation processes. After polarisation, the intensity of the 200 and 110 reflections does not change up to 150°C (Fig. 33b). Detailed analysis shows that a polymorphic transition of the $\alpha \rightarrow \beta$ type occurs in the polarisation cycles; this was detected relying on the typical change in the intensity ratio of reflections of the α - and β -phases and characteristic absorption bands in the IR spectra.¹⁸¹

The presence of a rotator phase is an important feature of thick lamellar crystals, which manifests itself at elevated temperatures (see Fig. 33a, b). This phase is responsible for a reflection with the angle position $2\theta \simeq 18^\circ$; therefore, it may be a modification of the paraelectric phase. The region in which the rotator phase is displayed depends on the structural features of the sample. This becomes clear upon comparison of the curves shown in Fig. 33a, b. In the initial sample, the lamellae contain a mixture of crystals of α - and β -modifications, which is confirmed by X-ray diffraction and spectroscopic data. In this case, the rotator phase starts to appear even at 100°C and is retained up to the melting point. After polarisation, this phase appears only at $\sim 150^\circ\text{C}$, the region of its existence being markedly narrower. After polarisation, the α -phase transforms into the polar β -modification and the intensity of bands responsible for the TGTG⁻ conformation in the IR spectra substantially decreases.¹⁸¹ Thus, the presence of α -phase regions (mixed with the β -phase) and the presence of conformational defects as sections of a helical conformation, with the planar zigzag being the major conformation, facilitate the appearance of the rotator phase.

High contents of VDF in copolymers with TrFE cause a number of structural features (Fig. 33d). If $x \leq 0.82$, a standard phase diagram is observed, *i.e.* on heating, the ferroelectric phase is converted into the paraelectric phase and then into the melt. For the $0.82 \leq x \leq 0.90$ region, in which thick lamellae are formed by crystals of α -, β - and γ -modifications, a multiplet character of transitions should be expected. As the temperature increases, the α -modification crystals are the first to pass into the rotator phase; they are followed by the γ -phase and then by the β -phase. The validity of this scheme is supported by the fact that endotherms for three transitions can be seen in the thermograms of the 88/12 copolymer.¹⁸¹ Some additional electrophysical data for the copolymers in question are listed in Table 12. It can be seen that all the samples with the morphology of thick lamellae are characterised by very high remanent polarisations, and, correspondingly, the electromechanical coupling coefficient. The increase in the VDF proportion in the copolymer is accompanied by a regular increase in the coercive field, as has been noted above. By comparing the E_c values for samples with $x = 0.81$, one can elucidate the influence of the texturing factor on E_c . Orientation of the film decreases E_c , which has also been noted in analysis of the results of other studies.²⁸ The piezoelectric constant d_{31} in textured films is, on average, more than twice as high as that for isotropic samples. However, the sound velocity is somewhat greater in the latter case. If the sound velocity is determined from the relation

$$v_s = \sqrt{\frac{c}{\rho}},$$

(c is the elasticity modulus, ρ is the substance density), it turns out that isotropic samples possess lower compliance ($1/c$) than

Table 12. Electrophysical characteristics of isotropic and oriented films of VDF/TrFE copolymers after annealing at a temperature of T_h and poling in the field E .¹⁸¹

[VDF] (mol.%)	$T_h/^\circ\text{C}$	E^a	K_t	$P_r/\text{mC m}^{-2}$	E_c (sec^{-1})	$v_s/\text{km s}^{-1}$	$d_{31}/\text{pC N}^{-1}$
Isotropic samples ^b							
81	140	100	0.29	120	39	2.42	9.4
86	156	130	0.25	110	44	2.58	8.5
88	160	110	0.22	100	48	2.48	8.0
94	160	110	0	0	—	—	—
Oriented samples ^c							
81	140	75	0.28	95	31	2.36	8.9
86	154	72	0.16	—	—	2.24	18.0
88	160	80	0.18	—	—	2.13	19.0
94	150	81	0.19	—	—	2.27	20.5
100	170	101	0.20	—	—	2.30	25.0

^a Expressed in MV m^{-1} . ^b Poling in an alternating field (triangular pulses with a frequency of 10^{-2} Hz) at room temperature. ^c Poling in a static field at $120\text{--}140^\circ\text{C}$.

oriented ones. This circumstance may be reflected in the features of the piezoelectric response of textured films.

Some details of structural transformations in the same copolymers with high proportions of VDF were elucidated in a study,¹⁸² in which crystallisation was carried out at high pressures and thus the morphology of thick lamellar crystals was ensured. The results of studies of ferro- and piezo-electric properties of these copolymers are presented in Table 13. For comparison, data for one copolymer crystallised at normal pressure are also given in the Table. It can be seen that for copolymers with VDF contents of at least 86 mol.%, the Curie point (T_C) proves to be higher than the melting temperature (T_m). On the one hand, this can be interpreted as being due to the large thickness of lamellar crystals. On the other hand, it can be seen that the morphology of ferroelectric crystals has no influence on the pattern of dependence of the coercive field on the copolymer composition. As in the case of other crystallisation methods, an increase in the proportion of TrFE regularly shifts E_c to lower values. However, some facts cannot be explained. For example, the P_r and, hence, the K_t values for all films crystallised at elevated pressures prove to be lower than those for samples crystallised at a pressure of 0.1 MPa. The reason for this fact is not entirely clear. To interpret this abnormal feature, Ohigashi *et al.*¹⁸² assumed, without adequate substantiation, that high-pressure crystallisation affords less perfect crystals. A practically valuable conclusion was drawn in this study, namely, the morphology of thick lamellar crystals can be used to produce energy converters based on the copolymers considered here with an extended temperature range of operation. This was confirmed by the data on the pulse echo signals from the 86/14 copolymer at 165°C .

Table 13. Ferro- and piezo-electric characteristics of VDF/TrFE crystallised at high pressures.¹⁸²

[VDF] (mol.%)	$T_m/^\circ\text{C}$	$T_C/^\circ\text{C}$	$E_c/\text{mV m}^{-1}$	$P_r/\text{mC m}^{-2}$	K_t	$v_s/\text{km s}^{-1}$
75	150	124	45	79	0.17	2.41
75 ^a	150	124	40	110	0.29	2.41
86	165	175	54	76	0.19	2.39
94	184	210	62	64	0.12	2.40
100	205	230	75	97	0.13	2.72

^a Crystallisation at 0.1 MPa and 140°C .

As noted above, thick lamellae are typical of ECC. Folded-chain crystals (FCC) are more often formed in polymers; however, ECC can also appear under specific conditions. This problem has been studied in detail for crystallisation of PE.¹⁸⁷ It was found that crystallisation from the orthorhombic phase yields FCC and crystallisation from the mobile hexagonal phase affords ECC.¹⁸⁸ For less dense packing of chains in the hexagonal phase, diffusion sliding processes are possible, which underlies the theory of thickening of lamellar crystals.^{189,190} In addition to PE, the formation of ECC has been noted for other crystallisable polymers, for example, polychlorotrifluoroethylene (PCTrFE), *trans*-1,4-polybutadiene,¹⁹¹ and in VDF/TrFE copolymers. If the composition of these copolymers is below the triple point ($x \approx 0.82$) (see Fig. 33d), they can crystallise (like PE) as orthorhombic (ferroelectric) and mobile hexagonal (paraelectric) phases. The mobile hexagonal phase can occur even under atmospheric pressure (a similar behaviour has been noted for PCTrFE and *trans*-1,4-polybutadiene); in the case of PE, this phase appears only at elevated pressures.¹⁸³

The first data on the formation of thick lamellae in PVDF were reported for crystallisation at elevated pressures.^{28,192,193} Subsequently, the possibility of the formation of ECC under atmospheric pressure has been verified. VDF/TrFE copolymers with VDF proportions (x) of 0.75 and 0.78 were chosen for this purpose. These values are lower than the x value in the triple point (0.82); therefore, in accordance with the phase diagram (see Fig. 33d), crystallisation can be carried out as the mobile hexagonal paraelectric HT phase. The data from scanning electron microscopy of samples crystallised at various degrees of supercooling show that the morphology of thick lamellar crystals is actually observed. At early stages of crystallisation, single lamellae were $\sim 0.3\text{-}\mu\text{m}$ thick. At later stages, stacking of lamellae into $\sim 0.8\text{-}\mu\text{m}$ thick stacks was noted. This aggregation in VDF/TrFE copolymers is observed more commonly than in PE, which is attributed to the greater role of screw dislocations in the former case. The particles arising are cigar-shaped and $20\text{--}30\text{-}\mu\text{m}$ long. Crystallisation of the same copolymers at high pressures (80 MPa) hardly changes the morphology arising. The thickness of single lamellae remains the same and the particle length is $10\text{--}20\text{ }\mu\text{m}$.¹⁸³ For copolymers with a known molecular mass, the full extended length was estimated to be $\sim 0.7\text{ }\mu\text{m}$. This means that chains fit almost entirely into the lamellae.

The theoretical possibility of the formation of thick lamellae, *i.e.* ECC, in the VDF/TrFE copolymer (see Fig. 33d) exists also when x is greater than that corresponding to the triple point. In fact, in the range of $0.82 \leq x \leq 0.9$, the mobile hexagonal (rotator) phase can exist.¹⁸¹ This hypothesis has been verified in a study.¹⁸⁵ VDF/TrFE copolymers with VDF proportions of 0.88 and 0.89 were studied. When conducting crystallisation from the melt under atmospheric pressure and with various degrees of supercooling, the researchers found cigar-shaped particles with dimensions approximately equal to those obtained upon crystallisation of copolymers with $x < 0.82$. Thus, it was confirmed experimentally that ECC can form even above the triple point in the phase diagram.

Nevertheless, in the study cited,¹⁸⁵ this finding was explained without assuming the existence of some rotator phase but proceeding from the Ostwald 'threshold' rule. The temperature dependences of the free energy for the three phases were derived, under certain assumptions,¹⁹⁴ as straight lines with different slopes. This results in two melting points, one for the hexagonal phase (T_m^h) and one for the orthorhombic phase (T_m^o). According to this diagram, crystallisation at a certain temperature T_{cr} converts the liquid in the supercooled state.

Specific defects referred to as 'entanglements' occur in the melt between the macromolecules. 'Untangling' of these defects on cooling the melt to T_{cr} takes some time; therefore, the liquid remains in the supercooled state for some period. After it has passed into the hexagonal phase, this phase occurs in the metastable state for some period of time. Its transition into the

more equilibrated orthorhombic phase also takes some time, because, in addition to the change in the type of lattice, this requires conformational rearrangements in the copolymer chains. The equilibrium in the hexagonal phase–orthorhombic phase (paraelectric–ferroelectric) system shifts with time towards the latter. Due to the enhanced molecular mobility, some of the crystals remaining in the metastable hexagonal phase form thick lamellar crystals as ECC.

The possibility of formation of thick lamellar crystals in the uniaxially stretched VDF homopolymer crystallised as the β -phase has been verified.¹⁸⁶ Two crystallisation modes were employed (Fig. 34a).

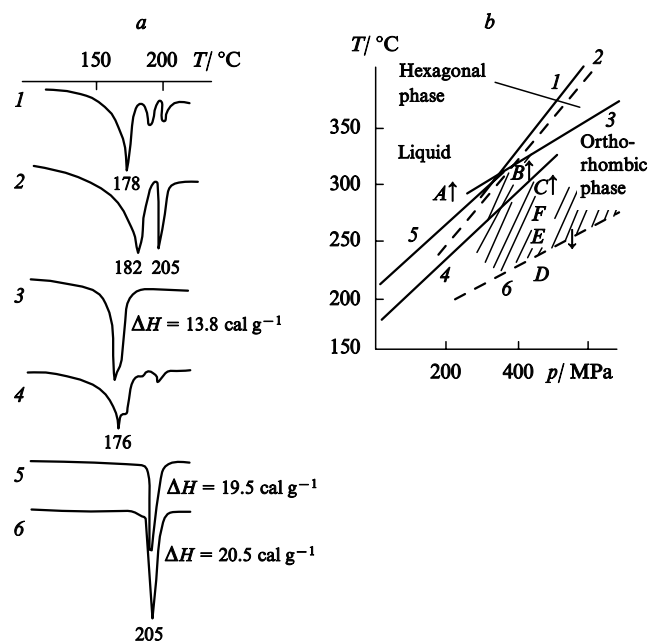


Figure 34. Melting thermograms of stretched PVDF films after high-pressure crystallisation in various regimes (a) and the T - p phase diagram (b).¹⁸⁶

(b): (1) T_m (hexagonal phase); (2) T_{cr} (hexagonal phase); (3) T_C for the orthorhombic–hexagonal phase transitions; (4) T_m for a uniaxially stretched film with the β -phase; (5) T_m for the β -phase ECC; (6) T_C for the hexagonal–orthorhombic phase transition during cooling. The region of regimes favourable for the formation of ECC is hatched. Points A–F correspond to the conditions of the crystallisation of samples (1–6) in (a).

Samples 1–3 were crystallised in the constant-pressure mode (200, 400 and 500 MPa, respectively), the temperature being increased to the maximum value (280, 300 and 300 °C, respectively). Samples 4–6 were crystallised under isothermal conditions (217, 262 and 282 °C, respectively), the pressure being increased from the initial value to the maximum value (100 $\rightarrow$ 500, 200 $\rightarrow$ 500, and 200 $\rightarrow$ 500 MPa, respectively). According to DSC data, the characters of melting endotherms observed for different samples are substantially different. The thermograms of samples 2, 5 and 6 with intense high-temperature peaks (maximum temperature 205 °C) can be distinguished. Analysis of the data of optical and electron microscopy for crystallised films demonstrated that it is in these samples that thick lamellar crystals are formed, *i.e.* the ECC morphology is realised. The transition enthalpies for samples 5 and 6 are 19.5 and 20.5 cal g⁻¹, respectively. These values are roughly equal to the sum of the enthalpies of the Curie transition and melting in the 74/26 VDF/TrFE copolymer.¹⁷⁹ This means that the Curie and melting points in PVDF films coincide; therefore, only one process is recorded.

The T - p phase diagram for PVDF shown in Fig. 34b helps in formulating the conditions for crystallisation yielding the ECC morphology. Since the Curie point in PVDF is very high, its crystallisation as the mobile hexagonal phase can be accompanied by thermal destruction processes. Certainly, they deteriorate the structural characteristics of ECC. Due to the large hysteresis in the Curie transition during heating and cooling, it is better to cool the melt and transform it into the hexagonal phase (metastable state); in this case, crystallisation can be carried out at markedly lower temperatures. Above the hatched region, thermal destruction exerts unfavourable influence, while below straight line 6 the system occurs as the orthorhombic phase, in which thick lamellar crystals do not form. The thickness of these crystals in samples 5 and 6 (see Fig. 34a) is 0.1–0.2 μm , which is comparable with the crystal thickness in 79/21 and 75/25 VDF/TrFE copolymers, although interplanar spacings of the 110 or 200 reflections (4.25 Å) in the samples under consideration are 5%–7% lower than those in these copolymers.^{178, 179}

Analysis of the X-ray diffraction data shows that even in sample 6 the lamellae consist of mixed crystals of the β - and γ -phases. On high-temperature polarisation of the films, the latter is transformed into the pure β -phase. Thus, the assumption that the morphology of thick lamellar crystals improves ferroelectric characteristics was confirmed once again. Comparison of the D - E hysteresis curves for the initial (oriented) film and sample 6 shows that the P_r value is greater in the latter case. More detailed data are presented in Table 14. The Curie point is found above the melting region (as in the case of copolymers with higher VDF contents). The highest sound velocities in these films and the minimum dielectric constants point indirectly to the highest degree of crystallinity in these polymers. However, this conclusion contradicts the reported data,¹⁴⁰ according to which an increase in the degree of crystallinity resulted in a decrease in the coercive field (see Fig. 31c), which was then found to be maximum for PVDF with ECC (see Table 14). In the opinion of Hattori *et al.*,¹⁸⁶ this can be attributed to the fact that the latter material does not form a pseudo-hexagonal lattice with $a/b = \sqrt{3}$. For PVDF with ECC, the a and b values are 8.66 and 4.25 Å, respectively, which do not yield this ratio.

The data on the structure of VDF/TrFE copolymers with critical compositions $0.82 \leq x \leq 0.90$ are the most contradictory. As noted above, thick lamellae have been detected in these copolymers.¹⁸¹ They should incorporate both ferroelectric β -phase crystals and nonpolar crystals of the α -phase (and, perhaps, even γ -phase) (see Fig. 33d). This assumption made it possible to explain why the Curie point and the melting point coincide. Thick lamellae with a size of $\sim 0.1 \mu\text{m}$ have also been detected¹⁹⁶ on slow cooling of copolymers with the composition 86/14. A low-angle X-ray scattering study showed the presence of

thin crystals ($l \approx 8.5 \text{ nm}$) apart from thick lamellae. If the hypothetical crystals of the α -, β - and γ -phases are assumed to coexist in both types of lamellae, two melting points and two Curie transitions should be expected, because thin lamellae disappear at 147–155 °C, whereas thick ones are retained up to 165–170 °C.¹⁹⁶ The α -phase melts more readily;²⁸ therefore, thin lamellae are likely to be formed by crystals of the α -phase, and thick lamellae are mainly formed by crystals of the β -phase.

In all probability, the morphology of thin lamellae is metastable because their content sharply diminishes at about ~ 150 °C.¹⁹⁷ The increase in the proportion of thick lamellae indicates that recrystallisation processes in this temperature region can be accompanied by solid-phase transformations of the $\alpha \rightarrow \beta$ type.²⁸ This assumption is not without reason because such a transition has actually been detected by the X-ray diffraction method in, for instance, the 94/6 VDF/TFE copolymer crystallised in the metastable state,^{28, 197} and in the case of the 86/14 VDF/TrFE copolymer, a decrease in the degree of crystallinity has been noted well before melting.¹⁹⁷ If the Curie transition occurs in this temperature range, it could be initiated to some extent by the dynamical changes in the disordered regions, as has been noted above.

VIII. Ferroelectricity of ultrathin films

Due to the pronounced influence of the morphology of thick lamellar crystals on the ferroelectric characteristics of PVDF and VDF copolymers, it is of interest to consider the results of studies of these characteristics in thin and ultrathin films. The electro-physical characteristics of the three-layer metal–dielectric–semiconductor system have been analysed.¹⁹⁸ The system contained a 32- or 150-nm thick dielectric film of the 73/27 VDF/TrFE copolymer deposited from a solution onto a silicon substrate with the hole type of conductivity. After the copolymer film had been coated by a protective SiO_2 layer (50–70 nm), the breakdown field intensity for this film was 230 MV m^{-1} , which is comparable with the values typical of films with a standard thickness. Analysis of the dependence of the capacity (at a frequency of 1 MHz) on the voltage applied on the metal–dielectric–semiconductor structure made it possible to estimate the remanent polarisation in the copolymer films after poling ($\sim 100 \text{ MV m}^{-1}$). For a 32-nm thick film, P_r amounts to 5.9 mC m^{-2} ; for a thickness of 150 nm, this value is 4.1 mC m^{-2} . These values are approximately an order of magnitude lower than the P_r values for ordinary films. The reason for this is obscure because the coercive fields in these films, like those in ordinary films, are about 40–33 MV m^{-1} (see Ref. 198).

In other studies,^{199, 200} copolymer films have been deposited by the vacuum vaporisation technique. In the case of 80/20

Table 14. Ferro- and piezo-electric properties of PVDF and VDF copolymers.¹⁸⁶

Sample	$T_m / ^\circ\text{C}$	$T_C / ^\circ\text{C}$	K_t	ε' (5–10 MHz)	$v_s /$ km s^{-1}	$P_r /$ mC m^{-2}	$E_c /$ MV m^{-1}	Note
VDF/TrFE								
75/25	152	124	0.29	5.3	2.41	111	38	The sample was annealed in the hexagonal phase at 0.1 MPa (Ref. 180).
88/12	170	177 ^a	0.22	5.3	2.43	100	48	The sample was crystallised in the metastable hexagonal phase at 0.1 MPa and transferred into the β -phase upon polarisation. (Ref. 181).
β -PVDF	175	—	0.20	6.2	2.26	60	50	Data of Ref. 195
β -PVDF (ECC)	205	240 ^a	0.27	5.9	2.72	95	70	The sample was polarised in an alternating field, first, at room temperature and then at an elevated temperature

^a T_C was estimated by extrapolation of the value found from the T - p diagram to a pressure of 0.1 MPa.

VDF/TrFE, a KBr crystal served as the substrate. Study of films of various thicknesses (~ 10 to 60 nm) by IR spectroscopy resulted in the conclusion that deposition is accompanied by thermal destruction of macromolecules. The destruction yields fragments retaining the initial chain conformation rather than the monomers.

The change in the substrate temperature leads to a changed orientation of chains with respect to the surface. At 35°C (cold substrate), the axes of macromolecules are arranged at right angles to the surface and at 80°C (hot substrate) they are parallel to the surface. Similar effects have also been described in other studies,^{201,202} which have also noted that the orientation of copolymer chains on the substrate also depends on the film thickness. The temperature effects on the formation of films on the substrates can be regarded as general because they are also manifested for the same films deposited by epitaxial growth from solutions.²⁸

It seems attractive to combine polarisation with deposition of thin films on the substrate. This attempt was made in a study,²⁰⁰ in which the 54/46 and 73/27 VDF/TrFE copolymers were sprayed onto quartz at a rate of 0.02 nm s^{-1} in a field of up to 30 MV m^{-1} . The 400-nm thick films of the copolymer with 54 mol.% of VDF displayed dielectric anomalies in the Curie transition region only in those cases where spraying was carried out in a field (30 MV m^{-1}); when deposition was performed without a field, no dielectric anomalies were observed. As in ordinary films, the Curie transition had signs of a second-order phase transition (without hysteresis). These facts confirm the significant role of electric field in the formation of a ferroelectric structure. The fact that no ferroelectricity was found in films that had not been exposed to an external electric field points indirectly to the occurrence of irregular sections, most probably, of a chemical nature, which hamper the formation of the ferroelectric phase.

This assumption is supported by the data obtained by the same researchers for 73/27 VDF/TrFE. Films prepared by spraying in a field displayed no dielectric anomalies near the Curie transition ($\sim 120^\circ\text{C}$) because the sample melted at 105°C . Melting could be due to chain rupture reactions, which efficiently proceed during deposition; they should markedly decrease the average molecular mass of the chain and, hence, the melting point. Thermal destruction should increase the concentration (and mobility) of ionic impurities. Indeed, the shape of the D – E hysteresis curves implies an enhanced role of free charge carriers.²⁰⁰ This can increase the probability of electric break-down of the films. The coercive fields were found to be lower (by two orders of magnitude). This can be explained qualitatively by assuming that the films thus obtained possess higher degrees of crystallinity (see Fig. 31). This situation can be a consequence of the substantial decrease in the average molecular mass upon thermal destruction, which apparently gives a low-molecular-mass product.

Thus, thin films deposited by spraying exhibit ferroelectric properties; however, the chain structure in these materials is transformed in such a way that ferroelectric characteristics prove most often to be poorer than those for thick films. The formation of thin films from solutions, which allows one to control the conformational characteristics of the chain and the phase state of the crystals formed due to the specific influence of a particular solvent, appears more promising.²⁸ This method brought the studies at a new level after Russian scientists had proved the possibility of producing monomolecular films of the polymers in question using the Langmuir–Blodgett technique.^{45,203–210}

These films are promising for the use in optical memory cells provided that ferroelectric switching has been detected in them. Films of the 70/30 VDF/TrFE copolymer, deposited from solutions in dimethyl sulfoxide with a copolymer concentration of 0.01 mass % have been studied.^{45,203–210} The Langmuir–Blodgett films were formed on the surface of doubly distilled water using a setup described in the literature.²¹¹ After the films had been transferred onto a metallic substrate and the upper electrode

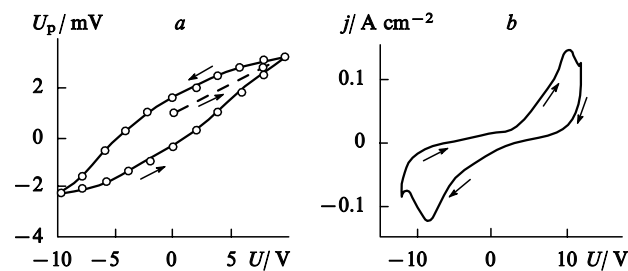


Figure 35. Pyroelectric response (a) and transpolarisation current density (b) vs electric voltage in a 15-nm thick Langmuir–Blodgett film of the 70/30 VDF/TrFE copolymer.²⁰⁶

had been deposited, it was possible to study electrophysical characteristics of the films. Analysis of surface tension isotherms showed that the thickness of a monomolecular film is ~ 0.5 nm.⁴⁵ Films composed of 5 to 40 monolayers were mostly used. Ferroelectric characteristics, in particular, spontaneous polarisation, were measured using the pyroeffect, namely, by recording the current arising on exposure of the film to a $100\text{-}\mu\text{s}$ pulse of the Nd-laser radiation ($\lambda = 1.06\text{ }\mu\text{m}$). Figure 35 shows the field dependences of the pyroelectric response and the transpolarisation current density in a Langmuir–Blodgett film composed of 30 monolayers. The presence of pyroactivity in the initial (non-polarised) film points to a non-zero residual (spontaneous) polarisation, which may be due to the specific conditions of the film formation.

The presence of switching effects indicates unambiguously that these films possess ferroelectricity, which is manifested in a special way. Firstly, the coercive field strengths, $E_c = 300\text{ MV m}^{-1}$, are almost an order of magnitude greater than those observed in ordinary films (see Fig. 35 and Table 9). Secondly, analysis of the scanning tunnelling microscopy data (STM) shows a two-dimensional lattice with two identity periods on the film surface. One of the periods ($2.6\text{ }\text{\AA}$) is virtually constant for all samples and is related to the lattice constant $c = 2.56\text{ }\text{\AA}$ (see Table 4) along the macromolecule axis. The other identity period varies from sample to sample from 2.2 to $4\text{ }\text{\AA}$ and characterises the intermolecular packing. Langmuir–Blodgett films are expected to have very high break-down fields (at least, 600 MV m^{-1}). These films are characterised by higher pyroelectric coefficients than ordinary films — $400\text{ }\mu\text{C m}^{-2}\text{ K}^{-1}$ against $\sim 30\text{ }\mu\text{C m}^{-2}\text{ K}^{-1}$.

If a denser, on the average, packing of chains is assumed for Langmuir–Blodgett films, the Curie point in these films may be expected to shift to higher temperatures relative to that in thick (block) films. It can be seen from Fig. 36 that the Curie transition in the Langmuir–Blodgett films is displaced to lower temperatures relative to that for ordinary films ($\sim 15\text{ }\mu\text{m}$).

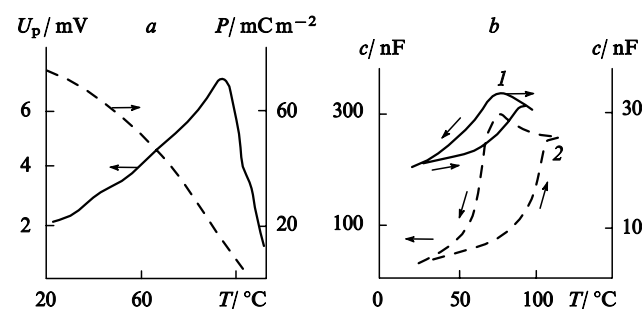


Figure 36. Temperature dependences of the pyroelectric voltage, polarisation (a) and capacity (b) in the Langmuir–Blodgett films (1) and ordinary films (2) of the 70/30 VDF/TrFE copolymer.^{206,212}

Thus, the shift of the Curie point observed experimentally is opposite to that suggested beforehand. In all probability, the reason for this anomaly is the same as for the unusual behaviour of the spontaneous polarisation, which starts to diminish well before the Curie point. These abnormal features are apparently due to different energy states of macromolecules on the film surface and in its bulk. Macroscopic ferroelectric characteristics in thick films should be determined by parameters of chains in the bulk, whereas in the case of Langmuir–Blodgett films, the chains located on the surface can contribute more significantly to the properties.

The appearance of ferroelectricity in 100–200 Å thick films implies that this layer permits the formation of a three-dimensional crystal of the ferroelectric phase. Chains in the planar zigzag conformation are packed in such a way that polar axis *b* becomes the predominant direction. The polarisation component directed at right angles to the film surface is usually measured; therefore, the transverse dimension of the crystal should be not less than the film thickness. The transverse dimension of the crystal can be estimated based on the width of the 200 and 110 intermolecular reflections of the ferroelectric phase. In the case of the thin lamellar morphology, this dimension for block films is ~100–200 Å (see, for example, Table 11). This means that only one crystal is formed in the perpendicular direction in a Langmuir–Blodgett film consisting of 30 monolayers, *i.e.* in this direction, the degree of crystallinity is 100%. This is confirmed indirectly by values of spontaneous polarisation equal to 0.1–0.15 C m⁻²,²⁰⁶ which are comparable with the values calculated for the crystal of the β -phase (0.13 C m⁻²).

More evidence for the advanced hypothesis could be provided by the magnitude of the component of the dielectric constant ϵ' along the perpendicular to the film. By using the dependences presented in Fig. 36, Palto *et al.*²¹² found that for room temperature, $\epsilon' = 4$, which is substantially lower than this value for a 15- μ m film ($\epsilon' = 12$). The high ϵ' value for ordinary films is due to the contribution of amorphous areas with developed cooperative mobility, in which the dielectric constant is much greater than in the crystal.²⁸ Therefore, the low ϵ values may point to the formation of single lamellar crystals across the Langmuir–Blodgett films. This assumption appears more natural than, for example, the hypothesis of Zhong *et al.*²¹³ concerning thin ferroelectric inorganic films.

The formation of the threshold thickness of the crystal (~150 Å) in the case of Langmuir–Blodgett films is an important point. Indeed, the electric resistance of these films containing 12 or 7 layers is markedly lower than that of ordinary films.²⁰³ Moreover, the coercitive field was found to increase regularly upon a decrease in the number of monomolecular layers in the film; for a film with 30 monolayers, $E_c \approx 300$, for a 12-monolayer film it is 400–700, and for a 7-monolayer films it is 1000–1200 MV m⁻¹.

Conduction by the tunnelling mechanism may arise in the Langmuir–Blodgett films under the action of a strong electric field. This phenomenon was actually observed in a study,²⁰³ in which the curves of pyroelectric hysteresis were measured (Fig. 37a). In addition to recording of the pyroelectric response, the conductance of the Langmuir–Blodgett films was estimated. Upon pyroelectric switching, the conductance changed by more than three orders of magnitude (from 10⁻⁶ to 10⁻⁹ Ω^{-1}).

One more difference between the characteristics of the Curie transition in ordinary films and in Langmuir–Blodgett films can be noted. It can be seen from Fig. 36b that in the latter case, the maximum capacity is only 1.6 times as high as that at room temperature. In the former case, it increases more than fivefold. The dielectric constants of the Langmuir–Blodgett film at room temperature is 4 (that for an ordinary film is ~12), and its maximum value is ~8.5 (that for an ordinary film is ~60). Assuming that one crystallite fits across the Langmuir–Blodgett film, this pronounced differences of the maximum ϵ' values for block films should be attributed to the presence of sections of the disordered phase. This proves once again the non-trivial role of

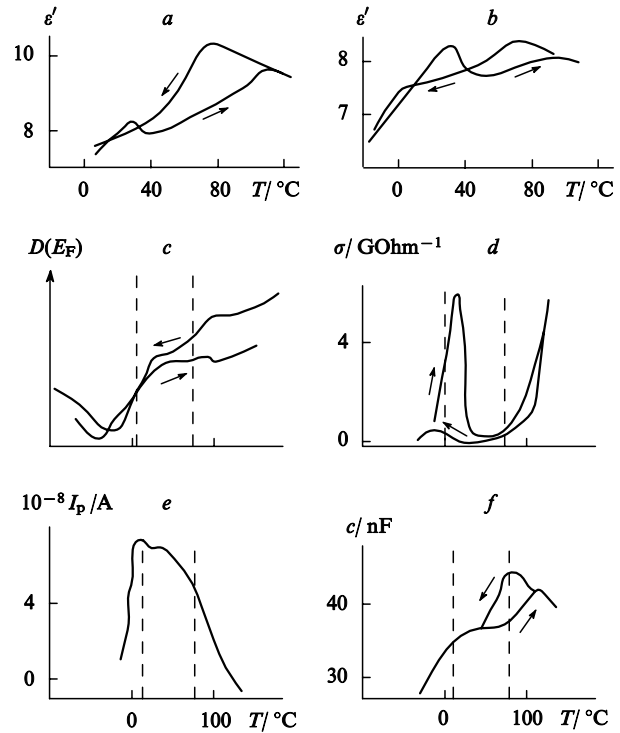


Figure 37. Temperature dependences of the dielectric constant (*a*, *b*), density of states at the Fermi level (*c*), conductivity (*d*), pyroelectric current (*e*) and capacity (*f*) in the Langmuir–Blodgett films of the 70/30 VDF/TrFE copolymer with a number of monolayers of 30 (*a*), 2 (*b*) and 5 (*c–f*).

this phase in the transition, although according to the classical views, it is expected to be associated with the crystalline phase.

The presence of amorphous regions with excess free space in ordinary films permits one to estimate the local field of ferroelectric crystals. This can be done by doping ferroelectric copolymers by particular dyes, which create admixture colour centres. The molecules of the doping additive are located in the regions with more free space, *i.e.* in the disordered phase. Dye molecules are usually characterised by high dipole moments; therefore, they should be captured by polar planes adjacent to amorphous areas. Thus, the dye molecules would be located in the ferroelectric crystal field and their optical characteristics would carry information about local crystal fields. This fact underlies the method for the estimation of these characteristics developed by Blinov *et al.*²⁰⁸.

The local field E_{loc} at some point of a dielectric polarised in external field E can be represented as the sum²⁰⁸

$$E_{loc} = E + E_1 + E_2 + E_3, \quad (43)$$

where E_1 is the depolarising field caused by the bound surface charge; E_2 is the Lorentzian field induced by the charge of the internal surface of the imaginary spherical cavity about the chosen point, and E_3 is the field of the charges inside this cavity. The last term is equal to zero for isotropic media and for crystals with cubic symmetry. In the short-circuited state after polarisation $E + E_1 = 0$; therefore, in the case of isotropic distribution of atoms

$$E_{loc} = E_2 = \frac{P}{3\epsilon_0}, \quad (44)$$

where P is the sum of the induced P_i and spontaneous P_s polarisations. Since for ferroelectrics $P_s > 100$ mC m⁻² and $P_s \gg P_i$,

$$E_{\text{loc}} = \frac{P_s}{3\epsilon_0}. \quad (45)$$

If one proceeds from the value $P_s = 100 \text{ mC m}^{-2}$, in conformity with Eqn (45), $E_{\text{loc}} \approx 4 \text{ GV m}^{-1}$. To verify this value experimentally, three dyes, rhodamine 6G (R6G), 4-diethylamino-4'-nitroazobenzene (DEANAB) and 4-diethylamino-4'-nitrostilbene (DEANS), parameters of the excited states for which are well known, were introduced into the VDF/TrFE copolymer.^{214–217} Absorption of a light quantum by a dye molecule is accompanied by a change in its static dipole moment μ and polarisability α .^{217,218} Therefore, the electric field E decreases the energies of the ground (denoted by subscript g) and excited (denoted by e) states to different extents

$$\Delta W_g = -\mu_g E - \frac{\alpha_g E^2}{2}, \quad (46)$$

and

$$\Delta W_e = -\mu_e E - \frac{\alpha_e E^2}{2}. \quad (47)$$

As a consequence, under the action of an electric field, the optical transition frequency (ν) shifts by²¹⁹

$$\Delta \nu = \frac{1}{hc} \left(\Delta \mu E + \frac{1}{2} \Delta \alpha E^2 \right), \quad (48)$$

where $\Delta \mu = \mu_e - \mu_0$ and $\Delta \alpha = \alpha_e - \alpha_0$ are the changes in the dipole moment and the average polarisability in the excited state.

The frequency shift consists of two components, linear and quadratic with respect to the field [see Eqn (48)]. The validity of this equation for doped VDF/TrFE copolymers was verified for the copolymer containing DEANAB in a concentration of 0.5 mass %. The films were not polarised; therefore, only the local field for the initial ferroelectric crystal E_l should be considered. In accordance with Eqn (45), below the Curie point $E_l \neq 0$, and in the paraelectric phase $E_l = 0$ because $P_s = 0$. Thus, on passing through the Curie point (~ 370 – 380 K), the absorption band should shift, which is actually observed by experiment.²⁰⁸ The absorption bands of the dyes DEANAB and R6G change in different ways near the Curie transition; in the former case, they shift to shorter wavelengths, and in the latter case, conversely, they shift to longer wavelengths. In addition, the magnitudes of these shifts for these dyes are also substantially different.²⁰⁸ These facts can also be explained in terms of the proposed model. In fact, it has been reported^{216,220} that for DEANAB, $\Delta \mu = 8$ – 10 D and $\Delta \alpha = +45 \text{ \AA}^3$, and for R6G these values are markedly lower — $\Delta \mu = 1.5 \text{ D}$ and $\Delta \alpha = -1.2 \text{ \AA}^3$. According to Eqn (48), this should result in a smaller shift of the band for R6G, which was actually observed in the experiments.

The model considered here makes it possible to estimate the local field after poling of a doped film. As noted above, polarisation can be accompanied by substantial structural changes, which influence E_l . Polarisation is attained using high-strength fields; therefore, charge carriers are injected from the electrode into the film and they also influence E_l . The local field can be calculated from the frequency shift of the absorption band after polarisation. This calculation was performed^{46,47} in relation to mixtures of PVDF with PMMA doped with a dye. Other researches tackled this problem more rigorously.²⁰⁸ They believed that direct recording of the shift of the bands is complicated because the bands are broad. Therefore, they proposed recording the degree of light modulation by an alternating field applied to the sample.^{218,220–222} Practically, the task was to measure the gain in the optical density ΔD at frequency ν corresponding to the chosen band following the imposition of an electric field on the sample. This value should be proportional to the first and second derivatives of the optical density with respect to frequency²¹⁸

$$\Delta D(\nu) = A_1 \nu \frac{\partial D(\nu)}{\partial \nu} + A_2 \frac{\partial^2 D(\nu)}{\partial \nu^2}. \quad (49)$$

Assuming a particular symmetry of the molecular distribution over the factors A_1 and A_2 for measurements at the first and second harmonics of the modulating field, one can find E_l .

Poling of a Langmuir–Blodgett film of PVDF in a $\pm 40 \text{ MV m}^{-1}$ field induces a substantial Stark effect, proportional to the first derivative $\partial D/\partial \nu$. When the direction of the polarising field changes, the sign of the linear Stark effect changes. This means that the dipole moments of the dye are also re-oriented in the opposite direction. If a constant field E_n is applied together with the modulating field, variation of the former induces the variation of the amplitude of the linear Stark effect in accordance with a pattern having a hysteresis. The hysteresis may arise due to the interaction of the dye dipoles with the internal field of the ferroelectric. The E_l value was found to be 300 MV m^{-1} . Thus, as in the studies cited above,^{46,47} the internal field was found to be much more intense than the polarising field.

The structures of Langmuir–Blodgett films have been considered²²³ in relation to the homopolymer PVDF, which usually crystallises as a nonpolar α -phase.²⁸ Primary attention was devoted to conformational characteristics of films prepared from a solution in DMSO.²²³ Analysis of the IR spectra showed that crystallisation in the thickest film (30 monolayers) gives a ferroelectric β -phase with planar zigzag conformations of chains.²⁸ This is confirmed by the presence of specific absorption bands at 470 , 509 , 840 and 1275 cm^{-1} . The formation of this conformation is apparently facilitated by the substrate on which the film is formed. This substrate is water, the molecules of which have a high dipole moment. Under these conditions, the minimum free energy can be attained by decreasing electrostatic interactions. The decrease is most pronounced if a chain in the planar zigzag conformation is parallel to the water surface.²²³

This role of water in the establishment of the conformation of PVDF chains is supported by the fact that polymerisation of VDF in aqueous media always results in a polymer crystallised as the polar β -phase.²²⁴ In addition, if the foregoing is true, the Langmuir–Blodgett film being formed (provided that the transfer on a solid substrate does not change the situation) should possess a non-zero spontaneous polarisation P_s . Indeed, a finite value of pyroelectric response has been noted experimentally for a non-polarised film.²²³

As the number of monomolecular layers n in the Langmuir–Blodgett films decreases, the conformations of macromolecules may change, due to the enhancement of the role of surface states differing in energy characteristics from those in the bulk. In order to verify this hypothesis, the IR spectra of films containing different numbers of monomolecular layers have been compared.²²³

A decrease in the number of monolayers in a Langmuir–Blodgett film ($n = 15$ and 10) brings about the appearance of conformational defects as the TGTG[−] and T₃GT₃G[−] isomers, which can be detected from the increase in the intensity of the absorption bands corresponding to them (Table 15). Apparently, these changes occur as accumulation of conformational defects as the above-mentioned isomers in the ferroelectric β -phase. The defects originate within long sequences of planar zigzag conformations (see Table 15). This is confirmed by the character of variation of the intensities of bands at 1275 and 840 cm^{-1} , sensitive to these sequences.^{28,225} The longest sequences are the first to be affected because the decrease in n from 30 to 10 results in the intensity of the band at 1275 cm^{-1} decreasing by 30% and that of the band at 840 cm^{-1} decreasing by only 10% .

The structural changes following a decrease in the thickness of a Langmuir–Blodgett film deteriorate the three-dimensional ordering in the ferroelectric crystal. This is indicated by the increase in the intensities of the two bands associated with the amorphous structure, 600 and 905 cm^{-1} . This conclusion is also supported by the variation of the intensity of the band at 470 cm^{-1} , which is attributed to *trans*-isomers in disordered areas in PVDF.²⁸ The increase in the intensity of this band

Table 15. Relative variation of the normalised intensities of several bands in the IR spectra of the Langmuir–Blodgett films of PVDF with various numbers of monolayers.²²³

Bands	Conformation	Phase ^a	<i>n</i>		
			30	15	10
470	TT	a	0.29	0.28	0.53
509	TT	a, c	0.21	0.18	0.19
530	TGTG [−]	—	0.04	0.16	0.28
600	—	a	0.09	0.74	1.14
612	TGTG [−]	—	0.06	0.40	0.43
770	T ₃ GT ₃ G [−]	—	<0.05	0.20	0.31
795	TGTG [−]	—	<0.01	0.08	0.14
813	T ₃ GT ₃ G [−]	—	0.05	—	0.14
840	(TT) _{<i>n</i>} (<i>n</i> ≥ 3)	—	1.09	1.02	0.97
905	—	a	0.06	0.36	0.22
F(β)	—	—	0.85	0.58	0.45
1275	(TT) _{<i>n</i>} (<i>n</i> ≥ 4)	—	2.2	1.7	1.5
1235	T ₃ GT ₃ G [−]	c	0.37	0.67	0.29
1142	—	—	0.67	0.62	0.32
1115	—	—	0.27	0.52	0.73
1097	—	—	0.18	0.062	0.11
1035	—	—	1.09	1.19	1.33
1011	—	—	0.12	0.26	0.22

^a Amorphous (a) and crystalline (c) phases.

following a decrease in *n*, points to the tendency for disordering of chains in the planar zigzag conformation.

The above structural changes in the studied films can also influence their electrophysical characteristics. If the structural changes in the Langmuir–Blodgett films of PVDF and VDF/TrFE copolymer are assumed to be similar, then regular features can be found for the latter, for example, in the parameters of the Curie transition.

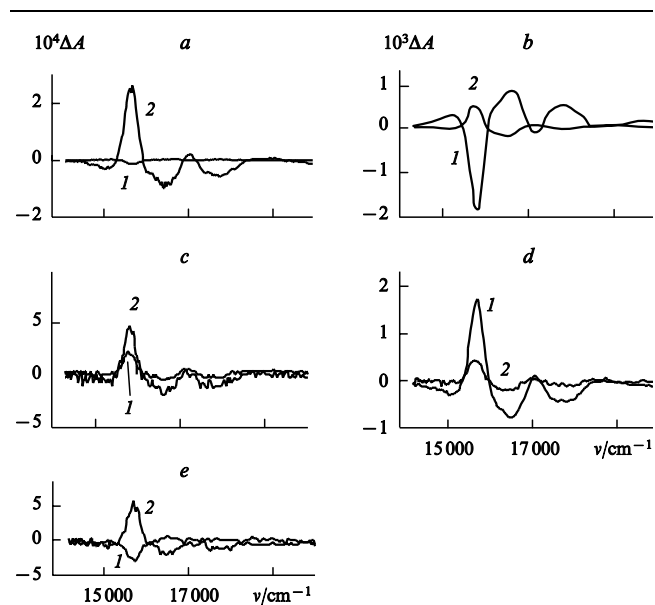
The dielectric anomalies (the maximum of the dielectric constant) near the Curie transition in the Langmuir–Blodgett films of the 70/30 VDF/TrFE copolymer have been considered.²²⁶ Two anomalous regions (a low-temperature and a high-temperature region), were found in all films (*n* varied from 30 to 2). Since the first anomaly becomes more pronounced as *n* decreases (see Fig. 37*a,b*), it was regarded as being due to the surface ferroelectric transition. The assumption that the structural changes in very thin Langmuir–Blodgett films formed from the copolymer and the homopolymer are similar entails an interesting conclusion. The low-temperature Curie transition can be ascribed to the crystals of the ferroelectric β-phase with high concentration of conformational defects and with the tendency for disruption of the three-dimensional ordering in the bulk.

The pyroelectric response curves for the switching of polarisation in the Langmuir–Blodgett films based on PVDF²²³ exhibit hysteresis similar to that observed in the Langmuir–Blodgett films based on the VDF/TrFE copolymer (see Fig. 35).²²³ For a PVDF film with *n* = 30, the calculated coercive field strength was 500 MV m^{−1}. This coincides in order of magnitude with that for the film based on the VDF/TrFE copolymer. Tentative experiments with the Langmuir–Blodgett films having *n* = 15 show that the switching voltage remains the same (8–10 V), *i.e.* the coercive field is enhanced by a factor of nearly two. As noted above, similar results have been observed for VDF/TrFE copolymer films. Thus, a decrease in the number of monomolecular layers in the Langmuir–Blodgett films of the polymers in question increases the coercive field. This fact together with the data on the structural changes in the PVDF film entail the following interesting conclusion. The increase in the intensity of the band at 600 cm^{−1} following the decrease in the number of monolayers formally implies a decrease in the degree of crystallinity; therefore, the enhancement of the coercive field is due to an increase in the

proportion of the disordered phase. This conclusion is confirmed by the results obtained for block PVDF films, in which a decrease in the degree of crystallinity also results in a linear increase in the coercive field, although these fields in block films are substantially lower in magnitude.¹⁴⁰

Analysis of the hysteresis curves for the pyroelectric response (see Fig. 35) displayed yet another specific feature of the Langmuir–Blodgett films. Judging by the voltage applied for measurement of the pyroelectric response, the intensity of the break-down field should be at least 1 GV m^{−1}. This value is much greater than the corresponding values for block films. The above-noted specific structural features of the Langmuir–Blodgett films may be responsible for this. This film can be regarded as a material with 100% degree of crystallinity in the direction perpendicular to its surface. The mobility of free charge carriers in this material is much lower than that in a material containing the amorphous phase, in which chains execute cooperative motions with large amplitudes.²⁸ The break-down in the Langmuir–Blodgett films under study is limited most likely by a thermal mechanism, which requires a particular free path length of the carriers. The free path length can happen to be longer than the film thickness. In this case, there are no prerequisites for an avalanche-like movement of charge carriers, which limits the currents for the thermal break-down mechanism.

The local fields created by ferroelectric crystals have been studied in detail²²⁷ by Stark spectroscopy. The optical probe used was a multilayer of the anthraquinone dye KD-78, having a principal absorption band at about 15700 cm^{−1}. The ferroelectric moiety of the film contained 70 monomolecular layers of PVDF and the probing moiety incorporated six bimolecular layers of KD-78. A symmetrical set of aluminium electrodes was used in the experiments. The change in the absorbance (Δ*A*) was measured at the principal frequency (*f*) and the second harmonic (2*f*). The relations derived by Palto²²⁷ were used to calculate two characteristics, namely, the amplitude of the local alternating field (*E*_i) and the static local field (*E*_{dc}). Figure 38 presents the experimental Stark spectra for the PVDF Langmuir–Blodgett

**Figure 38.** Spectra of the Stark effect at the first (1) and second (2) harmonics demonstrating bistable switching of the static local field in the initial nonpolarised (a) and polarised (b–e) Langmuir–Blodgett PVDF films;²²⁶

(b) a bias voltage, $U_{dc} = +10$ V, was applied to the sample; (c) $U_{dc} = 0$ after poling by a voltage of +10 V; (d) a bias voltage, $U_{dc} = -10$ V, was applied to the sample; (e) $U_{dc} = 0$ after poling by a voltage of -10 V. The spectra were measured at the alternating voltage amplitude $U = 5$ V, basic frequency $f = 1000$ Hz.

films; it is using this spectra that these characteristics were calculated. A clear-cut quadratic Stark effect of the probing layer measured at the second harmonic is observed in the initial non-polarised film. With allowance for the electrooptical constant for KD-78, $C_b = 5.7 \times 10^{-22} \text{ m}^2$, and the amplitude ΔA of the quadratic Stark effect, the local field was found to be 270 MV m^{-1} .

The Stark effect at the first harmonics for the initial sample is 20 times weaker ($\Delta A_1 \approx 1.2 \times 10^{-5}$); this corresponds to a static local field strength of -13 MV m^{-1} (see Ref. 227), which is due to the remanent polarisation in the initial film. After a constant bias voltage ($+10 \text{ V}$ with respect to the electrode) has been imposed on the substrate, the remanent polarisation sharply increases because the amplitude of the Stark effect at the first harmonics increases by more than two orders of magnitude (see Fig. 38b). The ΔA_2 also increases approximately twofold, and the above-mentioned local fields become $E_1 \approx 380 \text{ MV m}^{-1}$ and $E_{dc} \approx -1.4 \text{ GV m}^{-1}$. The ratio $E_{dc}/E_1 \approx -3.7$, which is much greater in magnitude than the ratio of the constant voltage to the alternating voltage amplitude, which is equal to two. Thus, the local field factor at zero frequencies is ~ 1.9 times greater than at a modulation frequency, equal to 1 kHz , *i.e.* dispersion of the local field factor is observed.

An unusual result was obtained after removal of the $+10 \text{ V}$ voltage (see Fig. 38c). It can be seen that the sign of the effect at the first harmonic changes, which indicates unambiguously the change in the local field direction with respect to that in the initial (non-polarised) sample. The static local field becomes $+170 \text{ MV m}^{-1}$, *i.e.* it is higher than that in the initial film by more than an order of magnitude. This may be due to substantial structural rearrangements (for instance, a sharp decrease in the number of conformational defects) in the Langmuir–Blodgett film after polarisation. A voltage with the opposite sign (-10 V , see Fig. 38d) does not change the Stark effect at the second harmonic, *i.e.* E_1 remains unchanged. However, the effect at the first harmonic does change. If the electric displacement is subsequently diminished to zero, the static field would be retained but its sign would be reversed, -170 MV m^{-1} . This field does not relax over a plausible period of time but it can be switched to the opposite one.

Thus, two directions of the local static field correspond to the two directions of the polarisation vector in the ferroelectric crystal. However, one contradiction has been noted.²²⁷ In fact, the direction of the local static field should coincide with the direction of the remanent polarisation. The opposite situation occurs in the experiment: the sign of the Stark effect at the first harmonic in the presence of a polarising field is opposite to the sign of the Stark effect after the removal of the bias field (see Fig. 38d, e).

A model has been developed²²⁷ which assumed full symmetry of the near-electrode areas with identical space charge distribution. Analysis of the situation in the absence of this symmetry shows that the direction of the local static field can be opposite to that of the polarisation. In this case, the question arises of whether the assumption of the asymmetry of the space charge on the sides of near-cathode and near-anode regions is physically substantiated.²²⁸ This question can be answered by using the results of some studies dealing with the behaviour of PVDF in strong electric fields. The pyroelectric characteristics of polarised samples on application of thermal pulses on the sides of the cathode and the anode has been studied.²²⁹ The pyroelectric effect was found to be higher in the latter case. This was interpreted as being indicative of an asymmetry of the space charge on the sides of the cathode and the anode.

Another independent group of experiments included elucidation of the possibility of the appearance of a bending moment in polarised films upon imposing an electric field.²³⁰ It was shown that in the case of a non-shielded electrode (*i.e.* when there were prerequisites for the injection of charge carriers from the electrode in the polymer) and not very high polarisation fields, bending

actually arose in the film when working in the mode of the inverse piezoelectric effect. This fact was unambiguously ascribed to the asymmetry of the arising space charge on the cathode and anode sides.²³⁰ This asymmetry can appear if the conditions for the injection of electrons and holes into the polymer are non-equivalent. Analysis of the voltammetric characteristics of PVDF films obtained in studies of the conduction in strong electric fields also confirms this assumption.²³¹ The authors of two studies cited^{229,230} arrived at the same conclusion, namely, that in the case of contact poling of PVDF, the injection of holes into the material is preferred over the injection of electrons. Thus, the interpretation of the abnormal behaviour of the local field direction after removal of the polarising voltage proposed by Palto²²⁷ is confirmed by independent experiments.

Apart from the electrophysical characteristics of thin Langmuir–Blodgett films ($n = 5$), the change in the direct and inverse photoemission spectra (DPES and IPES, respectively) was considered to be additional substantiation of the presence of surface ferroelectricity.²³² The methods of electronic spectroscopy, which are extremely sensitive to the state of the surface, can provide useful and independent information on this problem. Analysis of the temperature dependences of these spectra shows substantial changes in the electronic structure of the films near the low-temperature transition (20°C) (Fig. 37a, b, f), similar to those found in the surface layers of germanium^{233,234} and silicon.²³⁵ The density of states at the Fermi level in the low-temperature transition region changes markedly (see Fig. 37). This was interpreted as pointing to strong electron–phonon interactions near this transition. Assuming that the copolymer compositions at the surface and in the bulk are identical, Choi *et al.*²³² concluded that the difference between the electronic structures in the bulk and near the surface may be due to the lower coordination of atoms in the latter case. The presence of characteristic points on the temperature dependences of the conductivity, pyroelectric current, dielectric permittivity or electric capacity was also interpreted as being due to the presence of two types of transition — those on the surface and in the bulk.

The whole set of these data makes it possible to elucidate the mechanism of formation of the ferroelectric phase following a decrease in the thickness of Langmuir–Blodgett films somewhat more precisely. Indeed, the interpretation of experimental data^{226,232} does not account for some details of the experimental curves. For example, two dielectric anomalies of the temperature dependences of the dielectric permittivity are observed as well for the block films of the 65/35 VDF/TrFE copolymer (see Fig. 18 and 27). According to X-ray diffraction data, two types of ferroelectric phase, QL and LT, should be present in these compounds.²⁸ The less perfect QL phase may be responsible for the low-temperature transition.

Some indirect data supporting the interpretation of the anomalies observed^{226,232} which assumes the existence of ferroelectric QL and LT phases can also be found in earlier publications by the same authors. Indeed, no low-temperature transition was noted in a similar Langmuir–Blodgett film (see Fig. 36), *i.e.* this transition is not always reproducible. The low-temperature ‘anomaly’ of the dielectric permittivity is more clear-cut in the heating regime, whereas in the cooling regime it is weak and the high-temperature anomaly is more pronounced (see Fig. 37). Since this film is formed by only two copolymer monolayers (*i.e.* there is actually no bulk), it can be assumed that the film structures in the heating and cooling regimes should be different. A similar behaviour is also typical of thicker films ($n = 5$). Thus the conduction ‘anomaly’ observed in the region of the low-temperature transition is also more pronounced during heating (see Fig. 37d). Moreover, the electronic spectroscopy data indicate that the transition ascribed to the bulk is observed only in the cooling regime (see Fig. 37c).

These facts can be interpreted more simply taking into account the existence of the QL and LT phases. In this case, the different ratios of the ‘anomalies’ at 20 and 80°C are obviously

due to interconversion of these phases. In particular, during heating (to fairly high temperatures), annealing can occur, which is always accompanied by enhancement of the lattice ordering for crystallisable polymers. In this particular case, this is the QL $\rightarrow$ LT type transition. Apparently, an increase in the proportion of the latter (more perfect) phase accounts for the ‘anomalies’ noted for several characteristics of the transition in the heating–cooling cycles.

According to STM, Langmuir–Blodgett films of the copolymer²²⁶ contain chains with bent skeleton, which is consistent with one of the models of the QL phase structure (see Fig. 21a).²⁸ STM studies show²²⁷ that the identity period across the chain ranges from 2.7 to 5 Å for different regions of the film. This may be because areas of either phase differing in packing density across the chain can be present in the scanning area.^{28, 67}

Thus, it can be assumed that Langmuir–Blodgett films incorporate two types of ferroelectric phase with different degrees of perfection. The ratio of these phases can change upon a decrease in the film thickness towards a higher content of the less perfect ferroelectric phase. This is confirmed by IR spectroscopy (see Table 15).

The concept assuming the existence of two types of ferroelectric phase in PVDF and VDF copolymers can also help in the interpretation of yet another phenomenon observed in the Langmuir–Blodgett films of the VDF/TrFE copolymer. Ducharme *et al.*²³⁶ verified the hypothesis of Devonshire²³⁷ about the presence of a critical temperature (T_c) and a critical electric field (E_c) in ferroelectrics with a first-order phase transition (at the Curie point). Practically, the task was to follow the hysteresis curves of the dielectric permittivity ϵ' upon application of an alternating electric field on the Langmuir–Blodgett film. It was found that below 70 °C the field dependences of ϵ' display a single peak (although it is asymmetrical) falling on the region of the coercive field. In the temperature range from 90 to 140 °C, the $\epsilon'(E)$ curves have two maxima, the positions of which depend on the temperature.²³⁶ It was suggested to represent the E – T phase diagram for this temperature range (at 1 atm) as the linear plot for the Curie point *vs* the field strength (see Fig. 39b) similar to the plot that can be obtained for the block films of the 52/48 VDF/TrFE copolymer (see, e.g., Fig. 25).⁹⁵ By processing the experimental data,²³⁶ critical parameters of the films were determined. Data for these films and for other ferroelectrics are listed in Table 16. It can be seen that the critical field for the Langmuir–Blodgett film is higher by several orders of magnitude than the fields for other ferroelectrics. This fact is predictable for VDF copolymers because the coercive fields for them are also much higher. The difference between the T_c values for the Langmuir–Blodgett film and a block copolymer film raises more questions. Some of them can be answered upon examination of Fig. 39. When measurements are performed during heating in the absence of a field (curve 1), two types of transition

Table 16. Parameters of the ferroelectric phase transitions in the Langmuir–Blodgett ($n = 30$)²³⁶ and block²³⁸ films of the 70/30 VDF/TrFE copolymer, in BaTiO₃ (see²³⁹), in the crystals of deuterated potassium dihydrogen phosphate (DPDP)²⁴⁰ and in a liquid-crystal ferroelectric (LCF).²⁴¹

Parameter	Langmuir–Blodgett–film	Block film	BaTiO ₃	DPDP	LCF
$T_c / ^\circ\text{C}$	80 ± 10	102	108	–61	55.0
$T_{cr} / ^\circ\text{C}$	145.5	–	116	–60	55.8
$10^6 E_{cr} / \text{V m}^{-1}$	$(0.93 \pm 0.1) \times 10^3$	–	0.6	0.83	5.0
$\frac{dT_c}{dE} / \text{m (}^\circ\text{C)} \text{V}^{-1}$	$(7 \pm 2) \times 10^{-8}$	12×10^{-8}	6.5×10^{-4}	1.25×10^{-6}	1.6×10^{-7}

with temperatures of ~ 80 and ~ 110 °C are recorded, while in the cooling regime (curve 2) only one transition is detected taking into account the temperature hysteresis. This points to the presence of two types of ferroelectric phases, the ratio of which changes on passing from the heating regime to the cooling regime due to the QT $\rightarrow$ LT transition on annealing (heating). This transition can also be induced by an electric bias field because only one transition is observed in this case even during heating (see curve 3).

One circumstance which has not received adequate attention²³⁶ should be noted, namely, the exceptionally broad temperature range in which the double hysteresis loops of ϵ' are observed. For Langmuir–Blodgett films, this range is 65 °C, whereas for BaTiO₃ it covers only 8 °C (and even less for other ferroelectrics). This can also be interpreted with the aid of the assumed existence of two types of ferroelectric phase, QL and LT. If these phases differ in the degree of lattice perfection, their coercive fields should also differ, which is reflected as twin hysteresis loops on the $\epsilon'(E)$ curves.²³⁶ If this assumption is used to explain the broad range of critical temperatures (see Table 16, Fig. 39), an equally broad temperature range of coexistence of these phases should be expected. In fact, in the VDF/TrFE copolymer with the composition 65/35 (*i.e.* approximately the same as that of the copolymer studied in the publication under discussion²³⁶), the QL and LT phases coexist in a temperature range of not less than 70 °C (see Fig. 20). This value is close to that indicated by Fig. 39, which confirms once again the validity of this hypothesis.

Evidence that the ferroelectric QL phase can occur not only in VDF/TrFE copolymers but in the homopolymer and in other copolymers (for example, with TFE) can be found in the literature. If the low-temperature transition is assumed to be due to the QL $\rightarrow$ paraelectric transformation, it should also be expected in the Langmuir–Blodgett films based on PVDF. Tentative results show that this is actually the case.

In all probability, the QL phase reflects the existence of so-called quasi-domains, characterised by a particular type of long-range order, in the disordered phase of the objects considered. The presence of quasi-domains was judged relying on the ‘anomalies’ of the low-temperature dielectric relaxation processes in PVDF.²⁴² These processes are attributed to the mobility in the disordered phase.²⁸ The static dielectric permittivity in the temperature range studied has been found to increase with temperature, which is an atypical type of behaviour for most polymers. The general thermodynamic expression for the entropy of a dielectric in field E has the form²⁴³

$$S = S_0 + \frac{\partial \epsilon_0}{\partial T} \frac{E^2}{8\pi},$$

where S_0 is the entropy without a field. When a field is applied, the entropy increases. This can be interpreted only as an indication of

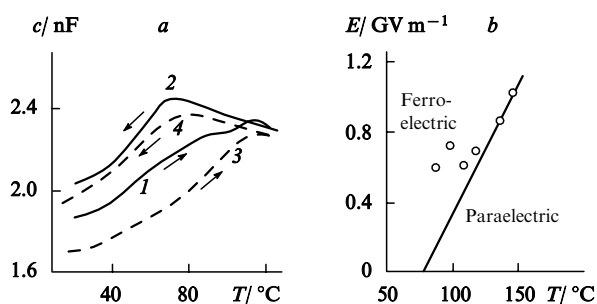


Figure 39. Temperature dependences of the capacity in the heating–cooling cycles in the absence of a field and with a bias field (a) and the E – T phase diagram ($p = 1$ atm) for the Langmuir–Blodgett films of the 70/30 VDF/TrFE copolymer with $n = 30$;²³⁶ (1, 2) without a bias field; (3, 4) with a bias field, $U = 5$ V.

existence of correlated chain sections with a definite long-range order in the disordered areas.²⁴³

The quasi-domains in question (like classical domains) should undergo a transition into a disordered (paraelectric) state. This is indicated by the dielectric anomalies (in particular, a maximum of the dielectric absorption $\Delta\epsilon$) found for the β -relaxation in PVDF.²⁴⁴ In the homopolymer, this maximum is often masked by the α_c -relaxation region.²⁸ The intensity of α_c -relaxation substantially decreases with a decrease in the degree of crystallinity. Therefore, the dielectric anomalies in the region of the hypothetical transition should be detected more easily in amorphised polymers of this class.

An efficient way of amorphisation of PVDF is its copolymerisation with comonomers having bulky substituents. In particular, hexafluoropropylene (HFP) can be used for these purpose. Indeed, the crystallinity of the 86/14 VDF/HFP copolymer proves to be markedly lower.²⁴⁵ The temperature dependences of the dielectric permittivity in the region of 40–50 °C has an anomaly, which was attributed to a smeared transition of quasi-domains into a disordered state.

The low-temperature dielectric anomaly in the Langmuir–Blodgett film of the 70/30 VDF/TrFE copolymer²²⁶ can be identified by a more detailed comparison of the dielectric data for samples obtained by the standard method (block films) and by the Langmuir–Blodgett method. It has been noted above that two transitions are detected for both types of films (see Fig. 18*a* and 37*a*, *b*, *f*). Some researchers separated the contributions of the dielectric constant components by the amorphous and crystalline phases to the overall curves.²⁴⁶ It was found that the amorphous phase in all the VDF/TrFE copolymers considered (73/27, 65/35 and 54/46) is characterised by a blurred maximum in the 0–40 °C range. The maxima of the dielectric constant of the Langmuir–Blodgett films derived from the VDF/TrFE copolymer,²²⁶ PVDF^{242, 244} and the VDF/HFP copolymer²⁴⁵ are located in about the same temperature range. Thus, these maxima can be considered to be of the same origin; in the case of block films, this is the transition of quasi-domains occurring in the disordered regions into the disordered state and for the Langmuir–Blodgett films, this is a similar transition occurring in the near-surface macromolecules, the conformational state of which is close to that in the amorphous phase of block films.²²³

Evidently, the reason for the formation of the quasi-domains (in other words, the QL phase) lies in the fact that the chains of the amorphous phase in the vicinity of the crystals of the ferroelectric β -phase occur under the influence of strong local fields. According to theoretical estimates,²⁴⁷ they can be as high as 9.28 GV m⁻¹ in PVDF (with crystals of the β -form) at room temperature. They are of the same order of magnitude (4 GV m⁻¹) for 70/30 VDF/TrFE copolymer, although the experimental values are somewhat lower. Such high fields in the area of localisation of chains of the disordered phase create conditions for them to be arranged in quasi-domains. In fact, in such a field, the potential energy of the CF₂ bond dipole in PVDF at room temperature is very high (11.7 kcal mol⁻¹).²⁴⁷ However, the formation of quasi-domains (QL phase) in the disordered phase is possible in this case only when the fluctuations are high-amplitude cooperative motions in this phase. A peculiar feature of PVDF and VDF copolymers is that, due to the low glass transition temperature, these motions really occur in the amorphous phase at room temperature (with relaxation times of $\sim 10^{-7}$ s);^{28, 242} therefore, it is quite likely that prerequisites for the formation of sections with an intermediate form of ordering would arise in the areas adjacent to the crystals.

Once the above-described nature of the formation of quasi-domains (QL phase) has been accepted, one reason for the transition of these fluctuation structures into the disordered state (low-temperature transition) can be explained as follows. The allowance made for the contribution of dipole oscillations in the ferroelectric crystal of the β -phase²⁴⁷ shows that an increase in the temperature diminishes the spontaneous polarisation and, correspondingly, the local field at the boundaries with the disordered

phase. Therefore, at a particular temperature, the quasi-domains would be destroyed, which is actually detected as the presence of the low-temperature dielectric anomaly.

One more piece of evidence for the existence of quasi-domains in the amorphous phase can be derived from the chain dynamics characteristics found by NMR. For example, the spin–lattice relaxation times T_1 for the amorphous (T_{1a}) and crystalline (T_{1c}) phases of VDF/TrFE copolymer have been compared.¹⁰⁰ These characteristics were found to differ by more than an order of magnitude below the Curie point and by a factor of only two above this point. Thus, the chain dynamics in the disordered phase is characterised by approximately the same parameters as that in the paraelectric phase. This fact can be regarded as indirect evidence for the existence in the amorphous phase of these quasi-domains with imperfect long-range order similar to that occurring in the paraelectric phase.

The results obtained by the broad-line technique, a modification of the NMR method, also point to the presence of quasi-domains in the amorphous phase. If the quasi-domains actually do exist, the dynamics in them should differ from the dynamics in the proper disordered (isotropic) phase and in the crystal. Information on this point can be derived by strict analysis of the line contours in the NMR spectra of the compounds in question. This was demonstrated in relation to the VDF/TrFE copolymers.¹¹⁰ In particular, if the composition is 70/30, the free induction signal (for ¹H nuclei) at 15–60 °C is described by three components. The widest component refers to the ferroelectric phase, and the narrowest one corresponds to the isotropic amorphous phase. The intermediate component is attributed to so-called stressed amorphous phase. This might imply the quasi-domains mentioned above, in which the dynamics should be more hindered than that in the isotropic amorphous phase due to the presence of a certain long-range order. Furthermore, the reported¹¹⁰ data on the temperature dependence of the intensity of the intermediate component can be interpreted in a different way. In the region of 60–120 °C (below the Curie point), the intensity of the intermediate component increases appreciably. This was attributed to partial transition of the ferroelectric phase into the paraelectric phase. However, this hypothesis provokes serious objections. The researchers cited noted themselves that the experimental value of the second moment ΔH_2^2 for this component is 2.5 G², which is substantially lower than the value calculated for the lattice of the paraelectric phase (11.6 G²).

To explain this contradiction, a definite type of motion in the paraelectric lattice, namely, rotation of the chains about their axes, had to be assumed. If the intermediate component is related to quasi-domains, this fact can be explained. In the 60–120 °C region, some of the domains (in small crystals with less perfect packing) can pass into a state with higher symmetry (quasi-domains). The packing in them is less perfect than in the paraelectric phase; therefore, the dynamics is less hindered, which accounts for the low experimental value of ΔH_2^2 .

The assumption that the ferroelectric QL phase is identical to the quasi-domains, found in the amorphous phase in some experiments, is supported to some extent by the temperature dependences of the X-ray diffraction parameters for isotropic and textured samples of the 94/6 VDF/TrFE copolymer.¹⁹⁶ At a temperature of 160 °C (below the melting point), two reflections are observed, one of them corresponding to the β -phase and the other diffuse halo reflection being due to the paraelectric phase (Fig. 40). This can be judged relying on the interplanar spacings, which coincide with those in the same phase of the VDF/TrFE copolymer (see Fig. 20).

In the 170–180 °C temperature range, the interplanar spacing in the paraelectric phase sharply increases (see Fig. 40*b*). This may imply that the ferroelectric and paraelectric phases coexist up to the melting point. If the Curie point is considered to overlap with the melting region (due to the very high proportion of VDF in the copolymer), melting should be accompanied by the ferroelectric–paraelectric transition. Actually, melting of paraelectric

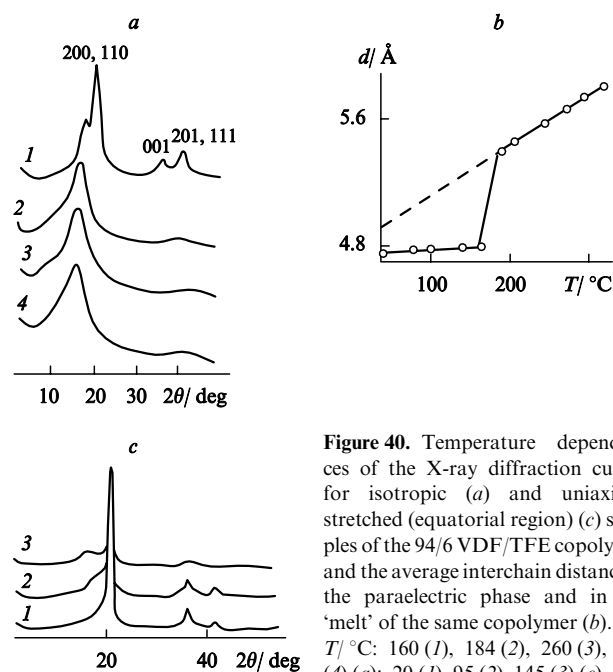


Figure 40. Temperature dependences of the X-ray diffraction curves for isotropic (a) and uniaxially stretched (equatorial region) (c) samples of the 94/6 VDF/TFE copolymer and the average interchain distance in the paraelectric phase and in the 'melt' of the same copolymer (b).¹⁹⁶ T /°C: 160 (1), 184 (2), 260 (3), 315 (4) (a); 20 (1), 95 (2), 145 (3) (c).

crystals can also be involved because the interplanar spacing in the lattice of the paraelectric phase sharply changes (see Fig. 40b). The halo reflection remaining for the melt ($T > 184$ °C) has a complex structure, *i.e.* in addition to the principal line, its asymmetry on the low-angle side is clearly observed. It can be seen that the half-width of the reflection (see Fig. 40a) is fairly small, which is unusual for isotropic systems with short-range order. Therefore, it was assumed¹⁹⁶ that the amorphous phase of the melt consists of two components. One component corresponds to the isotropic constituent, matched by the low-angle asymmetry of the halo reflection in the melt. The principal line characterises the presence of regions with anisotropic distribution of polymer segments. These regions can be characterised by a certain long-range order similar to that observed in the nematic phase of liquid crystals. These structures should be fairly stable to heating because the halo reflex is retained up to 315 °C (Fig. 40a).

If the energy of interatomic interaction is estimated based on the average interchain distance, this conclusion is also confirmed by Fig. 40b; extrapolation of the high-temperature straight line to room temperature gives $d = 4.92$ Å, whereas for the paraelectric phase $d = 4.76$ Å.

Upon texturing the copolymer samples (for example, by uniaxial stretching), the two components of the amorphous phase can be readily separated from one another. The isotropic component would be manifested as an azimuth-independent halo, and the anisotropic component would cause scattering only in the equatorial region.¹⁹⁶ The interaction energy in the areas described by the anisotropic component should be much lower than that in the ferroelectric crystal (see Fig. 40c). This can be judged by the temperature dependences of the average interchain distance for both phases. When measurements are carried out under isometric conditions (when disorientation of the β -phase crystallites is excluded), the anisotropic component of the X-ray diffraction patterns in the equatorial direction (see Fig. 40c) is better resolved from the principal intermolecular reflection of the ferroelectric phase at high temperatures.

Thus, analysis of the data listed above provides general characteristics of the nuances of the phase states of VDF-based polymeric ferroelectrics. The densest packing is found in the ferroelectric crystal lattices. If the density is characterised by the average interchain distance, it can be estimated based on the identity period d for the 200, 110 planes of the β -phase. In the 94/6 VDF/TFE copolymer at room temperature, this d value is

4.30 Å.¹⁹⁶ Transition from the ferroelectric phase to the paraelectric phase is accompanied by a substantial decrease in the packing density in the crystal — at room temperature d increases from 4.30 to 4.76 Å (see Fig. 40b). It is significant that in VDF/TrFE copolymers with high contents of the former component, the two phases can coexist up to the melting point. The Curie transition, in which the crystals in the ferroelectric phase pass into a non-polar form, occurs in the same region.

The amorphous phase of these polymers should incorporate two types of structure, one of them being typical of isotropic liquids. The anisotropic constituent of the amorphous phase should contain areas with a particular type of long-range order. The chain segments can be packed in these areas in such a way that the directions of their moments in particular regions are identical. Thus, so-called quasi-domains localised in the amorphous phase are formed; they can be classified as the imperfect ferroelectric QL phase. As noted above in analysing the NMR data, the energy of interaction in these quasi-domains should be close to that in the paraelectric phase.¹¹⁰

Thus, in quasi-domains, chains are packed more loosely than in the domains of the proper crystal phase (for the 94/6 VDF/TFE copolymer this difference is $\sim 15\%$). Therefore, two Curie transitions should occur in these compounds; they have been detected in both block films and Langmuir–Blodgett films. The specifics of the latter is that a decrease in the number of monolayers results in a higher proportion of chains in which three-dimensional order is lost and conformational defects are accumulated. Thus, the equilibrium in a domain–quasi-domain mixture (or a mixture of LT and QL phases) shifts towards higher contents of the latter component. Experimentally, this manifests itself as enhancement of the low-temperature transition.

IX. Conclusion

The analysis of the published data on the ferroelectricity in PVDF and VDF-based copolymers carried out in this review leads to the following main conclusions.

In the crystallisable polymers considered here, the amorphous phase is more than merely an inert matrix. The cooperative mobility in the disordered phase contributes to the switching of ferroelectric domains.

Polarisation is accompanied by an irreversible increase in the degree of crystallinity. This can be attained *via* an increase in the transverse dimension of crystallites of the β -phase due to incorporation of some chains of the disordered phase.

Unfreezing of the cooperative mobility in the amorphous phase facilitates field-induced structural rearrangements in it. The type and the degree of mobility in the disordered regions surrounding the ferroelectric crystals has a substantial effect on the coercive field.

The high dynamic heterogeneity of PVDF at room temperature can account for the stability of the ferroelectric characteristics, in particular, remanent polarisation. On exposure to a strong field, the new position of domains is stabilised upon 'shielding' by the space charge. The effective mobility of charge carriers is limited by the relaxation times of segments in the disordered phase, which are ~ 100 ns at room temperature. Under these conditions, a new equilibrium state of the space charge is attained over short periods, thus ensuring the above-noted stability of the switched domains.

The type of supermolecular structure was found to influence some ferroelectric characteristics. Specifically, the morphology of thick lamellar crystals proves to promote high spontaneous polarisation. If there are conditions for crystallisation of the chains in textured PVDF as ECC, the Curie point becomes markedly higher.

Two types of ferroelectric phase differing in the degree of perfection are characteristic of PVDF and VDF copolymers. The dielectric anomalies observed in the relaxation region ascribed to

glass transition imply that the QL phase can be localised in disordered regions of the polymer.

The Langmuir–Blodgett films derived from PVDF and VDF/TrFE copolymer possess single crystal textures because they display finite values of the pyroelectric response in the nonpolarised state. As the number of monolayers in these films decreases, conformational defects are accumulated and the crystallographic order tends to be violated.

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^a — *Polym. Sci. (Engl. Transl.)*

^b — *Russ. Crystallogr. (Engl. Transl.)*

^c — *Inorg. Matter. (Engl. Transl.)*

^d — *Physics-Uspekhi (Engl. Transl.)*

Methods for the synthesis of tritium-labelled fatty acids and their derivatives, oxylipins and steroids

V P Shevchenko, I Yu Nagaev, N F Myasoedov

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Abstract. The achievements in the field of synthesis and application of tritium-labelled oxylipins, steroids, fatty acids, phospho-, sphingo- and other lipids are reviewed. The importance of these studies for the solution of current problems of biochemistry, biology and pharmacology is exemplified in the application of labelled compounds. The bibliography includes 148 references.

I. Introduction

Methods used for the synthesis of tritium-labelled classical representatives of lipids and oxylipins (fatty acids, steroids, prostaglandins, sphingo- and phospholipids, *etc.*) and their biologically active analogues close in physicochemical properties to lipids have gained considerable popularity. The choice of lipids for investigation is based on the fact that apart from the ability of these compounds to accumulate metabolic fuel, which for many decades was considered to be their sole function,¹ two other important functions have been recently assigned to them. First, they are the principal structural components of cell membranes and, second, they are bioeffectors, which control intracellular biochemical reactions, intercellular interactions and other physiological processes occurring in the organism. Evidently, the interaction of bioeffectors with their targets and, consequently, the specificity of their action are largely determined by their structure.¹

The advantages of tritium as a radioactive label, *viz.*, low radiotoxicity, long half-life (12.26 years), high molar radioactivity (1.08 PBq g-atom⁻¹), *etc.*, are universally known.^{2–5} The methods used for the synthesis of tritium-labelled compounds include different versions of reactions of isotope exchange, chemical and enzymic methods. The mechanisms of labelling by isotope exchange[†] have been considered.^{5–15}

The labelling by a liquid-phase method is accompanied by reactions of isotope exchange; migration, isomerisation and hydrogenation of double bonds; selective hydrogenation of one of several double or triple bonds; dehalogenation and reduction of

the corresponding functional groups. Only a careful choice of reaction conditions can result in satisfactory yields of labelled target products. An important role is ascribed to the choice of a catalyst and a solvent and determination of optimum experimental parameters (the pressure of gaseous tritium, the reaction time, the catalyst : substrate : modifying additives ratio, *etc.*).

Classical methods have limited application, since only milligram and submilligram quantities of precursors are normally used in the synthesis of tritium-labelled compounds. As a result, the catalyst : precursor ratio should markedly exceed that prescribed for selective hydrogenation using classical procedures on purely technological grounds. In contrast, the proportional increase in catalyst-modifying additives (quinoline, pyridine, *etc.*) significantly decreases the yield of the labelled target product and considerably increases the total radioactivity of the reaction mass due to incorporation of the label into side products and modifying additives, which complicates the isolation and purification of the target compound.

If the components used in biological studies are sufficiently stable at elevated temperatures, a solid-phase method where the substance applied onto the catalyst is heated in the atmosphere of gaseous tritium is the most promising approach.^{9, 12, 13}

The method of isotope exchange with tritiated water in inert solvents is used for labelling compounds that are labile in hydrogenation conditions; the use of inert solvents prevents self-radiolysis of highly enriched tritiated water.² The latter is usually obtained by reduction of PdO with gaseous tritium. Palladium black and palladium catalysts immobilised on inert supports initiate the isotope exchange. Obviously, the more active the catalyst the higher the degree of isotope exchange with tritiated water, but the probability of degradation of the labile compound increases also.

As a rule, chemical syntheses of tritium-labelled lipids are preceded by the synthesis of the corresponding precursors^{4, 5, 16–22} containing triple or additional double bonds, halogen-substituted fragments, *etc.* Treatment of these compounds with gaseous tritium in the presence of a catalyst results in the formation of a labelled product. In some cases, tritium-labelled

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[†] Modern methods of isotope exchange can be conventionally divided into three main groups, *viz.*, heterogenous catalytic isotope exchange of gaseous tritium with an organic compound dissolved in a solvent (liquid-phase methods), heterogenous catalytic isotope exchange of gaseous tritium with a solid organic compound at elevated temperatures (solid-phase methods) and heterogenous catalytic isotope exchange of an organic compound dissolved in an aprotic solvent with tritiated water.

lipids are obtained by a multistep synthesis which utilises a labelled preparation as a starting compound. This approach requires the use of methods which not only ensure high yields of target products but also make the process technologically safe.

II. Synthesis of tritium-labelled fatty acids and their derivatives

1. Fatty acids

Fatty acids differ in the structure of the carbon backbone and the number of double bonds as well as in the presence and number of other functional groups. They are present in natural subjects, predominantly as esters. Fatty acids are constituents of phospholipids, sphingolipids, glycolipids, gangliosides, glycerides, steroid esters and vitamins. It had long been thought that the sole function of fatty acids was to provide membrane integrity and the optimum level of unsaturation of tissue lipids;²³ however, it has recently been established that these compounds also regulate the enzyme activity, modulate binding of steroid hormones to their specific receptors and control gene transcription.^{24–26} Indeed, a change in the fatty acid composition of membrane lipids changes the activity of membrane-bound enzymes and expression of receptors.²⁷

Isotopically labelled fatty acids can be synthesised by isotope exchange, selective hydrogenation of the corresponding acetylenic precursors with gaseous tritium as well as by chemical, microbiological and other methods.⁵

The liquid-phase method of isotope exchange is the simplest procedure for obtaining unsaturated fatty acids, since it allows direct labelling of the target compound. Besides, this procedure is devoid of many drawbacks of microbiological methods, *e.g.*, difficulties in isolation of labelled preparations from homogenates, isotopic dilution of the labelled target product with endogenous products derived from microbial cultures and the loss of the label in the course of biological conversions.^{4,5} For example, the molar radioactivity of labelled (5Z,8Z,11Z,14Z,17Z)-eicosapentaenoic (thymnodonic) acid synthesised from [8-³H]stearic acid⁵ using a culture of *Saprolegnia parasitica* (ATC 22284) decreased 250–400-fold in comparison with that of the original fatty acid.

The lability of alkenes in liquid-phase isotope exchange is the main property which restricts the application of this method for introducing the label into unsaturated fatty acids. It is known^{3–5} that hydrogenation, *cis-trans*-isomerisation and double bond migration occur extensively even with the Lindlar catalyst. The isomerisation reactions are equally probable, while the double bond migrates by 85%–88% towards the carboxy group. However, these restrictions did not prevent the labelling of both monoenoic and polyenoic acids by varying the reaction conditions (Table 1). Some data on the distribution of the label in molecules of these compounds will be given below.

Despite the relative simplicity of the liquid-phase isotope exchange, it is of limited use, since the molar radioactivity of target products seldom exceeds 0.1 PBq mol^{–1}. Molar radioactivities of polyenoic fatty acids are much higher, if chemical methods are used. Acetylenic precursors can be prepared either from the corresponding fatty acids or by total chemical synthesis. The former method was used in the synthesis of 5-acetylenic analogues of methyl arachidonate, methyl thymnodonate, the 14-acetylenic analogue of methyl arachidonate and the 4-acetylenic analogue of methyl (4Z,7Z,10Z,13Z,26Z,19Z)docosahexaenoate (methyl docosahexaenoate). This type of synthesis is illustrated in the example of 5-acetylenic analogues of eicosapolyenoic acids and the 14-acetylenic analogue of methyl arachidonate (Schemes 1 and 2).^{16, 17, 30}

The major difference in these schemes is that in the latter the epoxy acid is formed upon treatment of the starting compound with *m*-chloroperbenzoic acid in dichloromethane in the presence

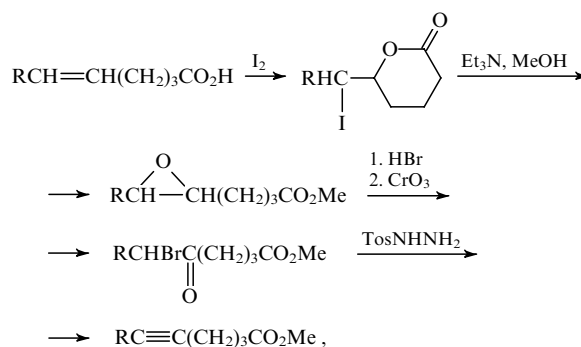
Table 1. The values of molar radioactivities (α) of labelled unsaturated fatty acids.^a

Starting compound	α /PBq mol ^{–1}	Ref.
Liquid phase isotope exchange		
Methyl oleate	0.146	28
Methyl linoleate	0.025	28
Methyl dihomo- γ -linolenate	0.034	28
Methyl arachidonate	0.092	28
Selective hydrogenation with gaseous tritium		
8,11,14-Triyne analogue of methyl dihomo- γ -linolenate	5.6	29
5,8,11,14-Tetrayne analogue of methyl arachidonate	7.4	29
5,8,11,14,17-Pentayne analogue of methyl thymnodonate	9.2	29
5-Acetylenic analogue of methyl arachidonate	1.3	16
14-Acetylenic analogue of methyl arachidonate	1.2	16
5-Acetylenic analogue of methyl thymnodonate	1.9	16
4-Acetylenic analogue of methyl docosahexaenoate	1.8	17

Note: In liquid-phase isotope exchange, the label is incorporated by isotope exchange of hydrogen atoms for tritium atoms; in hydrogenation with gaseous tritium, the label is incorporated owing to the reduction of triple bonds to double bonds.

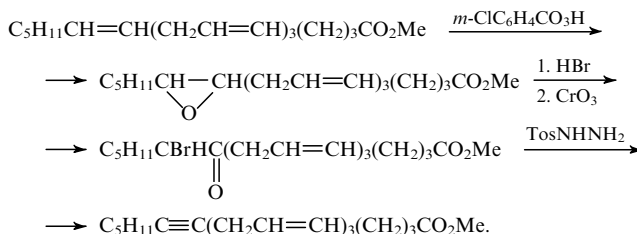
^a Free fatty acids were obtained by alkaline hydrolysis of their methyl esters.

Scheme 1



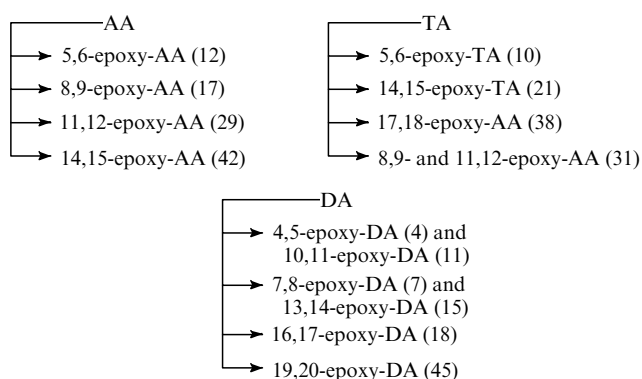
$\text{R} = \text{C}_5\text{H}_{11}\text{CH}=\text{CH}(\text{CH}_2\text{CH}=\text{CH})_n\text{CH}_2$ ($n = 2, 3$).

Scheme 2



of KHCO₃.¹⁶ It is known that the use of nonpolar solvents for epoxidation results in the formation of substantial amounts of diepoxides due to the high reactivity of the peroxy acid under the given experimental conditions; therefore, ethanol was used to increase the yield of monoepoxides.³⁰ This procedure was applied

Scheme 3



The figures in parentheses indicate the percentage of the monoepoxide with respect to the total monoepoxide content in the reaction mixture.

for the preparation of monoepoxides from arachidonic (AA), thymnodonic (TA) and docosahexaenoic acids (DA) (Scheme 3).

Acetylenic analogues of eicosapolyenoic acids, *viz.*, the 8,11,14-triayne analogue of methyl homo- γ -linolenate, the 5,8,11,14-tetrayne analogue of methyl arachidonate and the 5,8,11,14,17-pentayne analogue of methyl thymnodonate were synthesised by purely chemical methods (Scheme 4).

The reduction of triple bonds to double bonds in the atmosphere of gaseous tritium was used to prepare highly labelled polyenoic fatty acids (see Table 1). In order to increase the selectivity of hydrogenation of the corresponding acetylenic analogues, one had to modify palladium catalysts with lead diacetate, pyridine and quinoline. However, the yield of tritium-labelled alkenes did not exceed 10%–40% even when the hydrogenation of one triple bond was performed according to the previously described procedures (*cf.* Ref. 5). Satisfactory yields

were obtained with palladium on barium sulfate as a catalyst, which had been treated consecutively with methanolic solutions of lead diacetate [$\text{Pd}:\text{Pb} = 1:(0.5-1.0) \text{ mg mg}^{-1}$] and sodium borohydride [$\text{Pd}:\text{NaBH}_4 = 50:(0.4-4.0) \text{ mg mg}^{-1}$]. A 4:1 heptane–dioxane mixture was used as a solvent. The catalyst:substrate ratio was (2–6):1.²⁹ Under these conditions, the yield of the target products with a molar radioactivity of 1.2–1.8 PBq mol^{−1} per selectively reduced triple bond was 89%–99% after 25–35 min (see Table 1).

It is necessary to emphasise that the reaction conditions were optimised not only for the labelling of unsaturated fatty acids, but also for pheromones, attractants and lipid hormones the complete chemical synthesis of which includes selective hydrogenation of acetylenic precursors in the final stage.³¹ This can be exemplified in the use of acetylenic precursors in the synthesis of the *Lepidoptera* pheromones (Table 2).

Thus, bombykol (molar radioactivity 1.85 PBq mol^{−1}) was synthesised from hexadec-(10*E*)-en-12-yn-1-ol (see Ref. 29); the abscisic acid analogue (molar radioactivity 1.21 PBq mol^{−1}) (see Ref. 29) was prepared from (2*Z*)-5-(4-*tert*-butyl-*trans*-1-hydroxycyclohexyl)-3-methylpent-2-en-4-ynoic acid; retinoic acid (molar radioactivity 1.75 PBq mol^{−1}) (see Ref. 20) was obtained from 11,12-dehydroretinoic acid. (Z)-[11,12-³H]Hexadeca-1,11-dien-3-one, (Z)-[6,7-³H]eicos-6-en-11-one and some other labelled pheromones³² with a molar radioactivity of $\sim 1.5 \text{ PBq mol}^{-1}$ were obtained by selective hydrogenation of the acetylene bonds.

The use of the liquid-phase isotope exchange for labelling saturated fatty acids is not promising, since molar radioactivities of reaction products were of the order of several hundredths of PBq mol^{−1} (Table 3). However, in contrast with alkenes, the isotope exchange in saturated compounds is not accompanied by side reactions; therefore, investigations into the use of this method were carried out and some regularities were established. Thus it was found that the kinetic curves of the isotope exchange reaction reach the plateau rather rapidly. In this case, the degree of substitution of tritium for hydrogen is much smaller than could

Scheme 4

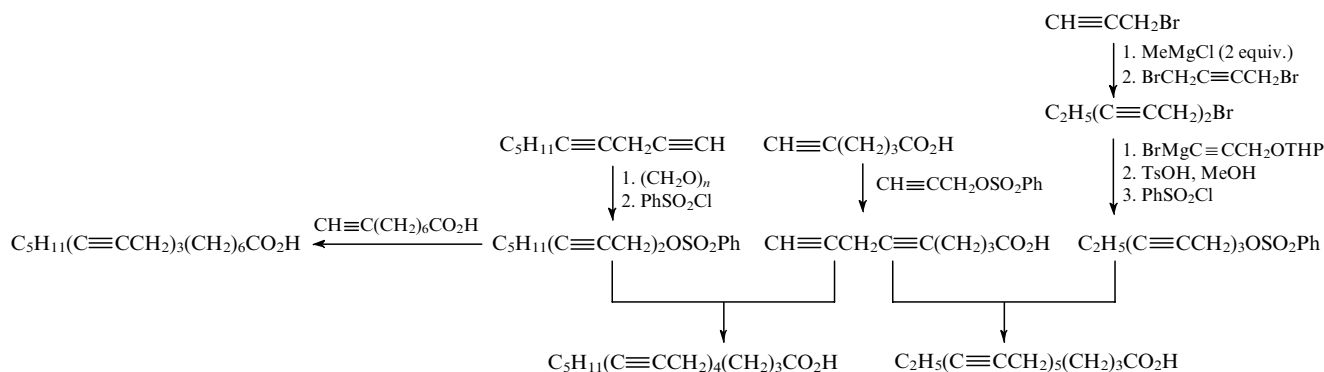


Table 2. Acetylenic precursors used in the synthesis of the pheromones of *Lepidoptera*.³¹

Acetylenic precursor	Pheromone component	Species
$\text{Me}(\text{CH}_2)_2\text{C}\equiv\text{C}(\text{CH}_2)_6\text{CH}_2\text{OH}$	(8 <i>Z</i>)-dodecenyl acetate	<i>Grapholitha molesta</i> , <i>Cydia molesta</i>
$\text{Me}(\text{CH}_2)_9\text{C}\equiv\text{C}(\text{CH}_2)_4\text{CHMe}_2$	(7 <i>Z</i> ,8 <i>Z</i>)-epoxy-2-methyloctadecane	<i>Porthetria dispar</i>
$\text{Me}(\text{CH}_2)_4\text{C}\equiv\text{C}(\text{CH}_2)_3\text{CH}(\text{OH})(\text{CH}_2)_9\text{Me}$	(6 <i>Z</i>)-heneicosen-11-one	<i>Orygia pseudotsugata</i>
$\text{Me}(\text{CH}_2)_5\text{C}\equiv\text{C}(\text{CH}_2)_3\text{C}(\text{O})(\text{CH}_2)_3\text{Me}$	(7 <i>Z</i>)-eicosen-11-one	<i>Carposina niponensis</i>
$\text{Me}(\text{CH}_2)_3\text{CH}=\text{CHC}\equiv\text{C}(\text{CH}_2)_3\text{CH}_2\text{OH}$	(5 <i>Z</i> ,7 <i>E</i>)-dodecadien-1-ol	<i>Dendrolimus spectabilis</i>
$\text{MeCH}_2\text{C}\equiv\text{CCH}=\text{CH}(\text{CH}_2)_5\text{CH}_2\text{OH}$	(7 <i>E</i> ,9 <i>Z</i>)-dodecadienyl acetate	<i>Lobesia botrana</i>
$\text{MeCH}=\text{CHCH}_2\text{C}\equiv\text{C}(\text{CH}_2)_7\text{CH}_2\text{OH}$	(9 <i>Z</i> ,12 <i>E</i>)-tetradecadienyl acetate	<i>Plodia interpunctella</i> , <i>Cadra cautella</i>
$\text{Me}(\text{CH}_2)_4\text{C}\equiv\text{CCH}_2\text{CH}=\text{CH}(\text{CH}_2)_2\text{CH}_2\text{OH}$	(4 <i>E</i> ,7 <i>Z</i>)-tridecadienyl acetate	<i>Phthorimaea operculella</i>
$\text{Me}(\text{CH}_2)_3\text{CH}=\text{CH}(\text{CH}_2)_2\text{C}\equiv\text{C}(\text{CH}_2)_6\text{OH}$	(7 <i>Z</i> ,11 <i>E</i>)-hexadecadienyl acetate	<i>Sitotroga cerealella</i>

Table 3. The values of molar radioactivities of saturated fatty acids.

Starting compound	α /PBq mol ⁻¹	Ref.
Liquid-phase isotope exchange		
Methyl stearate	0.036	28
Methyl palmitate	0.021	28
Methyl myristate	0.014	28
Methyl laurate	0.010	28
Solid-phase isotope exchange		
Stearic acid	13.50	33
Palmitic acid	12.90	33
Myristic acid	12.10	33
Lauric acid	11.50	33
3-Hydroxypalmitic acid	9.00	34
6-Ketopalmitic acid	27.80	29
Methyl stearate	38.00	29
11-Chloroundecanoic acid	6.30	34
Cetyl alcohol	5.50	33
Hexadecane	17.50	33
Solid-phase dehalogenation		
11-Chloroundecanoic acid	4.20	34
Hydrogenation with gaseous tritium		
Palmitoleic acid	1.47	35
Undec-10-enoic acid	2.96	14
5-(3-Octyloxy)pentanoic acid	3.89	36
12-Methoxydodec-1-ynoic acid	5.07	36

be expected from the equilibrium distribution of the tritium label. Besides, the kinetic curves of molar radioactivity have a complex shape, which is attributed to the different saturation of palladium with the hydrogen isotopes during the formation of the α -phase of palladium hydride and its subsequent transition into the β -phase.²⁸

The high thermal stability of alkanes has made it possible to use solid-phase isotope exchange for introducing the label into saturated compounds (see Table 3).

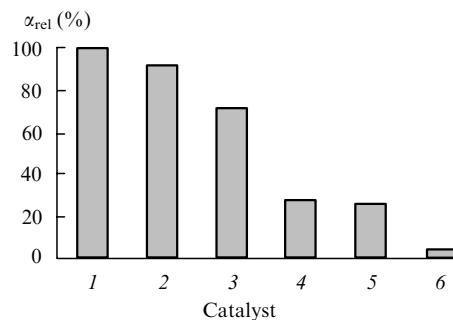
Studies of solid-phase isotope exchange with stearic acid as a model compound in the presence of palladium and platinum catalysts supported on different carriers showed that this reaction proceeded with the greatest efficiency on 5% Pt/C at 210 °C (the catalyst : substrate ratio = 10 : 1) (Figs 1–4).[‡]

Similar investigations were carried out with stearic acid homologues. It was demonstrated that in this case, too, the optimal conditions for a solid-phase isotope exchange were as follows: 5% Pt/C, the catalyst : substrate ratio = 10 : 1, reaction time = 15 min. Other regularities were also established. First, the dependence of changes in the molar radioactivities of fatty acid homologues on the length of the carbon chain was practically linear, which points to the random labelling by this method. Second, the temperature at which the degree of isotope substitution was a maximum ($T_{\max}$), was different for different analogues.

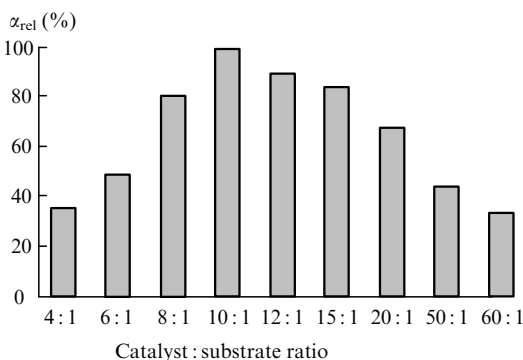
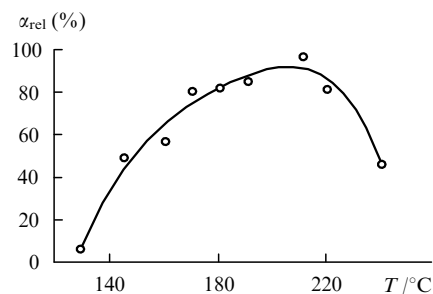
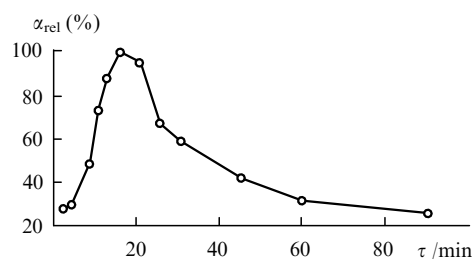
Acid	Lauric	Myristic	Palmitic	Stearic
M.p. /°C	44.3	58	64	70
$T_{\max}$ /°C	190	200	205–210	210

In all probability, this temperature depends on the phase transition temperature for representatives of the same homologous series (*e.g.*, fatty acids).

[‡] In the study aimed at establishing the relative degree of the label incorporation, α_{rel} , the maximum molar radioactivity of the preparation was taken as 100%.

**Figure 1.** The dependence of the relative degree of the label incorporation into stearic acid on the nature of the catalyst.

Catalyst: (1) 5% Pt/C, (2) 10% Pd/C, (3) 10% Pd/BaSO₄, (4) 5% Pd/C, (5) 5% Pd/BaSO₄, (6) 5% Rh/C.

**Figure 2.** The dependence of the relative degree of the label incorporation into stearic acid on the catalyst : substrate (5% Pt/C) ratio.**Figure 3.** The dependence of the relative degree of the label incorporation into stearic acid on temperature (the catalyst is 5% Pt/C, the catalyst : substrate ratio is 10 : 1).**Figure 4.** The kinetics of the label incorporation into stearic acid (the catalyst is 5% Pt/C, the catalyst : substrate ratio is 10 : 1, 210 °C).

It is evident that at certain temperatures the diffusion of these lipid molecules increases to such an extent that the rate of diffusion of the spill-over hydrogen no longer affects the rate of the overall reaction of isotope exchange. The efficiency of the isotope exchange decreases drastically after 10–15 min. The latter

circumstance can be rationalised as follows. The study of the valence state of hydrogen in hydrides of intermetallic compounds carried out by Semenenko *et al.*³⁷ has offered a new outlook on the problem of the valence state of hydrogen in systems of the Pd–H₂ type. Debates on this problem, which is of particular importance for hydride chemistry, have begun since the appearance of classical works of Ubbelohde,³⁸ who put forward a concept of a positively charged hydrogen atom on palladium, and of Gibb,³⁹ who proposed a model with a negatively charged hydride ion. Semenenko *et al.*³⁷ proposed and rationalised the concept according to which hydride dispersion is a result of a redox reaction associated with the formation of hydride ions, H^{δ−}, at a hydrogen concentration (*c*_H) in the solid hydride exceeding a critical concentration (*c*_{Hcrit}), which, in turn, depends on the redox potential of the reaction:



where M is the metal template of the catalyst. According to this model, the hydrogen chemisorbed on the active centres on the catalyst surface donates some of its *s*-electrons to the metal conduction band. In this context, at low values of *c*_H the behaviour of the absorbed hydrogen is well described in terms of the Ubbelohde model³⁸ which entails high diffusion mobility of the H^{δ+} ions and an increase (or, at least, the lack of a decrease) in electric conductivity of the hydride phase in comparison with the original metal. The value of *c*_{Hcrit} corresponds to the concentration of the oxidising agent (H^{δ+} species) at which the latter oxidise the metal template and become electron density acceptors being converted into bulky, practically immobile H^{δ−} ions. As a result, the metal conduction band is depleted in electrons. Obviously, at higher degrees of filling of cavities with H^{δ−} ions having a fairly large effective volume, the electron deficiency on the metal ions forming a metal sublattice in the crystalline structure of the catalyst should increase which probably restricts its ability for reversible hydrogen absorption. In this connection, the concentration of the species (*e.g.*, of tritium in the case of labelled preparations) which can enter into exchange reactions drops drastically, eventually resulting in a practically complete cessation of the isotope exchange.

Approaches to the synthesis of fatty acids with high molar radioactivity were successfully used for the preparation of other highly labelled saturated lipids, *viz.*, fatty acid derivatives, fatty alcohols and alkanes (*e.g.*, methyl stearate, 3-hydroxypalmitic, 6-ketopalmitic and chloroundecanoic acids, cetyl alcohol and hexadecane) (Tables 4–6).³⁴ It was found that the isotope exchange in halogen-containing saturated acids occurs much easier than dehalogenation. The experimental values of molar radioactivities reached tens of PBq mol^{−1}, which makes it possible to conduct biological experiments of any kind including ligand–receptor binding studies. The nonspecific label distribu-

Table 4. The values of the relative degree of isotope exchange in 11-chloroundecanoic acid at various temperatures and on different catalysts (the catalyst : substrate ratio = 5 : 1, reaction time = 20 min).³⁴

<i>T</i> / °C	5% Pt/C	10% Pd/C	5% Pd/C	10% Pd/BaSO ₄	5% Rh/C
50	1	—	—	—	—
70	9	—	—	—	10
90	16	—	2	—	—
120	40	43	8	48	38
140	55	64	12	50	32
160	51	59	25	75	29
170	—	—	—	100	—
180	22	50	20	90	21
190	—	43	—	48	—
200	10	19	9	41	19
210	—	18	—	35	6
220	9	14	9	16	1

Table 5. The values of the relative degree of isotope exchange in cetyl alcohol at various temperatures and on different catalysts (the catalyst : substrate ratio = 6 : 1, reaction time = 15 min).³⁴

<i>T</i> / °C	5% Pt/C	10% Pd/C	5% Pd/C	5% Rh/C
90	—	1	—	—
110	2	6	1	1
120	6	25	4	4
130	16	46	4	4
140	20	49	5	5
150	21	—	9	9
160	—	100	—	—
170	24	—	15	15
180	33	65	19	19
190	40	61	20	20
200	25	36	9	8
210	6	—	1	6
220	—	24	—	—

Table 6. The values of the relative degree of isotope exchange in hexadecane at various temperatures [the ratio 5% Pt/C : substrate = (6–10) : 1, reaction time = 15 min].³⁴

Compound	Temperature / °C							
	90	140	160	180	190	200	210	230
Methyl stearate	2	12	44	—	—	—	100	30
6-Oxopalmitic acid	17	72	100	—	—	—	84	33
3-Hydroxypalmitic acid	1	81	100	89	—	—	—	—
Palmitic acid	2	44	60	76	—	80	100	30
Myristic acid	—	41	—	77	85	100	62	61
Lauric acid	—	52	—	86	100	96	78	69
Hexadecane	2	100	61	—	—	—	44	43

tion in the products obtained upon the isotope exchange is the only disadvantage of this method.

Hydrogenation of double bonds (see Table 3) is used in the synthesis of saturated fatty acids with a definite position of the label (its precursor is an accessible unsaturated acid).^{4, 29, 35} Studies with [10,11-³H]undecanoic acid obtained by this method, which is a component of a termite pheromone, have shown that it comes to the pheromone glands with food or is biosynthesised.

Among other methods used for the synthesis of labelled fatty acids, thermal activation of tritium deserves special mention. The use of this procedure for labelling of methyl 12-hydroxystearate (0.56 TBq mol^{−1}) was described by Shevchenko and Myasoe-dov.⁴ The method consists in the application of a substance as a thin film onto the inner surface of a cylindrical vessel containing a tungsten filament placed along its axis. The system is evacuated, filled with tritium up to 0.67 Pa, cooled with liquid nitrogen and the tungsten filament is heated to 2000 K for 30 s. Tritium molecules dissociate, which significantly increases the degree of the isotope exchange.

[8L-³H]- and [8D-³H]Stearic acids⁵ were obtained by conversion of methyl 8D(8L)-hydroxystearate into the corresponding tosylate, which was further reduced with lithium aluminium tritide (6.6 TBq mol^{−1}). Stearic alcohols formed were oxidised with CrO₃ to yield the target product (3.3 TBq mol^{−1}).

Labelled fatty acids find application in biological studies and in the synthesis of various derivatives and labelled oxylipins based on them. Thus, they can be used in studies of cholesterol esters biosynthesis⁴⁰ or in the synthesis of monoepoxides (see Schemes 1–3), which are the products of the epoxigenase pathway of the arachidonic acid cascade or other polyunsaturated fatty acids. The biological activity of these epoxides is widely known. They stimulate the *in vitro* release of somatostatin from

the median tubercle of hypothalamus and the secretion of insulin and glucagon from pancreatic islets, inhibit the vasopressin-stimulated release of H₂O in bladder tumours, suppress aggregation of platelets and neutrophils, enhance the release of calcium from dog aortic smooth muscle microsomes and increase the cytosolic levels of free calcium. Under the action of various enzymes, these epoxides are converted into other, more oxidised products, *e.g.*, vicinal diols, 20- and 19-hydroxy derivatives.

2. Fatty acid derivatives

a. Fatty acid esters

Glycerides. The high biological activity of glycerides can be exemplified in the properties of 2-arachidonoylglycerol, which is an intermediate in tri- and diglyceride metabolism and an alternative precursor of arachidonic acid manifesting cannabimimetic activity.⁴¹ The use of a tritium-labelled analogue of this glyceride provided additional information about its pharmacological activity.

Labelled glycerides are usually obtained by condensation of the corresponding labelled fatty acids with glycerol.⁴ Different approaches to the synthesis of triglycerides (TG) have been considered.⁴² These lipids are formed upon heating of a mixture of glycerol and a fatty acid to 160–190 °C; the reaction proceeds more efficiently in the presence of toluenesulfonic acid with removal of water formed by distillation with xylene. Higher yields of TG are obtained in reactions of silver salts of fatty acids with 1,2,3-tribromopropane in boiling xylene and of acid chlorides or mixed anhydrides with glycerol. TG can also be synthesised under very mild conditions in the presence of dicyclohexylcarbodiimide and 4-dimethylaminopyridine. This procedure can also be used in the synthesis of the corresponding steroid esters. The use of this approach (the reaction was carried out in 1,2-dichloroethane; a solution of dicyclohexylcarbodiimide in benzene was added in several portions) resulted in labelled TG in more than 90% yield. Di- and monoglycerides can be prepared from triglycerides under the action of the corresponding lipases.⁴³ Thus 2-arachidonoylglycerol was prepared from triarachidonoylglycerol by treating it with *Rhizopus delemar* ('Seikagaku Kogyo', Japan) in 0.05 M AcONa–AcOH buffer (pH 5.6) containing 0.1 mmol litre^{−1} NaCl and 10 mmol litre^{−1} CaCl₂ with vigorous stirring for 60 min.⁴⁴

Among other methods used for glyceride synthesis, special mention should be made of the reduction of dihydroxyacetone 1,3-derivatives with sodium borotritide and the isotope exchange with tritiated water. Molar radioactivities of TG obtained by this method were by one order of magnitude lower than those of the tritiated water employed.⁴

Studies with 2-[³H]arachidonoylglycerol revealed that neuroblastoma N18TG2 cells contain nonspecific esterases. Hydrolysis of this monoglyceride was only partly (by less than 40%) inhibited by an excess of the unlabelled substrate, whereas the degree of selectivity of the esterase isolated from peripheral cells of the basophilic rat leukemia RBL-2H3 was much higher (74%). It was shown also that in contrast with 2-palmitoylglycerol, 2-linoleoylglycerol inhibited hydrolysis of 2-arachidonoylglycerol by intact cells as a result of which the concentration of 2-arachidonoylglycerol capable to activate the cannabinoid receptor increased considerably. The experimental results described by different authors^{41,45–49} suggest that non-cannabimimetic monoglycerides enhance the effect of 2-arachidonoylglycerol by increasing the half-time of its conversion and increase binding of 2-arachidonoylglycerol to the cannabinoid receptor (4–8-fold).

Phospholipids. Formerly, phospholipids were considered exclusively as structural components of biological membranes which fulfilled the barrier function in respect of electrolytes and served as a matrix for membrane-bound enzymes and receptors. However, it has presently been recognised that phospholipids and the products of their enzymic and free-radical conversions also perform important cell regulatory functions, being substantial for the manifestation of catalytic activities of many enzymes. Besides,

Table 7. The values of molar radioactivities of various phospholipids.

Compound	α /PBq mol ^{−1}	Ref.
Hydrogenation with gaseous tritium		
1- <i>O</i> -[³ H]Alkyl-2- <i>O</i> -methyl- <i>sn</i> -glycero-3-phosphocholine	2.30	53
Lyso[³ H]phosphatidylcholine	0.14	28
[³ H]Phosphatidylinositol	0.50	28
1- <i>O</i> -[³ H]Palmitoyl-2-acetyl- <i>sn</i> -glycero-3-phosphocholine	1.85	54
1- <i>O</i> -[³ H]Stearoyl- <i>sn</i> -glycero-3-phosphocholine	0.48	11
[³ H]Phosphatidylcholine	0.54	28
1-[1'-Palmitoyl-2'-[9,10- ³ H]stearoyl- <i>sn</i> -glycero-3'-phosphoryl]- <i>myo</i> -inositol-4-phosphate	0.39	29
Liquid-phase isotope exchange		
1,2-[³ H]Dipalmitoyl- <i>sn</i> -glycero-3-phosphocholine	0.02	29
Combination of chemical and enzymatic methods		
1,2-Dioleoyl- <i>sn</i> -[2- ³ H]glycero-3-phosphoserine	0.93	55

some phospholipids are endowed with hormone-like activities, play the role of platelet activation factors (PAF) (1-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine), accelerate wound healing (lyso-phosphatidic acid), *etc.* Hydrolysis of phosphoinositides and methylation of phosphatidylethanolamine are the key reactions in the transmission of intercellular signals.^{50–52}

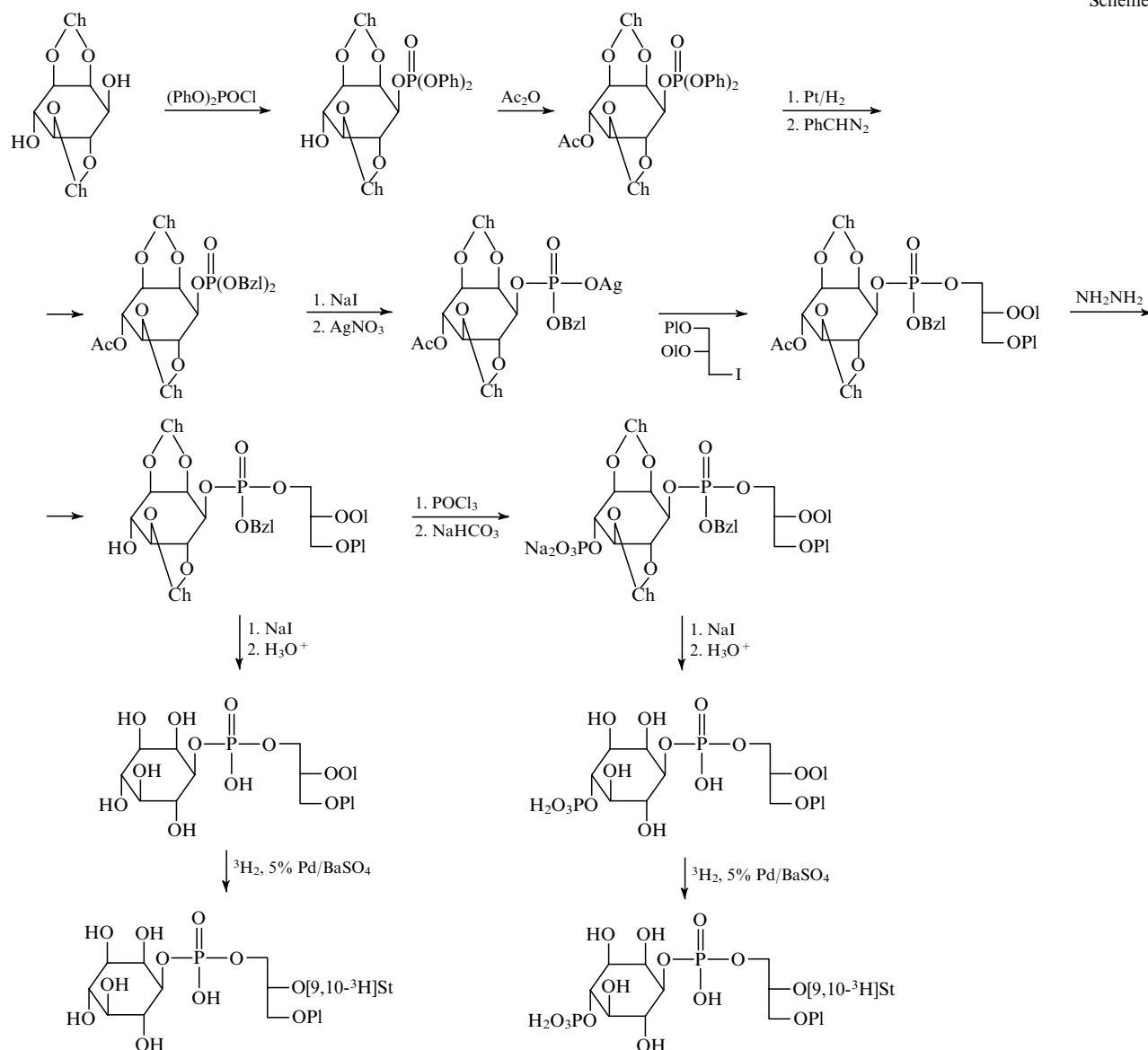
As a rule, the tritium label is introduced into phospholipids by hydrogenation of natural or synthetic unsaturated precursors (Table 7). The synthesis of tritium-labelled phosphatidylinositol and diphosphoinositide is shown in Scheme 5. Isotope exchange (Tables 7 and 8) and condensation of labelled fatty acids with the corresponding precursors as well as biological and enzymic methods and their combination are the most promising approaches.^{4,55}

Unsaturated precursors were synthesised in order to prepare labelled phosphatidylinositol and diphosphoinositide.⁵⁶ Several steps of their synthesis including deacetylation with hydrazine hydrate, were identical. If the phosphatidylinositol was the target product, the protective groups were removed by anionic debenzoylation and treatment with a cation-exchange resin (H⁺-form). In

Table 8. The kinetics of liquid-phase isotope exchange between gaseous tritium and dipalmitoylphosphatidylcholine.²⁸

Solvent	Time /min						
	15	30	45	60	90	150	180
Catalyst — 5% Pd/BaSO ₄							
Chloroform	19	41	47	54	65	80	88
Chloroform : : methanol (2 : 1)	33	50	56	73	78	97	100
Methanol	11	28	30	34	35	67	70
Lindlar catalyst							
Chloroform	1	2	2	2	2	3	4
Methanol	1	2	2	2	3	4	4
(Ph ₃ P) ₃ RhCl							
Chloroform	3	4	6	6	7	11	11

Scheme 5



Ch is cyclohexylidene, Pl — C₁₅H₃₁CO, Ol — C₁₇H₃₃CO, St — C₁₇H₃₅CO, Bzl is benzyl.

the synthesis of diphosphoinositide, inositol was phosphorylated at position 4 with an excess of phosphorus oxychloride in pyridine with subsequent deprotection. Hydrogenation of the unsaturated fatty acid residues in the *myo*-inositol derivatives in an atmosphere of gaseous tritium in the presence of a catalyst has led to highly labelled phospholipids.²⁹

These conditions proved to be versatile and can be used in the synthesis of labelled sterol esters. Thus, the hydrogenation of cholesteryl oleate was used to prepare cholesteryl [9,10-³H]-stearate²⁹ with a molar radioactivity of 1.98 PBq mol⁻¹. Condensation of [9,10-³H]oleic acid (0.07 PBq mol⁻¹) with lysophosphatidylcholine in the presence of dicyclohexylcarbodiimide and *N*-dimethylaminopyridine (1 : 1 : 1 : 100) in ether (stirring for 20 h at room temperature) affords lecithin (yield 35%–40%).⁴

The synthesis of phosphatidyl[³H]inositol can serve as an example of a synthesis of tritium-labelled fatty acid derivatives by biological methods.⁴ The starting compound, [2-³H]inositol, was synthesised by solid-phase reduction³⁵ of a commercially available *scillo*-inosose (2,4,6,3,5-pentahydroxycyclohexanone).³⁵ In a search for optimum conditions for *scillo*-inosose reduction, 5% Pd/CaCO₃, 5% Rh/Al₂O₃, 5% Pd/BaSO₄, 5% Pt/C, 5% Pd/C were tested as catalysts. The best results were obtained on a

rhodium catalyst (the catalyst : substrate ratio = 10 : 1) with heating to 150 °C for 15 min (the molar radioactivity of the labelled preparation was 0.56 PBq mol⁻¹, the yield was 25%). In addition, *scillo*-inosose with a molar radioactivity of 0.11 PBq mol⁻¹ was isolated from the reaction mixture in ~ 10% yield.

The biosynthesis of the labelled phospholipid was performed by incubation of [2-³H]inositol with a culture of *Kloeckera brevis* (ATCC 9774) (7 days, 25 °C). Subsequent extraction, chromatographic purification and desalting resulted in phosphatidyl[³H]inositol, which contained 54% of the original label and had a molar radioactivity ~ 2 times as low as that of the original [2-³H]inositol.

A combination of chemical and enzymic methods was used in the synthesis of 1,2-dioleoyl-*sn*-[2-³H]glycero-3-phosphoserine.⁵⁵ The first step included the chemical synthesis of [2-³H]glycerol; its incubation with glycerol kinase in the presence of ATP gave *sn*-[2-³H]glycerol-3-phosphate (yield 98%–99%). Boiling of the monotetraethylammonium *sn*-[2-³H]glycerol-3-phosphate tetraethylammonium oleate and oleic acid anhydride (1 : 10 : 10) in dry carbon tetrachloride (3 h, 80 °C) afforded 1,2-dioleoyl-*sn*-[2-³H]glycerol-3-phosphate in ~ 56% yield. The pyridinium salt of the latter was condensed with the benzhydryl ester of *N*-Boc-

serine in the presence of 2,4,6-triisopropylbenzenesulfonyl chloride (1 : 3.2 : 6.4) in dry pyridine (24 h, 30 °C). Deprotection under acidic conditions and chromatographic purification yielded 1,2-dioleoyl-*sn*-[2-³H]glycero-3-phosphoserine (total yield 12%, molar radioactivity 0.93 PBq mol⁻¹).

Labelled phospholipids play an important role in present-day biological studies. Thus in a study of the role of PAF in the regulation of cellular activity and cell-to-cell contacts, its labelled analogue was used in order to establish the effect of different antagonists blocking PAF activity at the level of PAF receptors on cell activation.⁵¹ A synthetic lipid antagonist CV-3988 inhibited the binding of the labelled phospholipid to platelets and suppressed the secretion and aggregation of platelets (0.1–0.15 µmol litre⁻¹).⁵⁷ The binding of this phospholipid to PAF receptors is known to trigger a cascade of biological reactions which result in the signal transfer into the cell and its subsequent activation.⁵¹ It has been shown⁵⁸ that 5 s after treatment of platelets with PAF, phosphatidylinositol-4,5-diphosphate undergoes hydrolysis to inositol-1,4,5-triphosphate. This hydrolysis is catalysed by membrane-bound phospholipase C. It was found also that the antagonists inhibit both the binding of labelled PAF to platelets and the formation of inositoltriphosphate in platelets.⁵⁹ The role of inositoltriphosphates in the regulation of the Ca²⁺ level in cell cytoplasm is immense, which may account for the pronounced effect of phospholipids on vital activity of cells in general.⁵⁰

b. Fatty acid amides

Ethanolamides of fatty acids represent highly active endogenous bioregulators. Arachidonic acid ethanolamides, which has been named later anandamide, was isolated from porcine brain in the early 1990's.⁶⁰ This compound proved to be an endogenous ligand of cannabinoid receptors, *viz.*, it competitively inhibited the specific binding of cannabinoids to receptors and mimicked their biological effects.^{60–67} Ethanolamides of other polyenoic fatty acids were isolated from mammalian brain more recently.^{68,69} These compounds also bind specifically to cannabinoid receptors. It is established now that mammalian tissues manifest synthase and amidase activities responsible for the synthesis and inactivation of anandamide.^{70–77} Tritium-labelled ethanolamides of fatty acids were used in studies of their metabolism, the activity of enzymes of the arachidonic acid cascade in the oxidation of these fatty acid derivatives and the effects of these labelled compounds on functioning of the arachidonic acid cascade in different animal and plant cells.

Ethanolamides can be labelled at both the acyl and ethanolamide fragments. Highly labelled fatty acids can be synthesised by selective hydrogenation in an atmosphere of gaseous tritium, while labelling of ethanolamine can only be done by solid-phase methods.^{78,79} Glycolic acid nitrile proved to be a promising starting compound, and 5% Pt/C, 5% Rh/C, 5% Pd/C, 5% Rh/Al₂O₃ and 5% Rh/CaCO₃ are effective catalysts. The highest yields were obtained with palladium catalysts; the molar radioactivity was higher on rhodium catalysts. The latter were used in the synthesis of labelled ethanolamine with a molar radioactivity of 1.04–1.48 PBq mol⁻¹, but the yields of target products were so insignificant that preparative syntheses of the labelled compound could be carried out only in the presence of 5% Pd/C. On platinum catalysts, dehydrogenation predominantly occurs.

The data summarised in Table 9 suggest that *T* = 100–120 °C is the optimum temperature. Under these conditions, the labelled product was obtained in 10%–20% yield and had a molar radioactivity of 0.15–0.22 PBq mol⁻¹.⁷⁸ Isobutyl chloroformate⁷⁸ or *N,N'*-diisopropylcarbodiimide⁷⁹ were used for condensation of fatty acids with ethanolamine (Table 10).

Studies on kinetics of oxidation of labelled anandamide and thymnodonic acid ethanolamide with soybean 15-lipoxygenase and on their possible oxidation in mouse splenocytes can serve as examples of application of these labelled compounds in biological studies.⁸⁰ It was found that the values of Michaelis constants (*K_m*)

Table 9. The values of the relative degree of the label incorporation and yield of ethanolamine in the hydrogenation of glycolonitrile for different times and at different temperatures (the ratio 5% Pd/C : substrate = 5 : 1).

<i>T</i> /°C (20 min)	Degree of label incorporation (α_{rel}) (%)	Reaction time /min (100 °C)	Yield (%)
20	10	5	6
50	31	10	7
70	55	15	11
90	66	20	15
100	100	30	15
120	100	40	13
140	65	50	12
160	32	60	8
180	12	75	6
190	6	90	3

Table 10. The values of molar radioactivities of ethanolamides.

Compound	α /PBq mol ⁻¹	Ref.
<i>N</i> -Arachidonoyl[³ H]ethanolamine	0.012	79
<i>N</i> -Dihomo- γ -linolenoyl[³ H]ethanolamine	0.019	79
<i>N</i> -Eicosa-11,14-dienoyl[³ H]ethanolamine	0.019	79
<i>N</i> -Eicosa-11-enoyl[³ H]ethanolamine	0.023	79
<i>N</i> -Palmitoyl[³ H]ethanolamine	0.012	79
<i>N</i> - γ -Linolenoyl[³ H]ethanolamine	0.026	79
<i>N</i> -[³ H]Arachidonoyl ethanolamine	4.4	78
<i>N</i> -Arachidonoyl[³ H]ethanolamine	0.18	78
<i>N</i> -Thymnodonoyl[³ H]ethanolamine	0.182	78
<i>N</i> -Docosahexaenoyl[³ H]ethanolamine	0.182	78

and *V_{max}* for these compounds were equal to 3.2 and 4.9 µmol litre⁻¹ and to 0.11 and 0.15 µmol l⁻¹ s⁻¹, respectively. These values are of the same order of magnitude as those for arachidonic acid.^{79,81} Experiments have shown that mouse splenocytes contain an anandamide-metabolising system. Splenocytes are related to cells continuously secreting 12-HETE and other eicosanoids. Anandamide-induced changes in the concentration of these products modulate functions of lymphocytes and other eicosanoid-controlled immune cells.

Sphingolipids pertain to the class of lipid molecules with different chemical structures and functional activities. Sphingene (sphingosine) is the most common sphingosine base of human and animal cell sphingolipids. The sphingene molecule contains two chiral carbon atoms and can exist in four stereoisomeric forms. Natural sphingene represents a *D-erythro*-isomer. *N*-Acylation of the amino group of sphingene with fatty acids results in ceramides, the precursors of more complex sphingolipids (sphingomyelin and glycosphingolipids).

Until the 1980's, the effect of the structure of the acyl residues of these lipids on their biological activity had been virtually neglected.⁸² However, studies carried out in the late 1980's provided evidence that sphingene inhibited cell differentiation,⁸³ while ceramides activated it.^{84–87} More recent studies have shown that the biological properties of the fatty acid residues of ceramides depend on their lengths. Thus it was found that C₁₈-ceramide does not inhibit lymphocyte proliferation (in contrast to the short-chain ceramides C₂ and C₆),⁸⁸ whereas hydroxy acids present in natural ceramides strongly suppressed the induction of apoptosis.⁸⁹ The activation of protein phosphatase with ceramides also depends on the length of the acyl chain.⁹⁰ This can be ascribed to the hydrophobic interactions between the hydrocarbon chains of sphingosine and the fatty acid which depend on the structure of both the sphingosine chain (length, the presence (sphingene) or the absence (sphinganine) of a double bond) and the fatty acid residue (length, the presence or the

absence of double bonds, their number, position, the presence of hydroxy groups, *etc.*). Such interactions may attenuate the differences in the effector activities of ceramides and dihydroceramides. Thus investigations into the mechanism of action of ceramides on target cells revealed that dihydroceramides, unlike the corresponding ceramides, inhibited (rather than stimulated) the activity of protein phosphatases,^{90,91} but had no effect on the activity of the protein kinase C isoform⁹² and phospholipase D,⁹³ which are inhibited by ceramides. However, in certain tests *N*-acetyl-sphingenin and *N*-acetyl-sphinganine manifested identical activities.

Radioactive labelling of sphingolipids can be performed in different ways, such as by condensation of the corresponding aminodiol with labelled fatty acids, by enzymic or chemical oxidation of hydroxy groups of sphingolipids with subsequent reduction with sodium or potassium borotritides, biosynthesis of labelled gangliosides starting from labelled *N*-acetyl-D-mannosamine and hydrogenation of the corresponding unsaturated precursors with gaseous tritium (Table 11).

The latter method was used for the synthesis of labelled gangliosides, sphingomyelin and ceramides. It was found^{4,5} that the ³H-label adds preferentially to the carbon atoms of multiple bonds. If liquid-phase isotope exchange is used for the labelling of unsaturated fatty acids, the label is predominantly incorporated into the allylic positions and into the double bonds. In phospholipids, the greater part of the label is localised in the fatty acid residues, whereas in the case of sphingolipids it is detected in both fatty acid and sphingosine moieties (Table 12).

Labelling of cerebrosides on the Lindlar catalyst results in the label incorporation into the fatty acid moiety, while on 5% Pd/BaSO₄ as a catalyst, it incorporates into the sphingosine moiety. This can be explained by the fact that the molecules of these compounds contain several polar groups (carboxy, hydroxy, amino, *etc.*), which compete with one another for the active centres on the catalyst's surface.²⁸ Presumably, the adsorption of the fatty acid residue on the Lindlar catalyst is more preferential than the adsorption of sphingosine bases. This fact determines the distribution of the tritium label.

It should be noted that chemical methods can be used for the synthesis of compounds with a predetermined position of the label.^{95,96} Complete chemical synthesis was used to obtain labelled *D*-erythro- and *L*-threo-sphingosines (Scheme 6).

Starting from galactose, azidosphingosines were prepared; the allylic hydroxy group was oxidised with 2,3-dichloro-5,6-dicyanobenzoquinone with subsequent reduction of the resulting ketone with sodium borotritide.⁹⁵

An attractive approach was proposed by Toyokuni *et al.*⁹⁶ Natural sphingenin was used as the starting compound; its primary hydroxy group was oxidised with CrO₃ (the Collins reagent) after protection of the amino group and the allylic

Table 11. The values of molar radioactivities of sphingolipids.

Compound	α /PBq mol ⁻¹	Ref.
Chemical methods		
<i>N</i> -Oleoylsphinganine ^a	7.78	94
(2 <i>S</i> ,3 <i>R</i> ,4 <i>E</i>)-2-Amino[3- ³ H]dodec-4-ene-1,3-diol ^b	0.019	95
(2 <i>S</i> ,3 <i>S</i> ,4 <i>E</i>)-2-Amino[3- ³ H]dodec-4-ene-1,3-diol ^b	0.034	95
(2 <i>S</i> ,3 <i>R</i> ,4 <i>E</i>)-2-Amino[3- ³ H]octadec-4-ene-1,3-diol ^b	0.020	95
(2 <i>S</i> ,3 <i>S</i> ,4 <i>E</i>)-2-Amino[3- ³ H]octadec-4-ene-1,3-diol ^b	0.036	95
(2 <i>S</i> ,3 <i>R</i> ,4 <i>E</i>)-2-Amino[1- ³ H]octadec-4-ene-1,3-diol ^b	0.004	96
Hydrogenation with gaseous tritium		
Sphingomyelin	0.218	28
Ganglioside		
GD1 α	0.115	28
GD2 β	0.137	28
GM1	0.196	28
GM2	0.496	28
GM3	0.014	28
G1	0.159	28
G2	0.107	28
Galactosyl ceramide ^c	1.94	4
Galactosyl ceramide ^d	0.895	4

Note: Brain and liver gangliosides are designated according to Svennerholm (GD1 α , GD2 β , GM1, GM2, GM3); sea urchin (*Strongylocentrotus intermedius*) gangliosides are designated as G1 (*N*-glycolylneuraminosyl-(α ,2 $\rightarrow$ 6)-glucosyl-(1 $\rightarrow$ 8)-*N*-glycolylneuraminosyl-(2 $\rightarrow$ 6)-glucosyl-(1 $\rightarrow$ 1)-ceramide) and G2 (8-sulfo-*N*-glycolylneuraminosyl-(α ,2 $\rightarrow$ 6)-glucosyl-(1 $\rightarrow$ 8)-*N*-glycolylneuraminosyl-(2 $\rightarrow$ 6)-glucosyl-(1 $\rightarrow$ 1)-ceramide).

^a The solid-phase method with subsequent condensation with oleic acid was used for introducing the label into sphinganine; ^b Sodium borotritide was used. ^c 5% Pd/BaSO₄ was used as a catalyst. ^d The Lindlar catalyst was used.

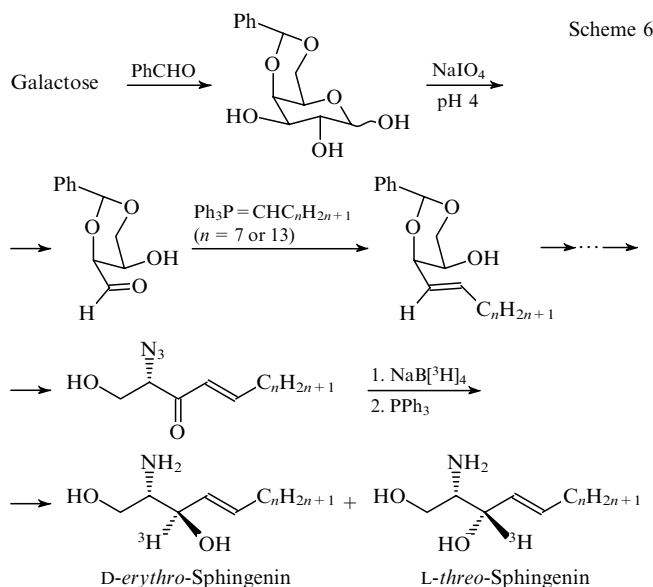
hydroxy group. The reduction of the aldehyde formed with sodium borotritide and deprotection gave [1-³H]sphingenin with the natural configuration.

Labelled sphingolipids were used to study the interaction of gangliosides with low density lipoproteins (using tritium-labelled ganglioside GM3)⁹⁷ and the role of gangliosides in the reception and penetration of the influenza virus into the cell.⁹⁸ In the latter

Table 12. The distribution of the tritium label in labelled glycosphingolipids after a catalytic reaction with gaseous tritium in solution.²⁸

Compound	Catalyst	Tritium activity /PBq mol ⁻¹			
		fatty acids	hydroxy fatty acids	sphingosine bases	polar fragments
Galactosyl ceramide	5% Pd/BaSO ₄	0.368 (19)	0.291 (15)	1.163 (60)	0.116 (6)
Galactosyl ceramide	Lindlar catalyst	0.260 (29)	0.340 (38)	0.296 (33)	—
Ganglioside					
GD1 α	5% Pd/BaSO ₄	0.009 (8)	—	0.094 (82)	0.012 (10)
G2	(Ph ₃ P) ₃ RhCl	0.086 (80)	—	0.020 (19)	0.001 (1)
G1	5% Pd/BaSO ₄	0.065 (33)	—	0.116 (59)	0.016 (8)
GM2	5% Pd/BaSO ₄	0.298 (60)	—	0.169 (34)	0.030 (6)
Sphingomyelin	Lindlar catalyst	0.140 (64)	—	0.076 (35)	0.002 (1)

Note: The percentage of the activity of a given moiety relative to the activity of the original molecule is given in parentheses.

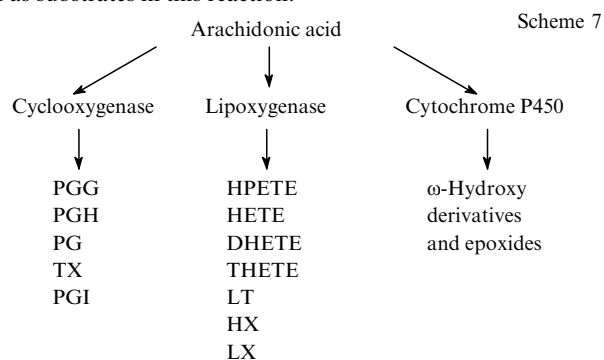


case, Ehrlich ascites carcinoma cells, which are efficient receptors of the influenza virus, were employed. The viral adsorption decreased drastically after treatment of cells with *Vibrio cholerae* neuraminidase which points to the fact that sialo-containing compounds (gangliosides) are specific receptors of the virus on the cell surface. Indeed, gangliosides GM_1 , $\text{GD}_{1\alpha}$ and $\text{GT}_{1\beta}$ restored the viral adsorption by cells. Based on the experimental data, it was concluded that: (1) the oligosaccharide chain of the ganglioside, $\text{Gal}\beta 1 \rightarrow 3 \text{GalNAc}\beta 1 \rightarrow 4(\text{NeuAc}\alpha 2 \rightarrow 3)\text{Gal}\beta 1 \rightarrow 4 \text{Glc}$, is the 'minimum' structural element providing the adsorption

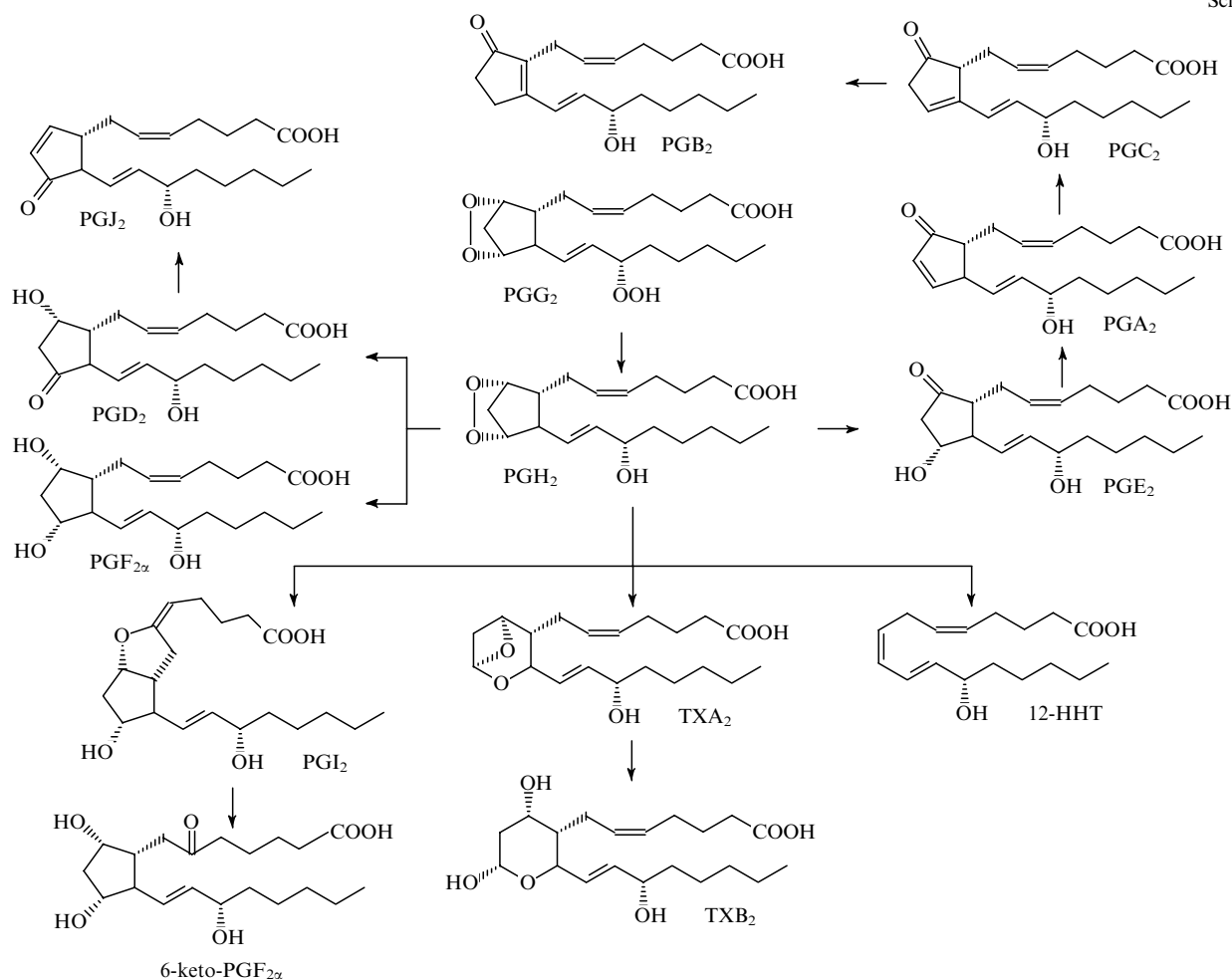
of the influenza virus by the gangliosides; (2) the gangliosides probably take part in both binding and penetration of the virus into the cell; one receptor site binds ~ 100 ganglioside molecules involved in the reception.

III. Oxylipins

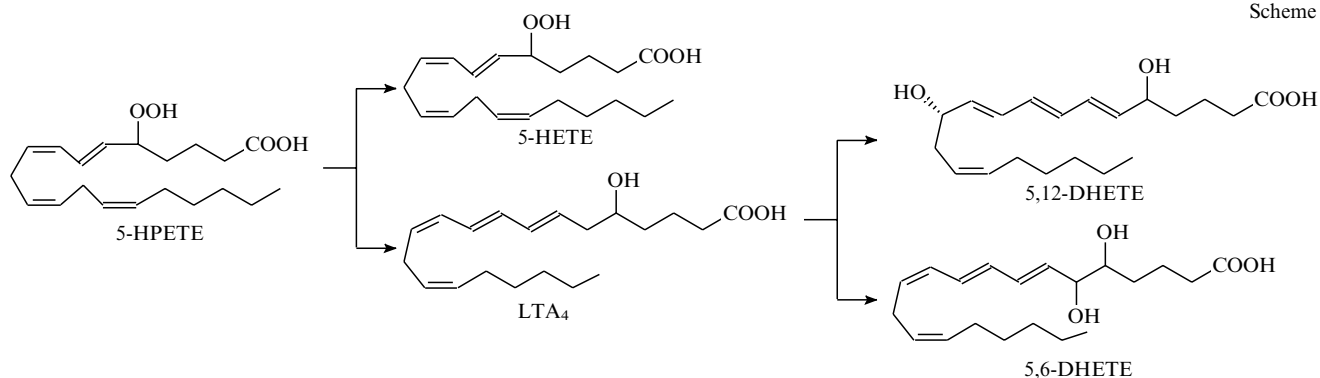
Oxylipins comprise eicosanoids and eicosanoid-like compounds with shortened or lengthened carbon chains, which are synthesised, for the most part, by cyclooxygenase, lipoxygenase and cytochrome P450 pathways.^{5,99} The main pathways of arachidonic acid metabolism resulting in oxylipins, *e.g.*, prostaglandins (PG), thromboxanes (TX), leukotrienes (LT), hydroxyeicosatetraenoic acids (HETE), hydroperoxyeicosatetraenoic acids (HPETE), lipoxins (LX), heptoxylins (HX), epoxytrieneoic acids (EET), *etc.*, are depicted in Scheme 7. It is of note that the scheme demonstrates exclusively transformations of arachidonic acid and its derivatives; however, other eicosapolyenoic acids can also be used as substrates in this reaction.



Scheme 8



Scheme 9

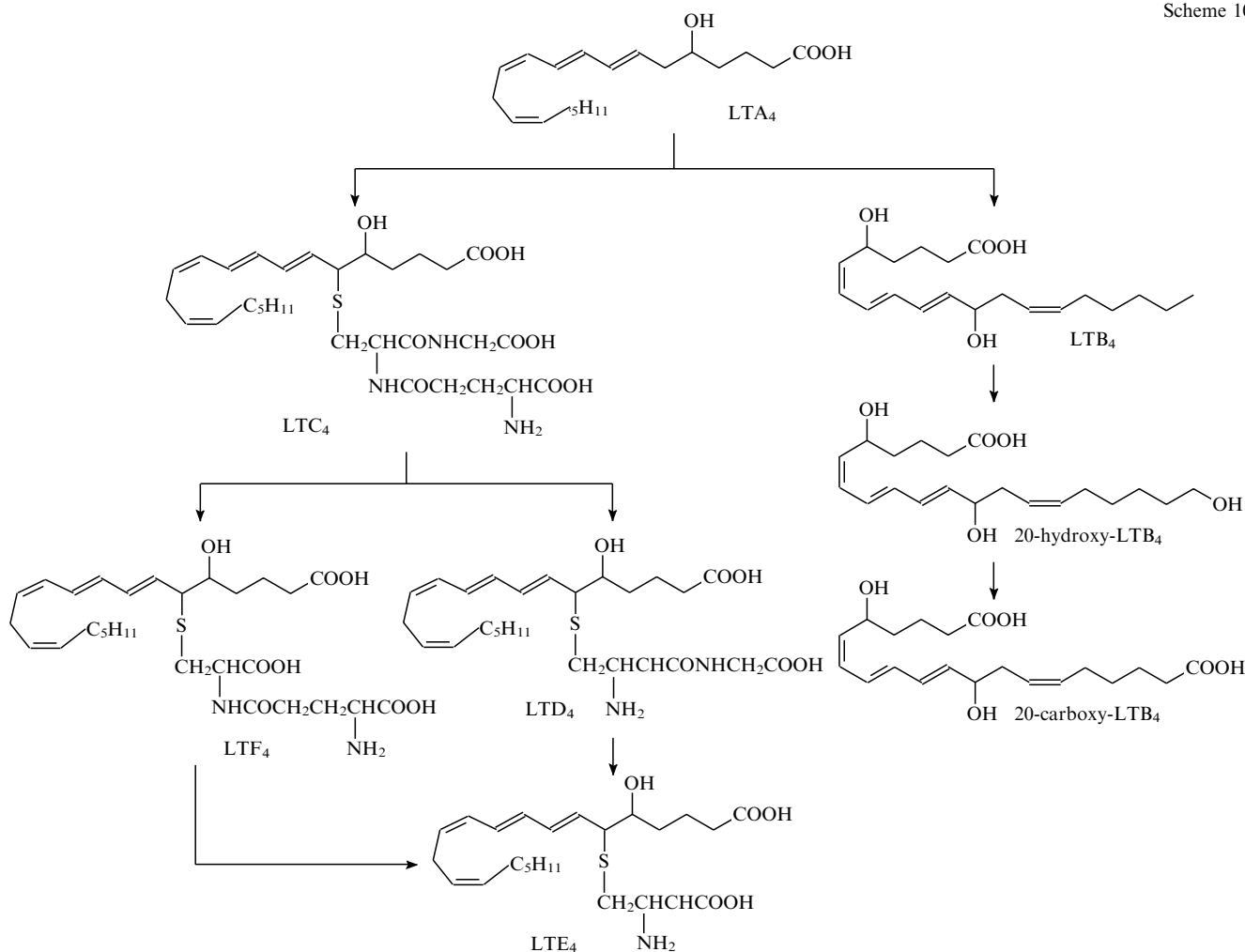


Under the action of enzymes, arachidonic acid yields: (1) PG, TX and prostacyclins (PGI), (2) hydroxy acids (LT, HX, LX); (3) epoxy and ω -hydroxy derivatives of fatty acids. Scheme 8 depicts preparation of PG and TX from prostaglandin G₂, Schemes 9 and 10, of hydroxy acids and LT from 5-HPETE, Schemes 11 and 12, of hydroxy acids, LX and HX from 12- and 15-HPETE. The synthesis of ω -hydroxy acids and epoxides is exemplified in oxidation of arachidonic acid in the presence of cytochromes P450 (Scheme 13).

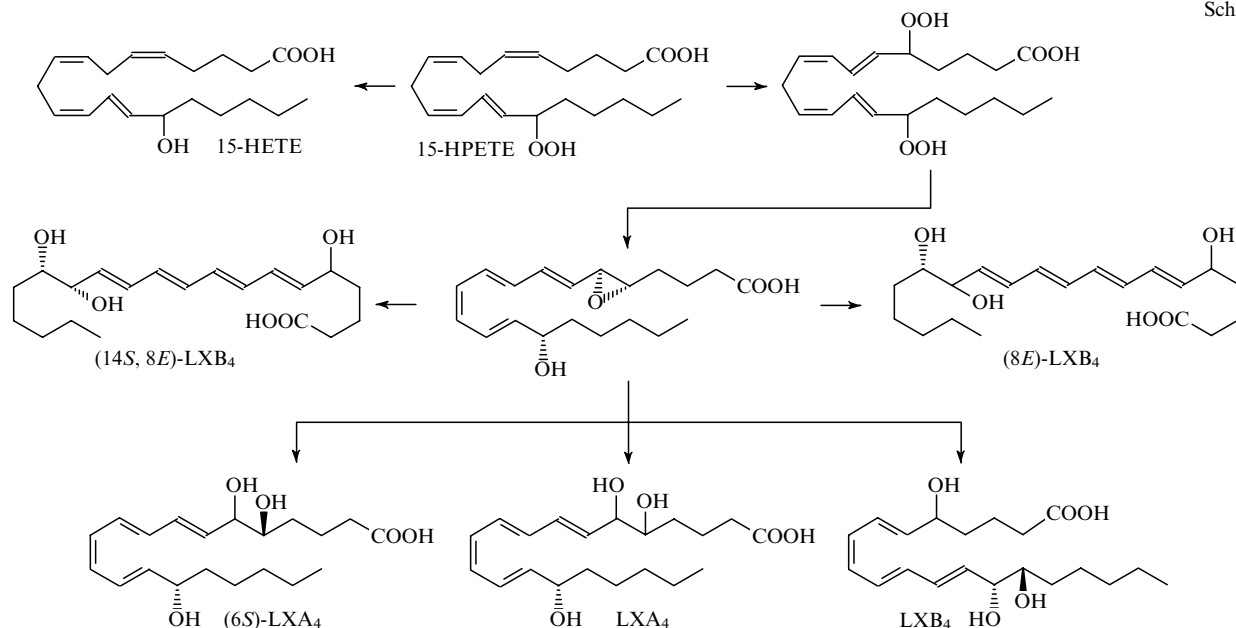
The biological and pharmacological effects of these compounds are extremely diverse. Thus lipoxins control the activity of killer cells and manifest spasmogenic activity;¹⁰⁰ heptoxylins are the releasing factors in insulin secretion by pancreatic cells and regulate the transmembrane transfer of calcium;¹⁰¹ leukotrienes

are mediators of hypersensitivity (allergy, anaphylaxis).¹⁰² Prostaglandins have a wide application as medicinal drugs.¹⁰³ However, despite the diversity of oxylipins and the broad spectrum of their biological activities, it is the continuous interaction of these compounds with one another that provides for the normal course of vitally important reactions occurring in the organism. The validity of this concept was confirmed in the studies of the role of arachidonic acid metabolites in the maintenance of the normal functioning of hemostasis in mammals.¹⁰⁴ There exist at least two ways of maintaining the necessary level of arachidonic acid in a hemostatic system, viz., from cell phospholipids and from plasma low density lipoproteins. The metabolites of polyunsaturated fatty acids (prostacyclin, 13-hydroxyoctadecadienoic acid, 6-keto-PGE₁, PGE₁, HETE and HPETE, TXA₂, PGE₂, PGF_{2 α} ,

Scheme 10



Scheme 11



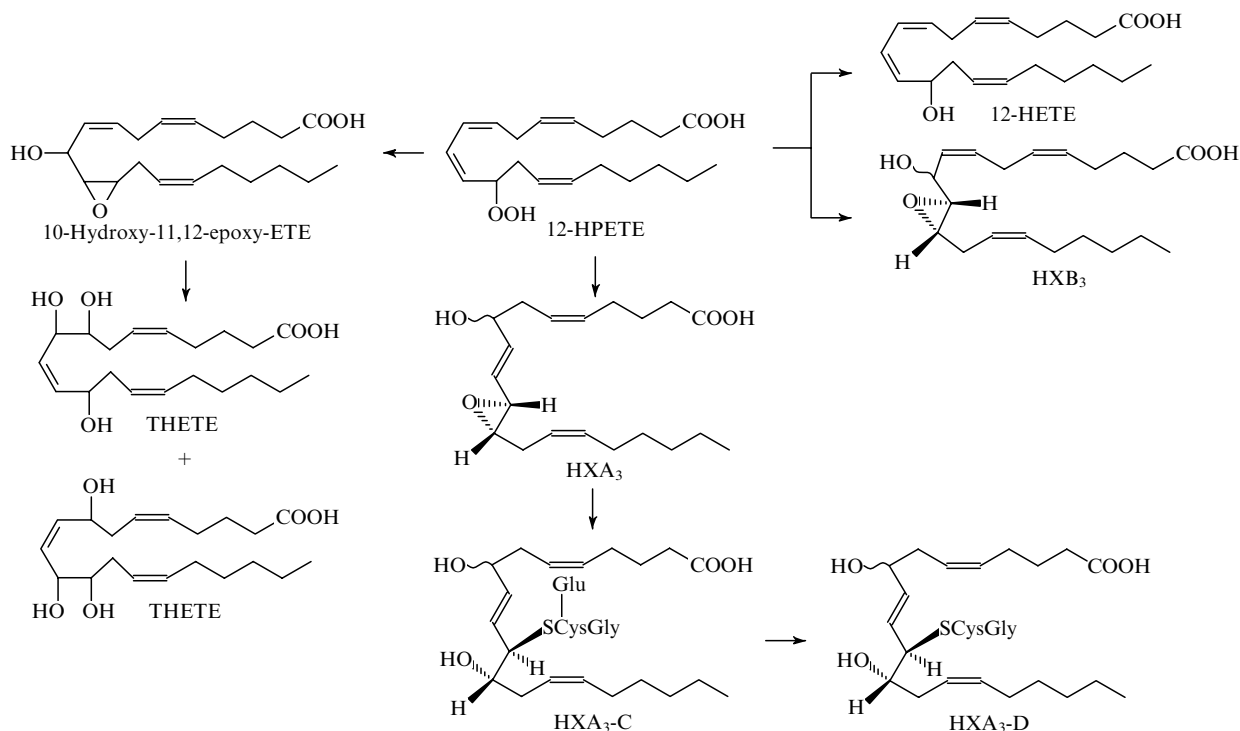
PGD₂, LTA₄, LTB₄) participate in the regulation of practically all units of the blood coagulating system as well as in reactions of the plasma component of hemostasis by influencing the fibrinolytic potential of blood and hemodynamic conditions. Thus, the urgency of investigations of these compounds is dictated by the fact that their effect on enzymic oxidation of polyenoic fatty acids is the central link in the mechanism of action of the majority of bioeffector lipids.

The main investigations in the field of oxylin with established structure are aimed at the study of their biosynthesis and metabolism. Labelled oxylin have played a prominent role in these studies. For this reason, a part of the present review which is devoted to the synthesis of labelled oxylin by enzymic methods can be regarded as an illustrative example of their application in

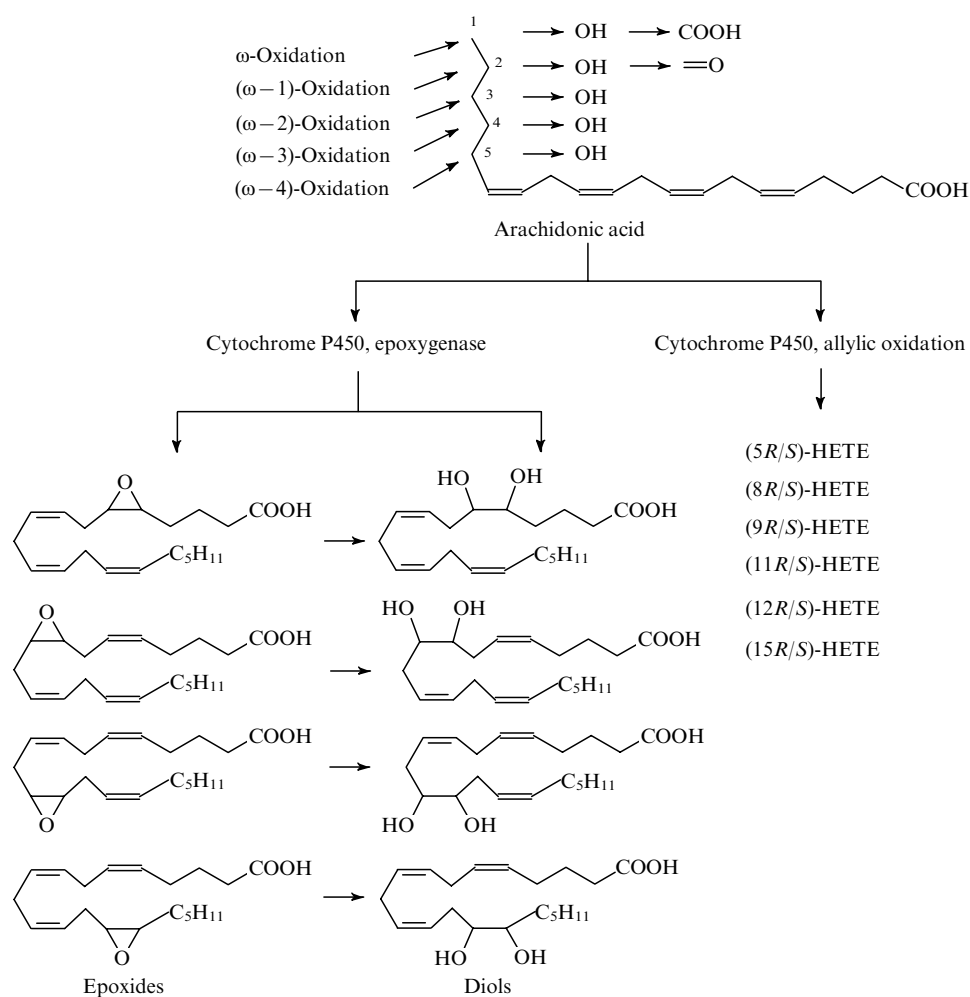
biological studies. In addition, studies of metabolic conversions of oxylin also consider their properties, *e.g.*, solubility, penetrability through biological membranes, *etc.* Labelled analogues turned out to be a helpful tool in pharmacokinetic studies of the first medicinal drugs (as a rule, natural prostaglandins and their synthetic analogues). Besides, they are indispensable components in the elaboration of highly sensitive methods for determination of oxylin in biological samples and in reception studies (interaction with protein molecules).

Radioactive labels can be introduced into eicosanoids by several routes. Isotope exchange or chemical methods are used for labelling synthetic derivatives of oxylin, where non-labelled prostaglandins are used as precursors or where the yields of the target products obtained by biological methods are negligibly

Scheme 12



Scheme 13

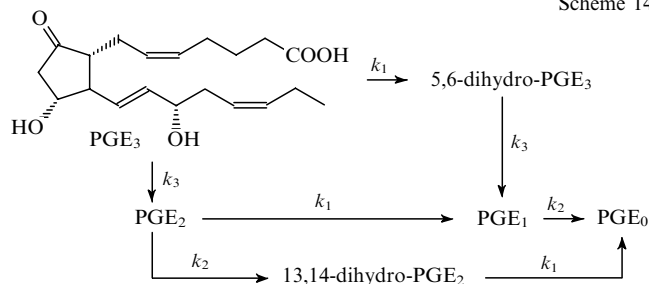


small (*e.g.*, the synthesis of epoxy compounds, prostacyclin, *etc.*), as well as for interconversion of labelled compounds.

The isotope exchange and chemical methods are indispensable tools in the synthesis of labelled eicosanoids having a non-natural structure, *e.g.*, (17*S*)-17-methyl-20-[11-³H]homoisocarbacycline,¹⁰⁵ fluoro prostaglandins,¹⁰⁶ *etc.* These methods were used to obtain fluorinated compounds with molar radioactivities varying from 0.09 to 1.1 PBq mol⁻¹ (Table 13).

Selective hydrogenation of prostaglandins of series 2 and 3 (*e.g.*, of PGE₃ to PGE₂ and PGE₁, Scheme 14) with gaseous tritium¹⁰⁷ afforded labelled preparations with molar radioactivities of 1.5–2.9 PBq mol⁻¹ (see Table 13).

Scheme 14



In the latter method, the results of calculations in assumption that the rates of all reactions are described by first-order equations showed good agreement with experimental results. In this case, the ratio of hydrogenation rate constants (k_1 , k_2 , k_3) were 2:1:4 for the reaction in acetone and 2:1:8 for the reaction in a benzene:acetone mixture. Obviously, for the synthesis of labelled

PGE₂ from PGE₃ the benzene:acetone mixture is more preferable; under these conditions, the yields of [17,18-³H]PGE₂ and [5,6,17,18-³H]PGE₁ were 40%–45% and 10%–15%, respectively.

The use of chemical methods for the synthesis of labelled compounds requires a detailed analysis of their chemical properties. Thus it is known⁵ that prostaglandins E are converted into PGA in acidic media, into PGB in alkaline media and into PGF after treatment with borohydrides. The latter in turn can serve as a precursor in the synthesis of prostacyclin or 6-keto-PGF_{1α} (see Table 13). Chemical methods can also be used for the synthesis of labelled methyl esters, *e.g.*, LTA₄ and 8-epi-PGF_{2α} (Scheme 15).^{108, 109, 110}

The choice of catalysts for selective hydrogenation with gaseous tritium was carried out as described in Section II.1. The best results were obtained with palladium catalysts poisoned with lead diacetate. In the case of more labile compounds, triethylamine was added to a solvent in order to minimise the formation of side products.

Selective hydrogenation with gaseous tritium can be used in the synthesis of other oxylipins, *e.g.*, [5,6,8,9,14,15-³H]hepoxylins B₃ (Scheme 16).¹⁹

Enzymic methods with the use of labelled eicosapolyenoic acids as the starting substrates (see Scheme 7) are the most popular methods for the synthesis of labelled eicosanoids. It is impossible to mention all of the currently known data concerning this problem in a single review; therefore, we shall confine our description to the consideration of a few examples illustrating the versatility of this approach.¹¹¹ Thus the use of only one enzyme, *e.g.*, PG synthase, which catalyses the transformation of eicosa-

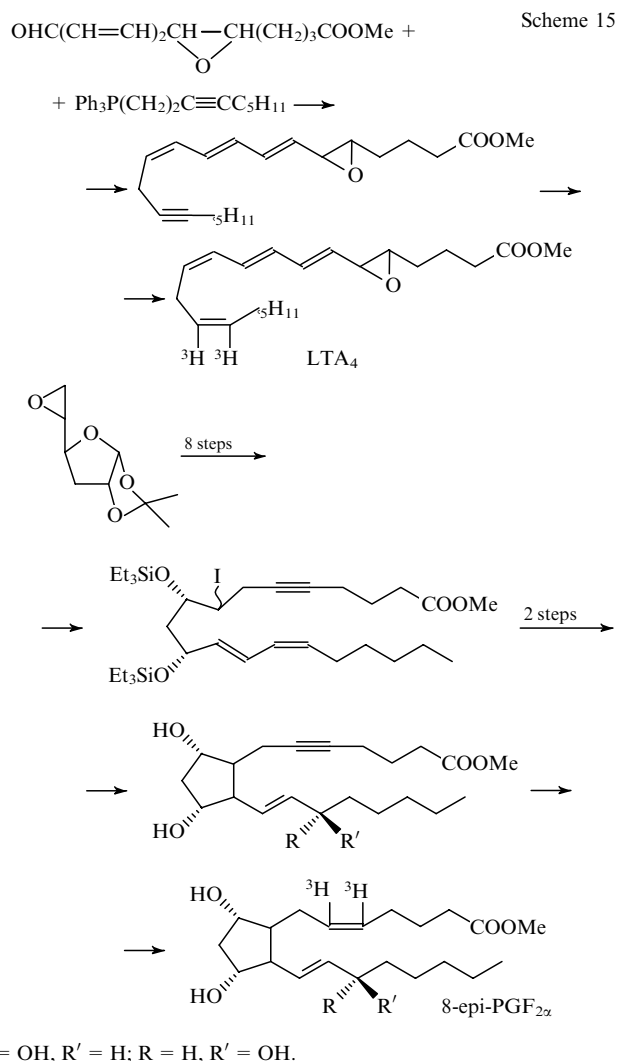
Table 13. The values of molar radioactivities of oxylipins obtained by hydrogenation with gaseous tritium, isotope exchange and chemical methods.

Compound	α /PBq mol ⁻¹	Ref.
Hydrogenation with gaseous tritium		
[13,14- ³ H]Leukotriene A ₄ ME	1.48–1.67	108
(15 <i>S</i>)-8-epi-[5,6- ³ H]PGF _{2α}	1.85–1.93	108
(15 <i>R</i>)-8-epi-[5,6- ³ H]PGF _{2α}	1.85–1.93	108
[5,6,8,9,14,15- ³ H]HXB ₃ ME	2–4	19
[17,18- ³ H]PGE ₂	1.5–1.6	29
[5,6,17,18- ³ H]PGE ₁	2.8–2.9	29
[5,6- ³ H]PGE ₁	1.8–2.0	29
Fluoro-15-deoxy-[5,6- ³ H]PGE ₁	0.9–1.1	29
11-Deoxy-[5,6,10,11- ³ H]PGE ₁	2.6–3.0	29
Liquid-phase isotope exchange		
15-Fluoro-11,15-dideoxy-[G- ³ H]PGE ₁ ME	0.13	29
15-Fluoro-15-deoxy-[G- ³ H]PGF _{2α} ME	0.09	29
5-Iodo-15-fluoro-15-deoxy-[G- ³ H]PGI ₁ ME	0.05	29
Chemical methods		
(17 <i>S</i>)-17-methyl-20-[11- ³ H]homoisocarbacycline ^a	0.68	105
[8,11,12,14,15- ³ H]PGA ₁ ^b	4.1	29
[5,6,8,11,12,14,15- ³ H]PGA ₂ ^b	5.2	29
[5,6,8,11,12,14,15,17,18- ³ H]PGA ₃ ^b	7.3	29
[11,14,15- ³ H]PGB ₁ ^b	2.9	29
[5,6,11,14,15- ³ H]PGB ₂ ^b	3.7	29
[5,6,11,14,15,17,18- ³ H]PGB ₃ ^b	5.7	29
[8,11,12,14,15- ³ H]PGF _{1α} ^b	4.6	29
[5,6,8,11,12,14,15- ³ H]PGF _{2α} ^b	5.8	29
[5,6,8,11,12,14,15,17,18- ³ H]PGF _{3α} ^b	7.3	29
[8,11,12,14,15- ³ H]PGF _{1β} ^b	4.6	29
[5,6,8,11,12,14,15- ³ H]PGF _{2β} ^b	5.8	29
[5,6,8,11,12,14,15,17,18- ³ H]PGF _{3β} ^b	7.3	29
[5,8,11,12,14,15- ³ H]PGI ₂ ME ^c	5.0	29
6-Keto-[5,8,11,12,14,15- ³ H]PGF _{1α} ME ^d	4.9	29

Note: ME is methyl ester. ^a Sodium borotritide with a molar radioactivity of 3.04 PBq mol⁻¹ was used. ^b Prepared from [³H]PGE. ^c Prepared from [³H]PGF_{2 α} ME; ^d Prepared from [³H]PGI₂ ME.

polyenoic acids into PGH (its half-life in aqueous media is ~ 5 min), made it possible to obtain a variety of labelled products, such as PDG, PGE, PGF _{α} and 12-hydroxyheptadecatrienoic acid (HHT) (see Scheme 8). The yield of labelled PGH and, consequently, of its degradation products depends on the concentrations of the eicosapolyenoic acid and PG synthase. Under optimum conditions, the yield of [5,6,8,9,11,12,14,15-³H]PGH₂ was 70%; those of [5,6,8,9,11,12,14,15,17,18-³H]PGH₃, [5,6,8,9,11,12-³H]HHT, [5,6,8,9,11,12,14,15-³H]PGF_{2 α} , [5,6,8,9,11,12,14,15,17,18-³H]PGF_{3 α} and [5,6,8,9,12,14,15,17,18-³H]PGD₃ were 45%, 35%, 63%, 27% and 25%, respectively. The ratio of products of non-enzymic degradation of PGH₂ in different buffer systems is variable (Table 14).

The use of two-enzyme systems has made it possible to find conditions for the predominant formation of only one reaction product and to synthesise compounds which cannot be obtained by spontaneous degradation of PGH. In this case, PG synthase was supplemented with the enzymes specifically converting labile [³H]PGH into [³H]PGE, [³H]PGD, labelled thromboxane and [³H]HHT, viz., PGE synthase for the synthesis of [³H]PGE, PGD synthase for the synthesis of [³H]PGD and TX synthase for the synthesis of [³H]TXB and [³H]HHT. In a study with individual enzymes, conditions for eicosanoid biosynthesis were optimised by varying the concentrations of each enzyme and their ratios.¹¹² All the preparations used in this study retained their activities



upon storage (6 months at -60 °C). Even highly labile PGE synthase retained up to 80% of activity for 12 days at -60 °C. Inactivation of enzymes (PG synthase, 12-lipoxygenase, TX synthase) in the course of biosynthesis was taken into consideration using the following kinetic equation:

$$\frac{de}{ds} = \frac{1}{V},$$

where e is the concentration of the active enzyme species, s is the substrate concentration and V is the dimensionless parameter reflecting the number of the enzyme turnovers up to complete inactivation and depending on the chemical nature of the

Scheme 16

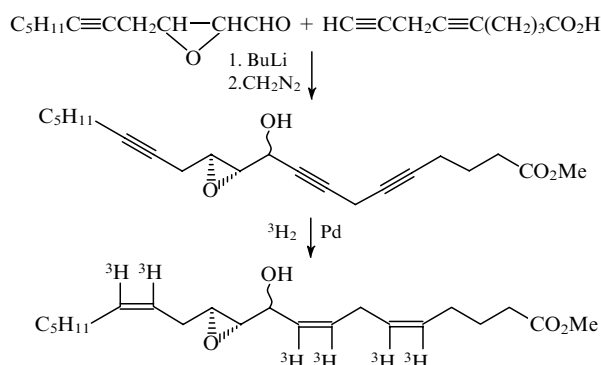


Table 14. The composition of PGH₂ nonenzymic degradation products obtained in a PG synthase reaction in various buffers.¹¹¹

Buffer	Buffer concentration /mmol litre ⁻¹	Prostaglandin content (%)		
		PGD ₂	PGE ₂	PGF _{2α}
Tris buffer, pH 9.5	10	12	23	65
Potassium phosphate buffer, pH 7.4	50	19	39	42
Potassium phosphate buffer, pH 7.4 ^a	50	29	26	45

^a After 30-s incubation, hydrochloric acid was added to the reaction mixture to pH 3.0 and the incubation was continued (1 h, 25 °C).

substrate. The experimental values of *V* for the PG synthase-catalysed conversions of arachidonic and thymnodonic acids¹¹⁰ differed more than 10-fold.

Quantitative calculations carried out with the use of a mathematical model and experiments with two-enzyme systems have shown¹¹² that the maximum yields of target products can only be obtained if the substrate is gradually added to the reaction mixture containing both enzymes. Under these conditions, the yields of target eicosanoids are restricted by enzyme inactivation in the course of the reaction. It was also found that the efficiency of a two-enzyme system can be significantly increased if some specified initial concentrations of the enzymes and the substrate are used.

Thus, the strategy of enzymic synthesis of labelled eicosanoids is based on the use of artificial two-enzyme systems and can be formulated as follows.¹¹² First, enzyme preparations must be purified to the maximum degree, since ballast proteins cause strong adsorption of the original labelled eicosapolyenoic acids, make them inaccessible for PG synthase and provoke undesirable conversions of PGH (Table 15).

Second, the enzyme:substrate ratio should be an optimum, *e.g.*, 747 and 63 nmoles of arachidonic and thymnodonic acids, respectively, should be taken per unit of PG synthase activity.

Third, high yields of target products can be obtained at high concentrations of PGH-converting enzymes. Thus in the case of PGE₂, a fourfold increase in the concentration of PGE synthase caused a 1.9-fold increase in the eicosanoid yield; in the case of PGD₂, a threefold increase in the concentration of PGD synthase increased the eicosanoid yield twofold, whereas in the case of TXB₂, a fivefold increase in the concentration of TX synthase

Table 15. The effect of the degree of purification of enzyme preparations on the eicosanoid content in the reaction mixture.¹¹¹

Enzyme preparation	Yield (%)
Synthesis of PGE ₂	
Ram vesicular gland microsomes	50
Partially purified PG and PGE synthases	80
Synthesis of PGE ₃	
Ram vesicular gland microsomes	30
Partially purified PG and PGE synthases	45
Synthesis of TXB ₂	
Ram vesicular gland microsomes and human platelets	15
Partially purified PG and thromboxane synthases	80
Synthesis of 12-HETE	
Human platelet microsomes	35
Partially purified 12-lipoxygenase	50

Table 16. The yields of eicosanoids in two-enzyme systems with simultaneous (I) and separate (II) addition of PG synthase and PGH-converting enzyme to the reaction mixture.¹¹¹

Eicosanoid	Yield (%)	
	I	II
PGD ₂	23	33
PGD ₃	17	25
TXB ₂	13	24
TXB ₃	10	18

increased the yield of the target product 2.4-fold. Probably, this is associated with the necessity for creation of conditions where the rates of enzymic conversions of PGH will markedly exceed the rate of its spontaneous degradation.

Fourth, the procedure of conducting the biosynthesis plays a very important role. The yield of the target product can be increased 1.5–2-fold by separate addition of the enzymes to the reaction mixture (Table 16). The optimum time of incubation of an eicosapolyenoic acid with PG synthase prior to the addition of the second enzyme is 1.5–2 min. Within this period, the accumulation of PGH is a maximum, *i.e.*, the rate of its formation by the PG synthase reaction coincides with the rate of its nonenzymic degradation.

Fifth, the temperature dependence of the yields of these eicosanoids in two-enzyme synthesis has a broad optimum (20–25 °C). This implies that the optimal yields of labelled eicosanoids can be attained at room temperature.

This strategy was successfully used in the synthesis of various highly labelled oxylipids (Table 17).

Considerable interest recently arose in the studies of functioning of various enzymic subsystems under heterophasic conditions.¹¹² This interest is due to the fact that the catalytic activity and stability of many enzymes under reaction conditions can be significantly increased. Thus a search for the ways aimed at increasing the 'productivity' of enzymes involved in prostaglandin synthesis, which undergo irreversible inactivation in the course of the reaction, has demonstrated high efficiency of macroheterogenous systems (water-in-octane and octane-in-water). It was found that the activities of the enzymes of eicosanoid synthesis (PG synthase, PGE synthase, TX synthase, 12-lipoxygenase) were retained in all heterophasic systems under study. The highest values of activity, *V*, for the PG synthase

Table 17. The values of molar radioactivities of various oxylipins obtained by enzymic methods.

Compound	α /PBq mol ⁻¹	Ref.
[8,11,12,14,15- ³ H]PGE ₁	4.65	29
[5,6,8,11,12,14,15- ³ H]PGE ₂	5.90	29
[5,6,8,9,11,12,14,15- ³ H]PGF _{2α}	6.10	29
[5,6,8,9,12,14,15- ³ H]PGD ₂	5.98	29
[5,6,8,9,11,12,14,15- ³ H]TXB ₂	5.27	29
[5,6,8,11,12,14,15,17,18- ³ H]PGE ₃	7.35	29
[5,6,8,9,12,14,15- ³ H]PGD ₂	4.44	113
13,14-Dihydro-15-keto-[³ H]PGD ₂ ^a	—	113
[9α,11β- ³ H]PGF ₂ ^a	—	113
[15- ³ H]HETE	6.20	114
[5,15- ³ H]DHETE	5.10	114
[8,15- ³ H]DHETE	6.00	114
12-[³ H]HPETE	5.26	115
[12- ³ H]HETE	5.26	115
[15- ³ H]HPETE	5.37	115
[15- ³ H]HETE	5.37	115

^a Prepared from [5,6,8,9,12,14,15-³H]PGD₂.

reaction were observed with octane-in-water emulsions stabilised with native microsomal membranes. It was also found that if water:octane:lyophilised membranes ratios were close to those at which the system is stratified, the catalytic activity of PG synthase increased nearly 10-fold in comparison with systems containing no organic solvents. Moreover, the main advantage of this approach to the synthesis of labelled preparations is that in stabilised emulsions the labelled eicosapolyenoic acid is predominantly accumulated in the organic solvent, whereas the oxidation products (*e.g.*, PGE₂) are detected only in the aqueous phase. As a result, the negative effect of radiolysis on the formation of target labelled eicosanoids is reduced and the reaction products, the enzyme and the nonconsumed substrate are readily separated by centrifugation.

In addition to these methods for the synthesis of labelled oxylipins, special mention should be made of the possibility of synthesis of certain labelled prostaglandins by enzymic modification of other labelled prostaglandins. The use of chemical methods is coupled with the formation of stereoisomers and the necessity to perform additional steps for protection of functional groups with similar reactivities. Enzymic syntheses of prostaglandins starting from other prostaglandins as substrates are devoid of these drawbacks. Thus 15-keto-PGF_{2α}, 13,14-dihydro-15-keto-PGF_{2α}, PGE₂, 15-keto-PGE₂, 13,14-dihydro-15-keto-PGE₂ and 9α,11β-PGF₂ were synthesised from [³H]PGF_{2α} and [³H]PGD₂ using 9- and 15-hydroxyprostaglandin dehydrogenases, PGF synthase, *etc.*, isolated from various sources (see Table 17).^{111–113}

Labelled 15-HETE, 5,15-DHETE, 8,15-DHETE and 12-HETE were synthesised in up to 60%–65%, 20%–25%, 10%–15% and 21%–51% yields, respectively, using enzymes of the lipoxygenase pathway of eicosapolyenoic acid metabolism (*e.g.*, 15- and 12-lipoxygenase) (see Schemes 11 and 12).

The optimum conditions for these reactions were selected in the studies of the dependence of the yields of target products on the presence of appropriate additives in the reaction mixture as well as on the substrate:enzyme ratio, substrate and enzyme concentrations, degree of enzyme purification, *etc.*^{111, 114, 115}

An analysis of the data presented in Table 18 suggests that if the 12-lipoxygenase reaction is conducted in the presence of certain reducing agents, the yield of 12-HETE increases considerably. However, the use of enzymes is not always successful. Thus labelled leukotriene B₄ was synthesised in but 0.1% yield using enzymes of the lipoxygenase pathway of eicosapolyenoic acid metabolism,²⁹ whereas the yields of lipoxins¹¹⁶ were negligibly small. These examples demonstrate that the use of enzymic methods demands a careful selection of reaction conditions and a thorough analysis of factors decreasing the yield of target products.

Table 18. The yields of 12-HETE from [³H]arachidonic acid depending on the nature of the reducing agents.¹¹¹

Reducing agent	Yield (%)
—	34
Dithiothreitol	51
Glutathione	49
L-Cysteine	44
L-Tryptophan	36
Aniline	34
L-Adrenaline	32
L-Methionine	32
NADH	31
Phenol	29

IV. Steroids

The fundamental problem of a relationship between the structure of biologically active compounds and their activities is still very

urgent. Its solution would make it possible to use both natural and modified steroids as medicinal drugs. It is known that steroid hormones fulfil several functions in the organism, each being mediated by a specific receptor. Studies of the mechanism of steroid–receptor interaction shed light on what fragments of the steroid molecule are responsible for one or another of its biological function. This knowledge will allow the minimising of potential side effects of natural steroids used as medicinal drugs, on the one hand, and influencing their particular biological function by modifying natural steroid molecules, on the other hand.²²

Tritium-labelled steroids possessing estrogenic, androgenic and anabolic activities are necessary for estimating the biological characteristics of pharmacological preparations used in studies on reproduction and increase of the productivity of animals. Labelled analogues of steroid hormones are used in investigation of various metabolic processes in normal and pathological states, in diagnostics of diseases and quantitation of steroids in various biological fluids.¹¹⁷ The topicality of synthesis of labelled steroids is connected with the application of their natural precursors in the treatment of various diseases, such as atherosclerosis, asthma, rheumatism, eczemas, allergies, polyarthritis, gout, radiation disease, diabetes mellitus, *etc.*

The label is introduced into steroids by various routes. Let us consider the methods used in the synthesis of labelled cholesterol as an example.

The data presented in Tables 19–21 suggest that dehalogenation, solid-phase isotope exchange and isotope exchange with

Table 19. The values of molar radioactivities of cholesterol obtained by isotope exchange and by chemical methods.

Method of labelling	α /TBq mol ^{−1}	Ref.
Using recoil atoms ⁶ Li(n,α) ³ H	0.0022	3, 4, 8, 118
Isotope exchange:		
incubation in an atmosphere of gaseous tritium (the Wiltzbach method)	74.1	3, 4, 8, 118
activation of the reaction with an electric charge	185.2	3, 4, 8, 118
addition of a carrier	0.0445	3, 4, 8, 118
microwave irradiation	0.9207	3, 4, 8, 118
liquid-phase isotope exchange	1.7	4
solid-phase isotope exchange	997.3	119
isotope exchange with tritiated water	218.0	121
Chemical methods:		
reduction with metal tritides	785.2	118
dehalogenation of the 7-halogeno derivative	370.0	120
dehalogenation of the 2,2-dihalogeno derivative	1129.6	118
hydrogenolysis of the 7,7-disulfur-containing derivative	300.1	122

Table 20. The relative degree of isotope exchange (*a*) and yields of steroids depending on duration of the reaction.¹²¹

τ /h	Progesterone		Estrilol		Cholesterol	
	<i>a</i>	yield (%)	<i>a</i>	yield (%)	<i>a</i>	yield (%)
2	48	95	22	95	27	95
4	75	90	48	85	69	85
6	97	85	81	75	84	80
10	100	70	100	60	100	65
24	98	20	95	18	95	15
50	100	10	96	10	94	10

Table 21. The values of molar radioactivities of steroids in isotope exchange with tritiated water.¹²¹

Compound	α /PBq mol ⁻¹
Progesterone	0.248
Estradiol	0.400
Cortisol	0.218
Methylandrosta-1,4-dien-17 α -ol	0.200
Methylandrosta-5-ene-3 β ,17 α -diol	0.226

tritiated water are the most promising methods.^{118–122} The label can successfully be introduced into androstanes, pregnanes and some other steroids by a modified Wiltzbach procedure (see Ref. 123). Labelled steroids can also be prepared by biological methods,¹²⁰ hydrogenation and selective hydrogenation of the corresponding precursors^{124–127} in combination with other chemical methods (Table 22).^{129–133}

Dehalogenation allows one to prepare stereospecifically labelled steroids. Molar radioactivities of the thus synthesised [³H]cholesterol, [³H]pregnenolone and [³H]dehydroepiandrosterone amount to 0.37 PBq mol⁻¹, and those of aromatic 2,4-dibromosteroids, to 1.1 PBq mol⁻¹.^{118–120}

Biological methods entail the conversion of labelled steroids into other steroids. Thus [16-³H]aldosterone (molar radioactivity 0.08 PBq mol⁻¹) was prepared from [16-³H]progesterone (0.5 PBq mol⁻¹) using bovine adrenal cortex enzymes, and [16-³H]cortisol (molar radioactivity 0.07 PBq mol⁻¹) was obtained from [16-³H]corticosterone with a molar radioactivity of 0.14 PBq mol⁻¹.¹²⁰

It is known that the reactivity of double bonds of unsaturated steroid hormones decreases in the following order: 1,2 > 6,7 > 16,17 > 4,5. By changing the reaction conditions (solvents, catalysts, *etc.*), one can perform selective hydrogenation of a definite bond and obtain the target steroid with high molar radioactivity.^{118,120} This method seems to be the most versatile for radioactive labelling of steroids; this results in steroids with high molar radioactivities.^{130,133} The syntheses of 17 α -ethynyl-19-nor[9,11-³H]testosterone and 18-methyl-17 α -ethynyl-17 β -hydroxyl[14 α ,15 α -³H]estr-4-en-3-one are shown in Schemes 17 and 18.

These schemes provide illustrative examples of the potentialities of chemical approaches to the synthesis of complex labelled compounds which are very labile under conditions of treatment with gaseous tritium in the presence of catalysts. If biological studies require labelled saturated steroids, solid-phase hydrogenation is the method of choice. In this case, the molar activity of steroids increases owing to the isotope exchange (Table 23).¹²⁰

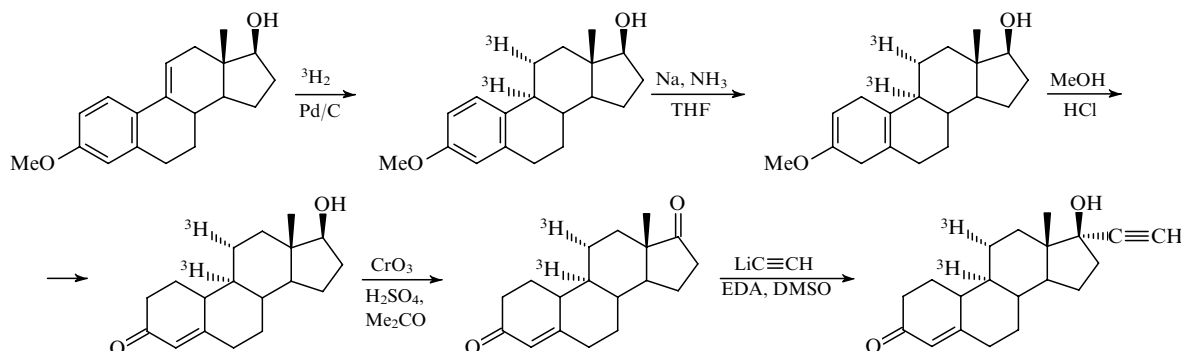
Selective hydrogenation is indispensable for the synthesis of labelled derivatives of natural steroids.^{22,129,134} As can be seen from Scheme 19, several tritium-labelled, biologically active progesterone analogues can be prepared from the same precursor (see Table 22).¹²⁹

Table 22. The values of molar radioactivities of labelled steroids.

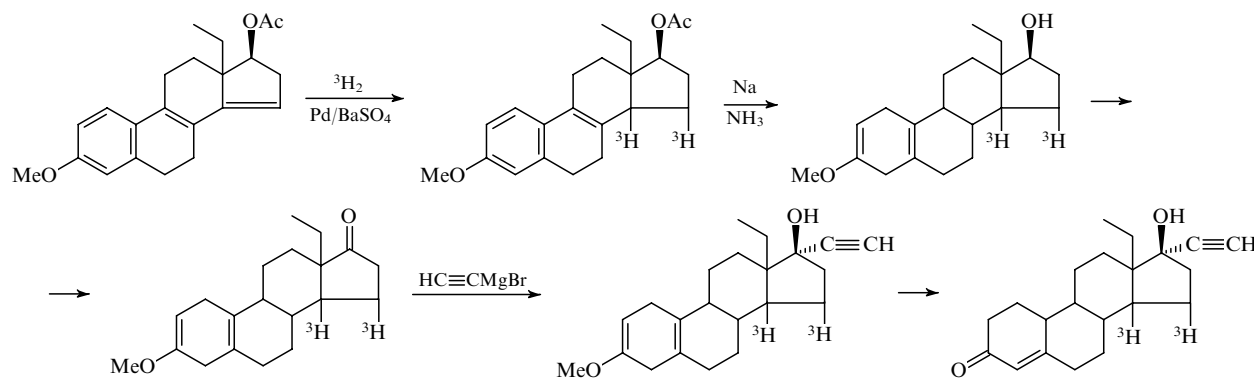
Compound	α /PBq mol ⁻¹	Ref.
Liquid-phase isotope exchange		
[G- ³ H]Cholestan-3 β -ol	0.0008	4
β -[G- ³ H]Sitosterine	0.0021	4
Solid-phase isotope exchange		
5 α -[G- ³ H]Dihydrotestosterone	0.56	120
5 α -[G- ³ H]Dihydrotestosterone enantate	1.50	120
Hydrogenation with gaseous tritium		
17 α -Ethynyl-17 β -acetoxy-19-nor-[6,7- ³ H]androst-4-en-3-one oxime	1.6	128
16 α ,17 α -[1,2- ³ H]Cyclopropanopregn-4-ene-3,20-dione	1.5	22
6 α -Methyl-16 α ,17-cyclohexano-[1,2- ³ H]pregna-1,4-diene-3,20-dione	1.6	22
16 α ,17 α -[3',4'- ³ H]Cyclohexanopregn-4-ene-3,20-dione	2.0	22
16 α ,17 α -[3',4'- ³ H]Cyclohexanopregna-1,4-diene-3,20-dione	1.5	129
16 α ,17 α -Cyclohex-3'-eno[1,2- ³ H]pregn-4-ene-3,20-dione	1.6	129
16 α ,17 α -[1,2,3',4'- ³ H]Cyclohexanopregn-4-ene-3,20-dione	3.2	129
5 α ,16 α ,17 α -[1,2,3',4'- ³ H]Cyclohexanopregnane-3,20-dione	3.2	129
5 β ,16 α ,17 α -[1,2,3',4'- ³ H]Cyclohexanopregnane-3,20-dione	3.2	129
3-O-Methyl-[9,11- ³ H]estradiol	2.1	130
5 α -[16,17- ³ H]Androstan-3-one	1.5–1.7	14
[4,5 β - ³ H]Cholestan-3-one	1.8–1.9	131
17 α -Hydroxy-[1,2- ³ H]androst-4-en-3-one	1.5	132
17 α -Hydroxy-5 α -[1,2,4,5- ³ H]androstan-3-one	1.9	132
18-Methyl-3-methoxy-[14 α ,15 α - ³ H]estra-1,3,5(10),8-tetraen-17 β -ol acetate	2.1	133

The selectivity of the process is achieved through the use of homogenous catalysts. Kinetic studies have shown that hydrogenation of the C(1)=C(2) bond occurs 1.5–2 times more easily than that of the C(3')=C(4') bond. However, reduction of the C(3')=C(4') bond is still the fast reaction, and after 1–1.5 h the reaction mixture did not contain even more stable 16 α ,17 α -[1,2-³H]cyclohex-3'-enopregn-4-ene-3,20-dione. Under optimum conditions (40 min), the reaction mixture contained 10%–15% of 16 α ,17 α -[3',4'-³H]cyclohexanopregna-1,4-diene-3,20-dione, 20%–25% of 16 α ,17 α -[1,2-³H]cyclohex-3'-enopregn-4-ene-3,20-dione {[³H]CHE} and 60%–70% of 16 α ,17 α -[1,2,3',4'-³H]cyclohexanopregn-4-ene-3,20-dione. Hydrogenation of the latter in the presence of heterogenous catalysts yielded two

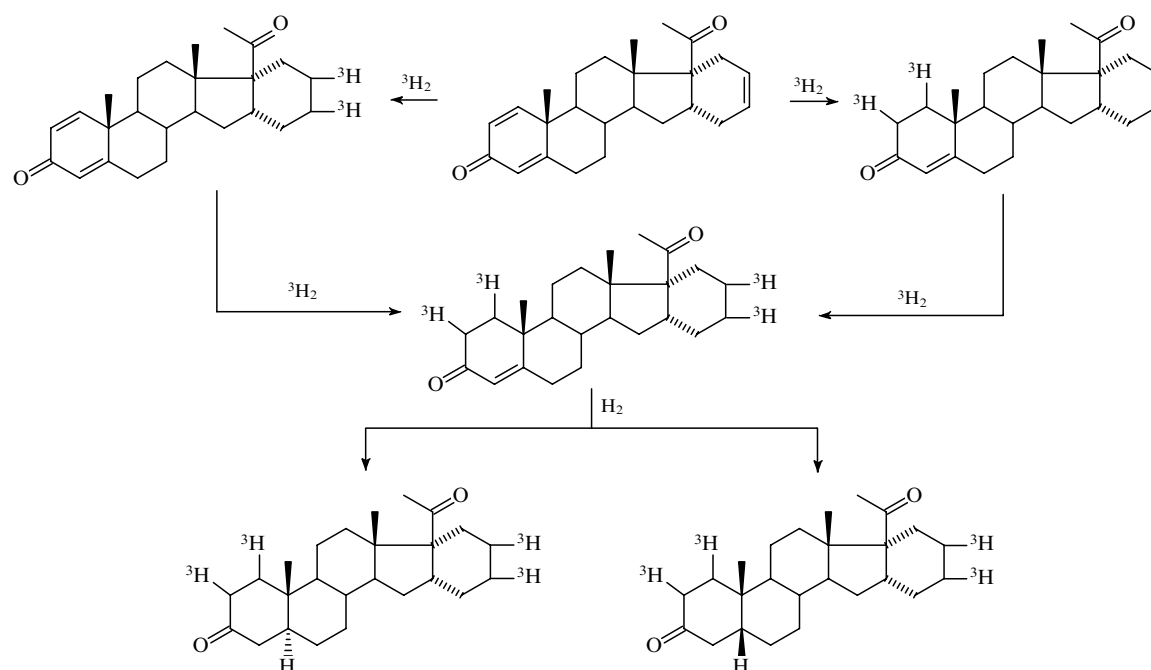
Scheme 17



Scheme 18



Scheme 19

**Table 23.** The values of molar radioactivities and the yields of labelled steroids obtained by a solid-phase method.¹²⁰

<i>T</i> / °C	<i>τ</i> / h	Target product	<i>α</i> / PBq mol ⁻¹
Starting compound — 17-hydroxyandrosta-1,4,6-trien-3-one			
120	5.0	androstenediol	6.65
120	50	androstanol	5.10
150	1.5	androstenediol	5.55
150	1.5	androstanol	4.5
Starting compound — androsta-1,4,6-triene-3,17-dione			
20	1.5	androstenediol	3.10
20	1.5	testosterone	3.14
50	26	androstenedione	4.85
50	26	androstenediol	6.5
50	26	androstanolone	6.5

additional labelled steroids, *viz.*, 5 α ,16 α ,17 α -[1,2,3,4'-³H]cyclohexanopregnane-3,20-dione and 5 β ,16 α ,17 α -[1,2,3',4'-³H]cyclohexanopregnane-3,20-dione.

The use of labelled reagents, *e.g.*, metal borotritides, has been mentioned above (see Table 19). Reactions with these reagents

and tritium-labelled methyl iodide and its derivatives afforded labelled steroids, such as [4-³H]- and [16-³H]cholesterols, 1 α ,3 β -dihydroxy-(20*S*)-[4-³H]-(3-hydroxy-3-methylbutyloxy)pregna-5,7-diene, 1 α ,25-dihydroxy-22-oxavitamin D₃ and some other compounds.^{3, 4, 118, 120, 135} The main disadvantage of this method is that the molar radioactivities of the resulting products depend on those of the labelled reagents, which are sometimes too low for conducting biological experiments. Presumably, syntheses of labelled preparations can be based on the use of non-labelled reagents and labelled steroidal precursors and reactions of condensation, oxidation, hydrolysis, acetylation or reduction.^{3, 136}

Several labelled 16 α ,17 α -cycloalkano- and 16 α ,17 α -cycloalkeno-substituted progesterones with different sizes of the additional ring *D'* were synthesised,^{22, 129} and their interactions with the progesterone receptor were studied for the first time in direct experiments. The steroid–receptor binding was studied using labelled 16 α ,17 α -cyclohexanopregn-4-ene-3,20-dione {[³H]CHA}, 16 α ,17 α -cyclopropanopregn-4-ene-3,20-dione {[³H]CPA} and proteins from the soluble fraction of rat uterus homogenates responsible for progesterone reception. The interaction of CPA and CHA with the progesterone receptor and other rat uterus proteins was assayed by cross-inhibitory analysis, which is based on the displacement of a labelled ligand from complexes of proteins with non-labelled steroids. The values of relative com-

Table 24. The values of relative competitive activity (RCA) of natural progesterone calculated from the displacement of labelled ligands from complexes with the progesterone receptor from the soluble fraction of pregnant rat uterus.

Labelled ligand	Unlabelled competitor	RCA ^a
³ H]Progesterone	CPA	1.02
	CHA	0.79
³ H]CPA	CPA	0.99
	CHA	0.57
³ H]CHA	CPA	1.57
	CHA	1.00

^a The progesterone activity was taken as unity.

petitive activity (RCA) were calculated from the concentration ratios of non-labelled compounds inducing 50% inhibition of specific binding of the labelled ligand (Table 24).

It was shown that a progesterone receptor in the soluble fraction of a rat uterus homogenate is a protein that specifically binds CHA and CPA and manifests almost identical parameters of competitive binding. The same regularity was observed with [³H]CHE. This compound binds by the protein which is identical with the progesterone receptor, no other specific binding species in the soluble fraction of rat uterus were detected. This conclusion was confirmed by analysis of CHE inhibitory effect on [³H]progesterone binding. During biological experiments, no metabolic conversions of labelled steroids occur. No significant differences were found in the mode of interaction of [³H]CHE and [³H]progesterone with a receptor isolated from the cells of different animals either. It is interesting to note that CHE as a representative of this class of steroids manifested higher activity in a pregnancy preservation test and a relatively low activity in an endometrium proliferation test upon systemic administration than progesterone.¹³⁷ These examples illustrate the possibility of the synthesis of steroid hormones with separated biological functions as regards progestagenic activity.

V. Conclusion

This review describes various methods for introducing tritium labels into biologically active compounds. Recent advances in radiochemistry have made it possible to solve numerous problems concerning the study of processes determining the vital activity of cells and the whole organism. There is no doubt, however, that further progress in medicine and biology will demand elaboration of novel and the development of existing methods of synthesis of labelled compounds. Studies on effects of micromodifications of molecules of various steroids are currently under way. These studies are necessary for the design of a new generation of medicinal drugs possessing strictly specific activity and having no adverse side effects.¹³⁸ New approaches to modification of oxylipins and polyenoic fatty acids are being developed in order to elucidate the relationship between the structure and function of these compounds, since the use of natural oxylipins as medicinal drugs is strongly restricted by the wide range of their pharmacological action and rapid metabolism.¹⁰⁶ The synthesis of some derivatives of polyunsaturated acids (e.g., dicarboxylic acids) required for the analysis of enzyme-substrate binding of mammalian 15-lipoxygenases has been carried out. This is important for continuing investigations in the field of gastroenterology, cardiology, angiology, oncology, etc.^{139,140} A vast variety of compounds (fungicides, immunodepressants, medicinal drugs influencing the central nervous system, pheromones, etc.), sometimes having an exotic structure, are being synthesised.¹⁴¹⁻¹⁴³

Considerable effort is devoted to a search for novel approaches to the synthesis of tritium-containing preparations. These investigations include an elaboration of original procedures for the synthesis of new catalysts and labelled reagents which

represent fragments of biologically active compounds or sources of radioactive labels, methods of enzymic synthesis of labelled oxylipins using organic solvents are being developed, etc.¹⁴⁴⁻¹⁴⁷ Thus data were obtained showing that enzymes functioning within micelles possess higher stability which increases the efficiency of synthesis of these labelled preparations.¹⁴⁸

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Regulation of cytochrome P450 activity by physicochemical methods

V V Shumyantseva, T V Bulko, A I Archakov

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Abstract. Physicochemical factors influencing the catalytic activities of hemoproteins (of cytochrome P450, in particular) that find use in biosensors and bioreactors are considered. The authors' data on the preparation of semisynthetic hemoproteins based on cytochrome P450 2B4 and NADPH-dependent cytochrome P450 reductase are presented. The use of alternative electron sources (electrochemical reduction and photoreduction) for the redox cycle of hemoproteins is discussed. The effects of temperature, pressure, chemical modification of proteins and organic solvents on the efficiency of hemoprotein-catalysed enzymic reactions are analysed. The bibliography includes 86 references.

I. Introduction

Cytochromes P450 are unique enzymes in that they are able to hydroxylate substrates with nonactivated C–H bonds. Cytochromes metabolise up to 200 000 compounds and catalyse about 60 types of chemical reactions, such as hydroxylation, N-, O- or S-demethylation, dealkylation, epoxidation, *etc.*¹ This feature of cytochromes P450 can be employed for quantification of medicinals and/or their metabolites and xenobiotics in different media as well as for stereodirected synthesis of steroids and other classes of biologically active compounds. The increase in the efficiency of catalysis by cytochromes P450 is a problem of considerable practical importance. The principles of bioelectrocatalysis have been discussed in detail.^{2,3}

The present review is devoted to the analysis of effects of various physicochemical factors on different stages of enzymic reactions with special emphasis on the advantages of alternative electron sources (electrochemical and photoreduction) over traditional reducing agents, such as NADH or NADPH. Reduction with the use of pyridine nucleotides is not a continuous process due to rapid exhaustion of NADH or NADPH. NADPH-

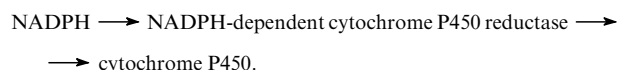
regenerating enzymes are normally introduced into a biochemical system to maintain the required concentration of reducing agents, which makes the system more complicated. The use of cathodic current instead of NADH or NADPH allows the reduction process to become more long-lasting and controllable by means of physicochemical factors, such as voltage and electric current. In the case of photoreduction, this process is monitored by recording the generated photocurrent and can be controlled by changing the excitation wavelength. The published data obtained in the past decade on cytochromes P450 are surveyed.

II. The use of electrochemical methods in the study of hemoproteins

1. The use of electrolysis for reduction of hemoproteins

Electron transport in biological systems normally occurs in the presence of electron donors (*e.g.*, NADH and NADPH) and an electron mediator, such as flavin nucleotides. In recent years, electrical systems are finding increasing use in the study of redox conversions of enzymes (of metalloenzymes, in particular).⁴ Electrons can be transferred to the electrode either directly, by electrochemical transport from the protein redox centre, or in the presence of mediator molecules.⁵ Different types of electrodes, such as graphite (glassy carbon, pyrolytic graphite), gold, platinum, semiconducting (indium oxide, tin oxide) and chemically modified graphite electrodes combined with redox catalysts (*e.g.*, rhodium catalysing oxygen reduction to hydrogen peroxide or water, metal complexes which efficiently mediate electron transport, *etc.*).^{6–8}

The electron transfer in enzyme systems containing cytochrome P450 occurs according to the scheme:



Here, NADPH is the electron donor and the microsomal flavo-protein (NADPH-dependent cytochrome P450 reductase) or a mitochondrial system consisting of a flavoprotein and a protein containing a Fe–S cluster is the electron carrier from NADPH to the hemoprotein (cytochrome P450).

The use of cathodic current instead of NADPH for electroreduction of flavins as mediators in oxygenase reactions has made it possible to obtain highly efficient electrochemical systems (Table 1).⁹ The hydroxylation of lauric acid in the presence of an

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Table 1. Comparison of rates of electrochemical and NADPH-dependent substrate metabolism reactions catalysed by recombinant proteins.⁹

Protein (reductase + cytochrome P450)	Substrate	Reaction	Reaction rate /nmol min ⁻¹ (nmol of P450) ⁻¹	
			electrochemical	NADPH-dependent
rF450(mBov17 α /mRatOR)L1	Progesterone	17 α -Hydroxylation	20	28
(reductase + P450 17 α)	Pregnenolone	"	5	5
rF450(mHum3A4/ mRatOR)L1	Testosterone	6 β -Hydroxylation	2.6	10.0
(reductase + P450 3A4)	Erythromycin	N-Demethylation	1.2	2.2
	Benzphetamine	"	2.0	4.6
rF450(mHum1A2/mRatOR)L1	Caffeine	"	0.75	1.5
(reductase + P450 1A2)	Imipramine	"	1.2	2.0
CYP102-BM3 (P450 BM3)	Lauric acid	ω -Hydroxylation	110	900

electrochemical system consisting of a gold or platinum electrode and a purified fused protein containing P450 4A1 and NADPH-dependent cytochrome P450 reductase has been studied.^{6, 9, 10} In addition to the fused protein, the electrochemical system contained a coordination compound of Co(III), *viz.*, [(S)-1,3,6,8,10,13,16,19-octaazabicyclo[6.6.6]eicosanocobalt(III)] as a mediator. The standard redox potential, *U*, of this compound is -350 mV (*vs.* standard hydrogen electrode). Presumably, the reduction of the Co(III) ion on the cathode occurs within the coordination compound according to the scheme: $\text{Co}^{3+} + e \rightarrow \text{Co}^{2+}$. If the electrolysis is carried out in a system containing only the flavoprotein (reductase) or a hemoprotein (cytochrome P450) no hydroxylation of lauric acid occurs, which suggests that the Co^{2+} ion plays the role of an activator. This reduces flavin nucleotides of the reductase, which, in turn, reduce the heme iron of cytochrome P450. Oxygen activation occurs on the reduced heme iron within the triple complex 'substrate- Fe^{2+} - O_2 '; in this case, the oxidation of various substrates under physiological conditions occurs at high rates.¹ Electrochemical reduction of the fusion protein generates hydrogen peroxide, which destroys the enzyme system. The addition of catalase increases the efficiency of the system in the hydroxylation reaction. It was shown that the highest rate of lauric acid hydroxylation is observed at -450 mV (*vs.* standard hydrogen electrode).^{6, 9, 10}

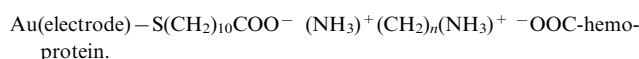
A semiartificial flavohemoprotein (flavocytochrome P450 2B4) possessing reductase and oxygenase activities was obtained earlier in our laboratory.^{11, 12} Using an electrochemical system consisting of flavocytochrome 2B4 or 1A2 and rhodium-graphite microelectrodes, we performed successful aniline *p*-hydroxylation, aminopyrine N-demethylation and 7-ethoxy- and 7-pentoxoresorufin O-dealkylation. The reduction was carried out at *U* = -450 mV (*vs.* AgCl electrode).¹³ The catalytic constants of NADPH-dependent and electrochemical reactions catalysed by flavocytochromes 1A2 and 2B4 were comparable.

Several factors have plagued direct electron transfer between electrodes and proteins. These include: (i) electroactive prosthetic groups deep within the protein structure, (ii) adsorptive denaturation of proteins onto electrodes, and (iii) unfavourable orientations at electrodes. Remarkable recent progress provides several strategies for achieving direct electron exchange between electrodes and proteins.

Immobilisation of enzymes on the electrode surface is used to increase the efficiency of the electron transfer from the electrode to the electroactive prosthetic group of the protein¹⁴⁻¹⁶ by means of adsorption, covalent binding and incorporation of enzymes into polymeric films coating the electrodes. For example, positively charged proteins are immobilised by adsorption on electrodes of pyrolytic graphite containing negatively charged carboxy groups, whereas immobilisation of hemoproteins on graphite electrodes involves covalent binding in the presence of a cross-linking bifunctional reagent (glutaraldehyde) and albumin.¹⁷ In the latter case, albumin is strongly adsorbed on the surface of graphite electrodes, while glutaraldehyde cross-links the redox protein with

albumin through the amino groups thereby binding the former to the electrode.

Yet another approach consists of the use of promoter molecules which favour the electron transport through proper orientation of the proteins on the electrode, which thus blocks their adsorptive denaturation. The role of promoters can be played by alkanethiols containing terminal functional groups (*e.g.*, mercaptoundecanoic acid).¹⁸ The chemisorption of mercaptoundecanoic acid on the surface of gold electrodes is accompanied by the formation of a stable monolayer, which facilitates subsequent binding (both covalent and ionic) of proteins to the electrode surface.



Double-stranded DNA, which is strongly adsorbed on electrodes of pyrolytic graphite, can also be used as a promoter molecule.¹⁹ Such DNA-containing electrodes can readily extract hemoproteins from the solution.

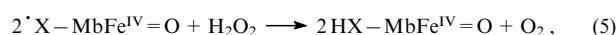
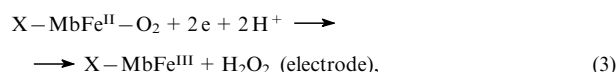
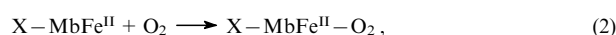
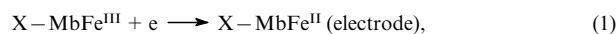
The rate of the electron transfer from the electrode to the redox protein, can be increased if the electrodes containing covalently bound or adsorbed electron transport mediators, such as riboflavin or methylviologen, are chemically modified;^{20, 21} the stability of hemoproteins in electrochemical systems is increased if they are incorporated into phospholipid films which coat the electrodes.²²⁻²⁴ Surfactants containing charged or polar head groups and a hydrophobic tail (didodecyldimethylammonium bromide, polystyrenesulfonate, dihexadecyl phosphate, dimyristoylphosphatidylcholine) are used as films mimicking natural biomembranes.

It is of note that electrochemical processes involving redox proteins are reversible only in liquid-crystalline films.²² If cytochrome P450_{cam} is incorporated into liquid-crystalline films formed by dimyristoyl-L- α -phosphatidylcholine or didodecyldimethylammonium bromide, direct reversible electron transfer occurs from the electrode to the heme iron of the enzyme as is judged by direct current cyclic voltammograms.²²⁻²⁴ Thus myoglobin reduction in liquid-crystalline didodecyldimethyldiammonium bromide films coating the pyrolytic graphite electrodes is reversible in contrast with its reduction on electrodes without biomembrane-like surfactant films.²⁴ On addition of a substrate (*e.g.*, trichloroacetic acid), this is reduced, as follows from the increase in the cathodic current. The incorporation of cytochrome P450_{cam} into DNA films adsorbed onto gold electrodes has made it possible to perform direct reduction of the heme iron and catalytic epoxidation of styrene.²⁵

Electrochemical reduction of metmyoglobin ($\text{X-MbFe}^{\text{III}}$), which is a perfect functional model of cytochrome P450 (the catalytic activity of myoglobin is close to that of cytochrome P450), was studied by Onuoha *et al.*²⁴ The electroreduction was carried out on electrodes of pyrolytic graphite at the potential, *U* = -400 mV (*vs.* SCE) in aqueous buffers or microemulsions of

hydrocarbons, water and cationic detergents. Under these conditions metmyoglobin is reduced on the electrode [Scheme 1, reaction (1)]. The reduced metmyoglobin rapidly reacts with oxygen to yield an $X-MbFe^{II}-O_2$ complex, which is reduced with the liberation of hydrogen peroxide on the electrode. The hydrogen peroxide evolved effects stepwise oxidation of metmyoglobin ($X-MbFe^{III}$) to ferrylmyoglobin ($HX-MbFe^{IV}=O_2$), an active oxidised form of myoglobin [Scheme 1, reactions (4) and (5)].

Scheme 1



where X is an amino acid residue, *e.g.*, tyrosine-130. Styrene added to the reaction system is oxidised by hydrogen peroxide to give styrene oxide and benzaldehyde.

The efficiency of electrolysis used for the reduction of hemoproteins is comparable with the traditional reduction with pyridine nucleotides. The results obtained in the study of electrochemical and NADPH-dependent reactions of several isoforms of cytochrome P450 are presented in Table 1.

At present, attempts are being undertaken aimed at designing cytochrome P450-containing bioreactors and biosensors based on electrochemical systems.^{9, 22, 26}

2. The use of inorganic semiconductors in redox systems

The effectiveness of inorganic semiconductors (TiO_2 , ZnO , CdS) in combination with enzymes (hydrogenases, dehydrogenases) in photoproduction of hydrogen, photoreduction of $NADP^+$ and photosynthesis of organic acids and amino acids has been demonstrated in a number of studies.^{27–31} The system 'inorganic semiconductor–enzyme' can transform light energy by semiconductor-photosensitised oxidation of organic electron donors and by enzyme-catalysed reduction of substrates (H^+ , $NADP^+$, organic acids and amino acids) with electrons photogenerated in the semiconductor. Coupling of an inorganic semiconductor with an enzyme is usually attained with the help of electron carriers (mediators), *e.g.*, methylviologen, a rhodium bipyridyl complex and other compounds subject to reversible oxidation–reduction. Direct mediator-free transfer of electrons photogenerated in the conduction band of the semiconductor to the enzyme reaction centre has been described by Nikandrov *et al.*²⁸ A prerequisite for the conjugate effect of a semiconductor and an enzyme in the absence of an electron carrier is the sorption of the enzyme on the semiconductor surface.

3. The construction of an enzymic 'galvanic couple' for redox reactions

The operating principle of a galvanic element is based on the difference in the electrode potentials of the oxidant and the reducing agent. Active metals (*e.g.*, zinc) are most commonly used as reducing agents, while hemoproteins are used as oxidants. Normally, hemoproteins have a more positive standard electrode potential than zinc [$E_0(Zn^0/Zn^{2+}) = -763$ mV]; therefore zinc serves as a reducing agent in a zinc–hemoprotein couple. We used metallic zinc as an electron donor and a hemin–human serum albumin complex as an artificial hemoprotein and succeeded in effecting N-demethylation of aromatic amines.³² The rates of these reactions were comparable with those of NADH-dependent reactions carried out in the presence of flavin nucleotides or riboflavin as electron transfer mediators.

Metallic cadmium [$E_0(Cd^0/Cd^{2+}) = -403$ mV, $E_0(NAD^+/NADH) = -340$ mV] was used as a reducing agent in a system

containing NAD^+ -dehydrogenase.³³ In this case, too, the 'galvanic couple' principle is realised.

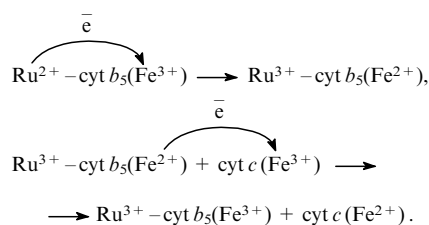
III. Photoinduced electron transport

Light energy is utilised not only in traditional photosynthetic reactions or in photoinduction of semiconductors, it also triggers electron transport in redox systems. Direct photoreduction of hemoproteins in the absence of electron donors has been described by Gu *et al.*³⁴ Metmyoglobin, cytochromes *c* and *b₅* and heme complexes with octapeptides and cytochrome P450 were photo-reduced upon laser irradiation at wavelengths of 430–254 nm. UV irradiation resulted in photooxidation. This study has shown that the heme ligands play a crucial role in photoreduction. The photoreduction products were characterised by UV and visible absorption spectra and Raman spectra and compared with the products formed upon chemical reduction.

Heme photoreduction in hemoproteins can be utilised for 'triggering' redox reactions, such as oxygen activation by cytochrome P450 or binding of ligands (*e.g.*, O_2) with myoglobin or hemoglobin. Studies of model complexes (hemin–octapeptides) corroborated the viewpoint that aromatic amino acids are not the primary electron donors, since the model peptides were devoid of aromatic amino acid residues. In the presence of organic solvents (glycerol and other alcohols), the rate of photoreduction increased.³⁴ Irradiation with a nonfocused laser ($\lambda = 457.9$ nm, power 40 mV) of a 'riboflavin–hemin–albumin' complex resulted in riboflavin photoreduction as could be evidenced from changes in the absorption spectrum of the complex. Amine demethylation and aniline hydroxylation products were formed in the presence of *N*-substituted amines or aniline; the rate constants (k_{cat}) for dimethylaniline N-demethylation and aniline hydroxylation are equal to 0.5 min^{-1} and 0.13 min^{-1} , respectively, *i.e.*, they are comparable with those of NADPH-dependent reactions.³²

The photooxidation of the reduced flavocytochrome b_2^+ from *Saccharomyces cerevisiae* (lactate dehydrogenase) upon irradiation with a laser ($\lambda = 400$ nm) has been described by Hazzard *et al.*³⁵ At this wavelength, the oxidised form of 5-deazariboflavin passes into an excited triplet state; it is this state that is involved in the oxidation of the reduced heme. The rate of intermolecular electron transport was 2200 s^{-1} .

A series of investigations^{36–40} have been devoted to the study of electron transport in hemoproteins (in cytochromes *c* and *b₅*, in particular) modified with ruthenium or cobalt complexes. A characteristic feature of ruthenium complexes is their ability to undergo reversible photoreduction and to transfer electrons to other acceptors. Thus a ruthenium complex covalently bound to cysteine-65 of cytochrome *b₅* effected rapid reduction of cytochrome *c* according to the scheme.³⁶



The electron transfer in these systems was studied in direct photoreduction of ruthenium complexes and using a flash-photolysis technique. The photoreduction of the flavoprotein cytochrome P450 reductase in the presence of electron acceptors (ferricyanide, Tetrazolium Nitro Blue) could be carried out in the absence of NADPH.⁴⁰

† Reduced flavocytochrome was obtained by titration of the oxidised enzyme with a 1.5-fold excess of L-lactate.

Thus, photoinduced electron transport can serve as an alternative source of electrons in redox reactions provided the proteins contain photosensitive prosthetic groups or their analogues.

IV. Changes in the microenvironment of the protein and its active centre

1. Modelling of the membrane environment

The environment, especially the cell membrane, strongly influences the enzyme activity in living organisms. The construction of an artificial membrane-like environment may significantly enhance the enzyme activity. Among various synthetic membranes studied, synthetic membrane-like phospholipid bilayers were shown to possess an activating effect.⁴¹ Cytochrome *c* incorporated into such membranes increases the rate of H₂O₂-induced *N,N*-dimethylaniline *N*-demethylation 10.6-fold. A 20-fold decrease in the Michaelis constant for H₂O₂ is observed, which suggests increased affinity of the enzyme towards hydrogen peroxide. Changes in the spectral characteristics of cytochrome *c* incorporated into the phospholipid bilayer suggest significant structural and functional changes. The oxidised form of the protein is characterised by a short-wave shift of the optical density maximum (from 408 to 406 nm) upon incorporation, the absorption maximum of the reduced form is shifted from 416 to 426 nm and one maximum at 550 nm is observed instead of two maxima at 520 and 550 nm.

The incorporation of myoglobin into membrane-like films results in a decrease in the activation energy of electrochemical reduction of dibromoethylene and trichloroacetic acid, the rate of electron transport increases 1000-fold.¹⁶ Acetylcholinesterase, cholinesterase and horseradish peroxidase incorporated into polymeric films prepared from polyvinylpyridine and polyethylene glycol can be used as amperometric sensors for detecting acetylcholine, choline and hydrogen peroxide.⁸

2. Enzymatic catalysis in reversed micelles and organic solvents

Many properties of biological membranes are efficiently mimicked by reversed micelles of surfactants in organic solvents, which can be regarded as biomembrane models.

In 1977, Martinek *et al.*⁴² showed that enzymes solubilised in organic solvents with the aid of reversed micelles of synthetic surfactants retain their catalytic activities. Some hemoproteins, *e.g.*, cytochrome *c* and methemoglobin, induce the formation of reversed micelles by incorporating into bilayer membranes with simultaneous preservation of their enzymic activities.^{43–45} Horseradish peroxidase solubilised in a sodium diisooctyl sulfosuccinate–water–octane system catalyses pyrogallol oxidation by hydrogen peroxide much more efficiently than the water-soluble enzyme.⁴⁶

Efficient catalysis of redox reactions by hemoproteins incorporated into reversed micelles of surfactants was used for increasing the operational stability of catalase, superoxide dismutase and glutathione peroxidase.⁴⁷ Systems mimicking hemoproteins (albumin–hemin complexes and ferritin) were also incorporated into reversed micelles.⁴⁸

Cytochrome P450 1B1 and cytochrome P450 reductase as a fusion protein was incorporated into oil-in-water macroemulsion, termed polyaphron, (the internal organic phase content was more than 0.74). The efficiency of such immobilisation exceeded 85%; the enzyme preparation remained active towards substrates (erythromycin, chlorotolurone) for 24 h at 15 °C.⁴⁹

In order to decrease the water content in colloidal media, the substitution of a water-organic mixture for the water surrounding the enzyme in reversed micelles of surfactants was suggested.⁵⁰ The hemoglobin-catalysed oxidation of dibenzothiophene in various water-organic mixtures was studied by Klyachko and Klivanov.⁵¹ The preparation of suspensions of lyophilised enzymes in organic solvents is an alternative procedure for

excluding water. The enzymes suspended in organic solvents acquire new properties, which affects virtually all the aspects of their functioning, *viz.*, catalytic activity, substrate specificity, stereoselectivity, thermal stability, *etc.*^{52, 53}

In addition to ordinary enzymic reactions, the reactions nonspecific for enzyme behaviour in aqueous media may occur either in nonaqueous organic solvents or in organic solvents with the H₂O content of 0.01 vol.%. The reasons for the alteration of the substrate specificities are different for individual enzymes. Nevertheless, enzymatic catalysis in organic solvents obeys the Michaelis–Menten kinetics, which suggests the formation of a classical enzyme–substrate complex in nonaqueous solutions.

The phenomenon of ‘enzyme memory’ has been discovered in experiments with enzyme suspensions in organic solvents. An enzyme lyophilised from an aqueous solution containing a specific ligand and then suspended in an organic solvent binds the ligand several tens of times more efficiently. This property disappears after repeated dissolution in water. A possible explanation of this phenomenon is that the enzyme retains an ‘imprint’ of the ligand even after its removal upon lyophilisation. In nonaqueous media where the conformation of the protein molecule becomes more rigid, the enzyme manifests higher affinity for the ligand.^{54, 55} The ability of enzymes to retain the ‘imprints’ of ligands has a certain practical significance for the synthesis of chiral pharmacologically useful intermediates.

The effects of organic solvents on the properties of cytochrome P450 have been studied to a lesser degree. It was found that organic solvents favour the transition of cytochrome P450 into the inactive form, P420.⁵⁶ This transition is due to the changes in the nearest coordination sphere (sulfur atoms) around the iron atom. A similar transition is observed in the case of chloroperoxidase.⁵⁶ However, cytochrome *c* suspended in tetrahydrofuran containing 1% D₂O fully preserves its tertiary structure.⁵⁷ These conclusions were made on the basis of analysis of the tertiary structure of cytochrome *c* by two-dimensional NMR spectroscopy.

V. Chemical modification of proteins for triggering new catalytic functions

This section considers the methods used for enhancement of the enzymatic activity by introducing new catalytically active groups into the enzyme molecule.

Thus cytochrome P450 manifests monooxygenase activity only within a complex with the flavoprotein reductase. Here flavin nucleotides represent electron carriers which reduce the heme iron of cytochrome P450. The introduction of flavin nucleotides or their analogues into cytochrome P450 converts the latter into a self-competent enzyme which does not require the involvement of partner proteins in the catalytic cycle.

Semisynthetic flavohemoglobin was prepared by attachment of activated flavin derivatives⁵⁸ to the β -subunit of hemoglobin used in a 2:1 ratio.^{59, 60} Hemoglobin catalyses monooxygenase reactions occurring in a system containing a hemoprotein, oxygen, NADPH and a flavoprotein (NADPH-dependent cytochrome P450 reductase). Covalent binding of flavin to hemoglobin makes it possible to conduct similar reactions in the absence of reductase. The rates of the catalytic reaction of aniline hydroxylation in the presence of flavohemoglobin and the microsomal monooxygenase system are comparable. The rate of aniline hydroxylation in the presence of semisynthetic flavohemoglobin increased in comparison with hydroxylation rates in the presence of hemoglobin and the hemoglobin–reductase system (7.7- and 1.3-fold, respectively).

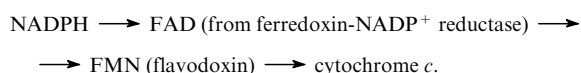
The catalytic activity of the covalent complexes ‘cytochrome P450–flavin adenine dinucleotide’ (FAD) and ‘cytochrome P450–flavin mononucleotide’ (FMN) has been studied by Uvarov *et al.*⁶¹ The complex in which cytochrome P450 is covalently bound to FMN (1:3) turned out to be more active. The catalytic rate constants for dimethylaniline and aminopyrine

N-demethylation and aniline hydroxylation were about 2 times lower than those of the analogous reactions catalysed by microsomes, which represent natural complexes of cytochrome P450 and reductase. The rates of reactions catalysed by covalent and noncovalent P450–FAD complexes are 10 times lower than those of microsome-catalysed reactions.

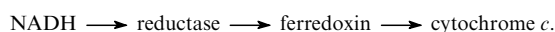
A monomolecular monooxygenase system formed by covalent binding of the electron-accepting antibiotic bleomycin to a flavoprotein (NADPH-dependent cytochrome P450 reductase) has been described by the same authors.⁶¹ The rates of reactions involving the reductase–bleomycin complex are 10 times lower than those of microsome-catalysed reactions.

Reductase does not possess its own catalytic activity in monooxygenase reactions; however, after incorporation of 1 to 10 heme residues into the reductase molecule the semi-artificial hemoreductase manifested activity in NADPH-dependent N-demethylation of amidopyrine ($k_{\text{cat}} = 0.7 \text{ min}^{-1}$). The k_{cat} values for the analogous reactions catalysed by the microsomal monooxygenase system and the semi-artificial flavocytochrome 2B4 are 2.4 and 0.98 min^{-1} , respectively.^{11,12} A semi-artificial hemoreductase⁶² which represents a covalent complex of heme and NADPH-dependent cytochrome P450 reductase manifested reductase activity with respect to electron acceptors, such as potassium ferricyanide, cytochrome *c* and hemein.

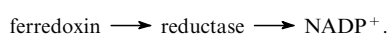
The covalent binding of flavodoxin to ferredoxin–NADP⁺ reductase⁶³ (1:1) gave an artificial enzyme which catalyses the reduction of cytochrome *c* with high efficiency. The transfer of electrons in this system occurs according to the same scheme as in NADPH-dependent cytochrome P450 reductase.



Ferredoxin–NADP⁺ reductase modified with viologen in the presence of carbodiimide manifests oxidase activity, which is absent in the native enzyme.⁶⁴ In the absence of ferredoxin, the reductase does not reduce cytochrome *c*, whereas the modified enzyme displays high activity. In the presence of electron acceptors such as 2,6-dichloroindophenol and ferricyanide, the activity of the modified enzyme decreases twofold, whereas the rate of the cytochrome *c* reductase reactions increases 30-fold. The scheme of electron transport in a system with the nature enzyme appears as:



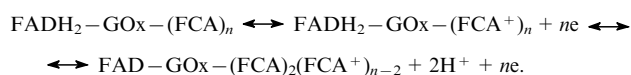
When the reactions are carried out in the presence of superoxide dismutase, the viologen–reductase systems utilise the oxygen molecule reduced to the superoxide radical anion as the final electron acceptor. It is the presence of active oxygen species that accounts for the appearance of oxidase activity in the modified enzyme. Titration of the reduced viologen–reductase system revealed that the electron transfer to viologen occurs through the flavin group of FAD present in the reductase. The standard electrode potential of viologen covalently bound to ferredoxin–NADP⁺ reductase is -365 mV , while that of soluble viologen is -420 mV . The electrode potentials of other reaction participants are -320 mV (NADPH), -344 mV (reductase) and -420 mV (ferredoxin). The electrochemical preparation of NADPH using the native enzyme requires an electron donor capable of reduction of ferredoxin, since in this case the scheme of electron transport appears as:



The electric current generated by the electrochemical system ‘viologen–reductase’ in the presence of NADP⁺ points to the electron transfer between the electrodes and the system. The latter can therefore be used for regeneration of NADPH.

Ferrocene and its derivatives are known to be efficient electron carriers. Modification of glucose oxidase (GOx) with ferrocene-carboxylic acids (FCA) has been described by Badia *et al.*⁶⁵ Covalent derivatisation of the GOx molecule containing two

FAD molecules with additional electron carrier groups imparts the ability to be involved in the electrochemical reaction. The optimum number of FCA groups is 13 residues per GOx molecule. In native glucose oxidase, reduced FADH₂ is oxidised with atmospheric oxygen, whereas the role of oxygen in ferroceneglucose oxidase is played by FCA responsible for ‘internal’ electron transport. Ferroceneglucose oxidase undergoes electrochemical conversions on the electrodes according to the scheme:



The arrangement of bound FCA residues relative to the FAD molecule is more important for electron transport than their number. The electrode potential of the FADH₂/FADH[•] couple is -219 mV , that of the FCA⁺/FCA couple is $+773 \text{ mV}$. Hence, the motive force of the electron transport in the given system is about 1 V.

Modification of cytochrome P450_{cam} and β-lactamase with a new electron-active reagent, *N*-(2-ferrocenylethyl)maleimide, was described by Gleria *et al.*^{66–68} who showed that modified enzymes are electrochemically active. These authors suggest using *N*-(2-ferrocenylethyl)maleimide as a promising reagent for the conversion of electropassive enzymes into electroactive ones as well as for the design of electrochemical sensors and for studies of mechanisms of intraprotein electron transport.

The covalent binding of glutathione reductase to the photosensitive dye eosin (1:2) was used to obtain a photoactivated system which can be used for glutathione reduction.⁶⁹ Eosin-modified glutathione reductase retains 50% of activity of the native enzyme in a NADPH-dependent reaction. However, the photosystem thus obtained was 1000 times less active in glutathione reduction than the glutathione reductase with NADPH as the electron source.

VI. Effect of temperature on hemoprotein-catalysed reactions

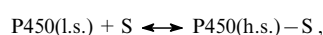
Studies of reactions catalysed by cytochrome P450 2B4 have shown that an increase in temperature causes an increase in the rate of substrate hydroxylation. For example, with a rise in temperature from 20 to 37 °C, the catalytic constant, k_{cat} , for peroxide-dependent O-dealkylation of *p*-nitroanisole increases twofold.⁷⁰

The catalytic cycle of cytochrome P450 is rather complex and comprises at least seven steps.^{1,71} The effect of temperature on the binding of various substrates (*e.g.*, benzphetamine) to cytochrome P450 and on the spin equilibrium between low- and high-spin forms of the hemoprotein was studied in most detail. It was shown⁷² that a change in temperature from 12 to 27 °C has no effect on the absorption spectra of cytochrome P450 2B4. The spectra are not changed after addition of benzphetamine ($0.8 \text{ mol litre}^{-1}$) either. The dissociation constants (K_d) and concentration $[\text{ES}]_{\text{max}}$ of enzyme–substrate complexes show the following temperature dependence:

Temperature / °C	$K_d / \mu\text{mol litre}^{-1}$	$[\text{ES}]_{\text{max}} / \mu\text{mol litre}^{-1}$
13.8	189 ± 5	0.085 ± 0.002
23.8	86 ± 5	0.087 ± 0.004

As can be seen, the concentration of enzyme–substrate complexes is practically constant at different temperatures. However, the use of the ‘temperature jump’ technique, which consists of instantaneous increase in the temperature in the reaction cell upon high-power electric discharge revealed enhanced binding of the substrate to the enzyme.⁷²

The substrate-induced spin equilibrium obeys a bimolecular mechanism:



where l.s. and h.s. are the concentrations of the low-spin and high-spin forms of the enzyme, respectively. The catalytic constant of this reaction can be written as:

$$k_{\text{cat}} = \frac{1}{\tau_f} = k_1([E]_{\text{eq}} + [S]_{\text{eq}}) + k_{-1},$$

where τ_f is the fast relaxation time, *i.e.*, the time during which the system passes into a new state and $[E]_{\text{eq}}$ and $[S]_{\text{eq}}$ are the equilibrium concentrations of the enzyme and the substrate, respectively. In the absence of the substrate, the relaxation does not occur, which is consistent with the experimental data concerning the effect of temperature on the absorption spectra of cytochrome P450 not bound to the substrate.

A study of temperature-dependent electrochemical reduction of the fusion protein[‡] (within the temperature range of 4–36 °C) revealed that the rate of reduction is a maximum at 22 °C.⁶ The reason should be sought in the simultaneous occurrence of several parallel reactions in electrochemical systems that are differently affected by temperature.

VII. Effect of high pressure on the catalytic activity of hemoproteins

The effect of high pressure on the kinetics and dynamics of conformational conversions of proteins has been studied by Morild.⁷³ High pressures are used for shifting chemical and biochemical equilibria as well as for changing the rates of individual steps of enzymatic reactions.

The changes in the reaction and activation (ΔV^* and ΔV^{**}) volumes calculated from the experimental data on the effect of high pressure can be utilised in the study of molecular mechanisms of different enzymes and their transition states during the formation of new bonds. If ΔV^* and ΔV^{**} values are negative, an increase in pressure will shift the equilibrium towards the formation of enzymatic reaction products in accordance with the Le Châtelier principle.^{74, 75}

The effect of high pressure on bacterial camphor-metabolising cytochrome P450_{cam} was extensively studied by several authors.^{76–79} It was found that the pressure affects the equilibrium between low-spin and high-spin states. An increase in pressure to 2.2 kbar induces the transition of cytochrome P450_{cam} into the inactive form, P420. Chloroperoxidase is also converted into C420 at high pressure.⁷⁵ The effect of high pressure on the redox potential of cytochrome *c* was studied by Tschirret-Guth *et al.*⁸⁰ By measuring changes in the standard potential (E^0) as the function of pressure (P), one can calculate the reaction volume, ΔV^0 :

$$\left(\frac{\partial E^0}{\partial P}\right)_T = \frac{\Delta V^0}{nF},$$

where F is the Faraday constant, $\Delta V^0 = \sum V_p^0 - \sum V_r^0$ ($\sum V_p^0$ and $\sum V_r^0$ are the sums of standard molar volumes of the products and reactants, respectively). As the pressure is increased, the reaction accompanied by a decrease in the molar volume will be preferred. In the case of a redox process, this will induce a positive shift of the redox potential. According to Tschirret-Guth *et al.*,⁸⁰ the increase in pressure to 5 kbar results in the changes of the potential from –5 mV to +76 mV; the molar volume also changes upon transition from the oxidised to the reduced form of cytochrome *c*:

$$V[\text{cyt } c(\text{Fe}^{2+})] - V[\text{cyt } c(\text{Fe}^{3+})] = -24 \text{ ml mol}^{-1}.$$

These findings are consistent with the results of structural and physicochemical studies, *viz.*, ferrocycytochrome *c* has a more compact structure than ferricytochrome *c*. By changing the pressure on the enzymic system, one can shift the chemical

equilibrium in redox hemoproteins towards the formation of the reduced form.

VIII. Conclusion

Most enzymes, including hemoproteins, are rather sensitive to physical and chemical influences which can induce complete or partial loss of their activities. This necessitates the design of artificial enzymes based on proteins with higher resistance to such influences. In some studies, artificial hemoproteins were prepared as a result of the formation of noncovalent specific complexes of hemin^{32, 81} or its analogues (cobalt octaethylbis-porphyrinate, cobalt octapyridinemethylphthalocyanine and lute-cium diphthalocyanine)⁸² with human or bovine serum albumin and synthetic peptides.^{83, 84} These complexes manifest oxygenase-like catalytic activity in aminopyrine N-demethylation and aniline hydroxylation. Yet another trend, *viz.*, the design and *de novo* synthesis of artificial proteins with predetermined structure and functional properties by gene engineering methods is also in progress.^{85, 86}

This review summarises the data on targeted action of various physicochemical factors on individual steps of enzymic reactions catalysed by hemoproteins. A rational combination of physicochemical approaches to the study of natural, semi-artificial and artificial enzymic systems can be useful in the design of new effective biosensors, test systems and bioreactors.

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^d — *Mol. Biol. (Engl. Transl.)*

Fullerenes: functionalisation and prospects for the use of derivatives

E N Karaulova, E I Bagrii

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Abstract. Published data on the functionalisation of fullerenes (mainly, C_{60}) including those using addition reactions (cyclo addition, hydrogenation, oxidation, etc.) are surveyed. The participation of fullerenes in catalysis and fullerene-containing polymers are considered and the prospects for the practical use of fullerene derivatives are discussed. The bibliography includes 191 references.

I. Introduction

Synthesis of polyhedral carbon clusters, fullerenes C_{60} , C_{70} and so on,¹ from hot carbon plasma has initiated and triggered vigorous development of a new line of research in the chemistry of cage compounds, namely, study of the reactivity of fullerenes. In 1996, Kroto, Curl and Smalley were awarded the Nobel Prize in chemistry for the discovery of fullerenes, a new allotropic modification of carbon. In this respect, it is pertinent to consider the essence of this discovery, the history of which is presented in detail in the Nobel lectures of the authors.^{2–4}

A necessary condition of the success was the original apparatus designed by Smalley for the preparation and investigation of clusters formed on heating of high-melting compounds. This was a supersonic source of cluster beams with laser vaporisation. In this setup, a slowly rotating graphite disc was exposed to the radiation of a pulsed laser. The carbon vapour was treated with a helium flow in the supersonic flash regime and cooled to a temperature of several Kelvins by adiabatic expansion. The cluster beams were directed into a time-of-flight mass spectrometer with photoionisation of the molecular beam.

By varying the conditions of clustering and the time of cooling, the researchers attained the predominance of the stable C_{60} cluster in the mixture. The researchers^{2–4} proposed and substantiated the structure of C_{60} fullerene as a spherical hollow molecule shaped like a truncated icosahedron (Fig. 1). To verify the presence of a cavity inside the C_{60} spheroid, the graphite disc of

the setup was impregnated with an aqueous solution of lanthanum chloride; in this case, laser vaporisation gave a stable complex with the metal located inside the fullerene cage.

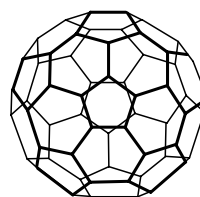


Figure 1. C_{60} fullerene (see Ref. 3).

Calculations for the C_{60} molecule, which gave rise to the suggestion that this molecule should be stable, had been performed^{5,6} fifteen years ahead of the experiments of Smalley *et al.*¹ (according to Kroto's assertion,³ they were not acquainted with these data).

Vigorous development of the physics and chemistry of fullerene became possible only when Krätschmer, Lamb, Fostiropoulos and Huffman⁷ had developed a method for the preparation of macroscopic quantities of fullerenes. The fact that fullerenes are formed during vaporisation of graphite electrodes in an electric arc in a helium atmosphere, discovered by these investigators, served as the basis for this method. The researchers⁷ prepared and studied crystals of the C_{60} cluster.

The development of the preparative-scale method for the synthesis of fullerenes brought about an avalanche-like increase in the number of publications devoted to this topic. Osawa, who had predicted the stability of icosahedral fullerenes in 1970,⁵ composed a computer database (fullerene literature data base, FLDB), based on reprinting from *Current Contents*.⁸

The journal *Fullerene Science and Technology* was founded in 1993, the to-be Nobel Prize winners being among its editors.

Reviews on fullerenes are published routinely (see, for example Refs 9–17). A widely cited monograph by Hirsch¹⁸ on fullerene chemistry appeared in Germany in 1994 (a year later it was re-edited in the USA).

In the present review, we cover the most important recent achievements in the functionalisation of fullerenes, mainly C_{60}

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fullerene, and new prospects for the use of fullerenes including participation in polymerisation and in catalysis.

II. General aspects, synthesis and separation

Fullerenes constitute a subclass of polyhedranes, closed cage structures consisting of tricoordinated carbon atoms and having 12 pentagonal and $n/2 - 10$ hexagonal faces ($n \geq 20$), each pentagon adjoining only hexagons.

The nomenclature and atom numbering in fullerene systems were proposed in 1993 by Taylor.¹⁹ In 1995 Diederich *et al.*²⁰ introduced a system of numbering for chiral fullerene derivatives. The chemical and electronic structures of fullerene have been considered comprehensively in the report by Sokolov and Stankevich.⁹ An algorithm for the bond designation based on the spiral pattern of numbering generally accepted for fullerene derivatives⁹ has been proposed;²¹ it permits unambiguous assignment of the [6-6] and [5-6] bonds in addition products (compatible with the rules proposed in another publication²⁰). In 1997, the Commission on Nomenclature of the IUPAC, having Taylor as a member, accepted a terminology and a tentative nomenclature of fullerenes (see Refs 22 and 23 and the Atlas of Fullerenes²⁴).

A system of numbering for fullerenes based on the Schlegel diagrams⁹ (Fig. 2) is described in detail in a special appendix to a study by Wudl *et al.*²² In this review, we mainly adhere to the nomenclature used in the publications cited.

Carbon clusters, *i.e.* chains of carbon atoms, were discovered by astrophysicists in the spectra of some extraterrestrial objects (carbon stars, comet tails and interstellar dust),²⁵ but the hypothesis that these include C_{60} , C_{70} or C_{60}^+ clusters has not been confirmed.² Corannulene $C_{20}H_{10}$, a possible hydrocarbon precursor of C_{60} , which could be formed upon condensation of corannulene with carbon vapour, has been detected in meteorites.²⁶

Natural fullerenes have been found in some minerals. The $C_{70}:C_{60}$ ratio in them varies from 0.21 to 0.36.²⁵ Fullerenes are assumed to favour migration and accumulation of some elements, in particular, they presumably influence the formation of diamond deposits.²⁵ Kinetic measurements and mathematical simulation of the fullerene synthesis in an arc reactor led researchers to the conclusion^{27,28} that the $C_{60}:C_{70}$ ratio remains invariant over a broad range of the arc process parameters and amounts to $\sim 85:15$.

One of the preparative methods for the synthesis of higher fullerenes (up to C_{108}) is combustion of benzene in a mixture of oxygen and argon.²⁹ To increase the yield of higher fullerenes in

the arc synthesis, carbon electrodes are doped with hafnium, zirconium or titanium.³⁰ The lower limit of the temperature of fullerene formation is 1200–1500 °C. Recently, a pyrogenetic process for the production of fullerene soot has been developed.³¹ According to this method, a hot mixture of H_2 and a carbon-containing compound is fed through a nozzle into a water-cooled spherical reactor; the best results are attained with C_2Cl_4 as the carbon precursor. At the outlet of the nozzle, plasma is formed. The yield is 0.2 g of fullerenes per kV, which corresponds to the conversion of 2.1% of the carbon from the C_2Cl_4 introduced. The $C_{60}:C_{70}$ ratio depends on the cooling conditions.

Several mechanisms have been proposed for the formation of fullerenes from the precursor nuclei. Thus it has been assumed³² that the first stage of this process is a gas–liquid transition in the expanding flow of supersaturated carbon vapour and this is followed by the formation of small clusters with a dendrite³² or corannulene (curled sheet) structure.³³ It has been found³⁴ that on heating, pure C_{60} crystals are transformed into amorphous carbon. Based on this finding, the researchers conclude that the C_{60} liquid phase, described previously, does not actually exist.

Mixtures of C_{60} with 5%–15% of C_{70} are often used for the functionalisation of C_{60} because C_{70} usually does not enter into reactions. However, in some cases, especially in the measurements of physical characteristics of processes, it is required that C_{60} should have a purity of $\geq 99\%$. Nowadays, C_{60} and C_{70} are normally separated by HPLC, which sharply increases the cost of the product; therefore, the interest in the optimisation of methods for fullerene isolation does not abate. The sorbents currently used for this purpose consist of polyaromatic compounds, π -acids, porphyrins and phthalocyanines immobilised on silica gel.³⁵ The commercially available Buckyclutcher, which is 3,3,3-tris(dinitrobenzene)propyl silica gel, is commonly used. The use of tetraphenylporphyrin immobilised on silica gel ensures the preparation of C_{60} with 98.5% purity and C_{70} with a $> 99\%$ purity for a 5-mg batch.³⁶ Preparative quantities of C_{60} and C_{70} have been successfully separated using the chromotropic acid tetramer with formaldehyde bound to γ -aminopropyl silica gel as the sorbent.³⁵ A sorbent based on Al(X) tetraphenylporphyrin fixed on hydroxydimethylsilyl silica gel has been proposed for the separation of large amounts of fullerenes.³⁷

Recently it has been found³⁸ that the solubility of C_{60} exhibits an abnormal temperature dependence: the maximum of the fullerene solubility in toluene and carbon disulfide falls down to 0 °C, and that in *o*-xylene is observed at 30 °C. In the case of C_{70} , the temperature variation of the solubility follows a standard pattern. This fact might prove useful for the separation of mixtures of C_{60} and C_{70} .

The main distinctive features of the C_{60} fullerene molecule permitting its functionalisation are the 'pseudo-aromaticity',⁹ which governs the reactions with nucleophiles, carbenes and free-radical species to give various adducts, and the presence of the spherical cavity within the cage.²

III. Complexes and inclusion compounds

A unique chemical feature of fullerenes is the formation of metallofullerenes, endohedral complexes, in which one or several metal atoms reside inside the carbon cage.[†] A metal atom occurring as a cation cannot be extracted from the fullerene polyhedron without complete destruction of the cage, which can take place, for example, in the presence of oxygen.

Fullerenes are capable of forming charge transfer complexes (CTC).³⁹ Strictly speaking, the formation of CTC and endometallofullerenes cannot be regarded as functionalisation of fullerenes; nevertheless, we present here some novel data concern-

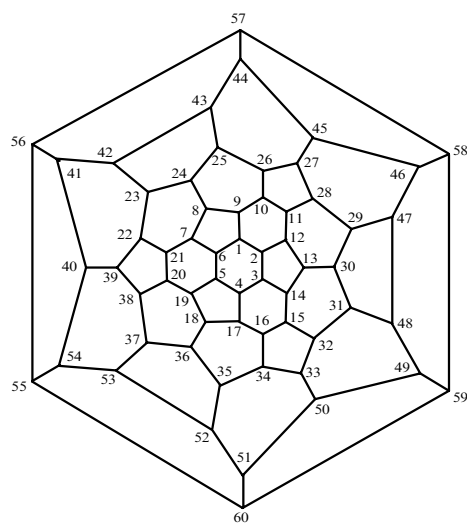


Figure 2. Numbering of carbon atoms in C_{60} fullerene (Schlegel diagram).¹⁹

[†] Endohedral complexes of fullerenes are designated using the character @. The metal atoms occurring inside the cage are written to the left of this character, *e.g.*, La@ C_{82} .

ing this type of reaction in order to characterise the properties of fullerenes more fully and because these compounds are highly promising.

Even a weak nucleophile such as iodine forms a CTC with fullerene of the composition $C_{60} \cdot I_2$. This complex is unstable, its stability constant is $< 0.1 \text{ litre mol}^{-1}$ (see Ref. 40). In an earlier study,⁹ it was reported that this complex was not formed.

A new method for the synthesis of CTC of fullerenes, in particular the complex with iodine, has been proposed;⁴¹ the method involves doping with iodine of other CTC prepared beforehand (for example, complexes with substituted tetrathiafulvalenes).

In the syntheses of potential precursors of new superconductors, special attention is paid to CTC of C_{60} fullerene having layered structures. For example, a complex of this type with tetramethyltetraselenofulvalene has been synthesised.⁴² Doping of the octamethylenetetrafulvalene $\cdot C_{60}$ benzene complex with potassium resulted in the detection of superconductivity with $T_c = 17\text{--}18.8 \text{ K}$, while doping with rubidium produced superconductivity with $T_c = 23\text{--}26 \text{ K}$.⁴³

A new type of superconductor has been obtained by the inclusion of potassium into non-superconducting Ba_3C_{60} .⁴⁴ The compound KBa_3C_{60} , which possesses block superconductivity at 5.6 K , is synthesised by heating a mixture of K and Ba_3C_{60} powders in a sealed glass tube for three days in a high vacuum at 260°C .

Endohedral fullerene complexes $M@C_n$ are usually prepared in an arc discharge with a metal–graphite composite as the positive electrode. These complexes were isolated in a pure state only in 1994,⁴⁵ and since 1996 they have been studied successfully using scanning tunnelling microscopy.⁴⁵

The C_{82} fullerene forms complexes with Sc, La, Y, Ce, Pr and Gd; they are most stable in air. The data obtained by electron paramagnetic resonance showed the occurrence of ‘intrafullerene’ transfer of electrons from the endohedral atom to the carbon cage. According to X-ray diffraction data,⁴⁵ the metal atom does not reside in the centre of the cage but, perhaps, wanders inside the spheroid; strong metal–cage interaction takes place in this system. Endohedral complexes are mixtures of isomers with different arrangements of five- and six-membered rings in the cage with respect to the metal.⁴⁵ The cages of some higher fullerenes can accommodate two or three metal atoms.⁴⁶ For instance, the complexes $Sc_2@C_{84}$, $Sc_3@C_{82}$ and $La_2@C_{80}$ have been isolated. It was established for the latter complex that the La atoms execute a circular motion inside the spheroid.⁴⁵

The data from high-energy spectroscopy provided the basis for the conclusion that the lanthanide ion in $Tm@C_{82}$ is in the divalent state.⁴⁷ The synthesis, isolation, and, what is the most important, purification of the compound $Dy@C_{82}$ have been described in detail.⁴⁸

Endometallofullerenes with calcium were synthesised for the first time by evaporation of a graphite anode filled with calcium carbide particles in an arc discharge.⁴⁹ Extraction with carbon disulfide gave a reaction product in which the majority of $C_{58}\text{--}C_{100}$ fullerenes contained one calcium atom but some held two calcium atoms inside the cage.

Endohedral complexes of fullerenes find use in studies of cells in molecular biology.⁴⁵ The variation of the EPR spectra of solutions of the endohedral metallofullerenes $La@C_{82}$ and $Y@C_{82}$ (their preparative synthesis has been reported⁵⁰) as functions of the oxygen concentration can be employed for the monitoring of oxygen in biological, physical and chemical processes.^{51, 52}

IV. Addition reactions

The most important line in functionalisation of C_{60} is exohedral addition to the fullerene cage. The exohedral covalent attachment

to the fullerene cage is possible for many classes of compounds. From 1990 to 1995, cycloaddition, radical and nucleophilic addition, hydrogenation, oxidation and halogenation as well as complex formation with transition metals had been studied. The features of the fullerene reactivity have been considered in detail in reviews by Diederich and Thilgen^{12, 17} and Hirsch,¹³ which cover publications up to the end of 1995.

The C_{60} molecule is constructed of 12 five-membered rings, each being surrounded by six-membered rings (20 altogether). It has thirty bonds between six-membered rings ([6-6] bonds) and sixty bonds between six- and five-membered rings ([6-5] bonds). The fact that [6-6] bonds are shorter ($1.38 \text{ \AA}$) than the [6-5] bonds ($1.45 \text{ \AA}$) influences the chemical behaviour of C_{60} .

The conjugated π -system in C_{60} is not completely delocalised, the reactivity of this cluster being similar to that of an electron-deficient polyolefin. The electrophilic double [6-6] bonds readily add nucleophiles and radicals. The addition of 34 methyl radicals to C_{60} has been detected by mass spectrometry.¹⁰ Therefore, C_{60} fullerene is referred to as a ‘radical sponge’.

In the adducts, some of the carbon atoms in the functionalised fullerene cage have changed the hybridisation from sp^2 to sp^3 . Nucleophilic and carbene attacks, cycloaddition and hydrogenation usually occur as 1,2-addition, while radical reactions, for example, halogenation, follow the 1,4-addition pattern. However, the latter type of addition is also possible for nucleophilic reactions if they involve bulky fragments. Thus adducts **A** and **B** have been described¹² (Fig. 3).

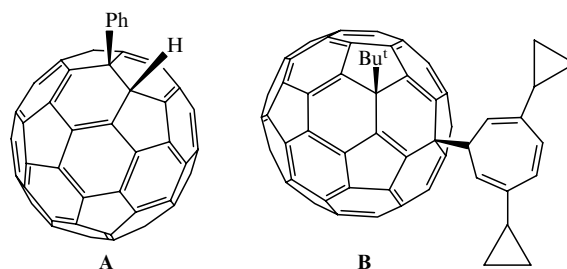


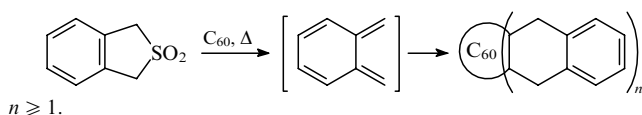
Figure 3. Addition to the C_{60} molecule. **A** is 1,2-adduct, **B** is 1,4-adduct.

When porphyrins or phthalocyanines contain fullerene fragments, the photoinitiated electrical conductivity of their solutions increases. In this case, photoinitiated electron transfer with participation of C_{60}^* and C_{70}^* takes place to give $C_{60}^{\cdot-}/C_{70}^{\cdot-}$ (see Ref. 53). The unpaired electron in the $RC_{60}^{\cdot}$ radicals is mainly delocalised over the atoms of the two six-membered rings adjacent to the $C\text{--}CR$ bond.¹⁰ The molecule of C_{70} , unlike C_{60} , contains five types of nonequivalent atoms; therefore, free-radical addition to C_{70} can yield five isomeric $RC_{70}^{\cdot}$ radicals.¹⁰

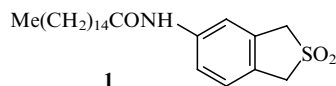
1. Cycloaddition reactions

Cycloaddition to fullerenes gives mainly products of monoaddition, commonly, 1,2-addition to a [6-6] bond, which is energetically more favourable than addition to a [6-5] bond.¹³ The reaction products are used as the initial compounds for further functionalisation. The $[m+2]$ cycloaddition reactions with C_{60} ($m = 1\text{--}4$) have found wide use, because they are facilitated by the low LUMO energy; $[4+2]$ cycloaddition and, in particular, Diels–Alder reactions, proceed especially easily; [6-6] bond is always dienophilic. The addition of various alkenes has been considered in a review.¹³

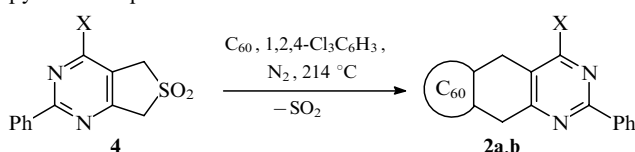
In recent years, quinodimethanes are successfully used as dienes in reactions with fullerenes. These compounds are either synthesised beforehand or formed *in situ* upon thermally induced elimination of SO_2 from heterocyclic sulfones or sultines



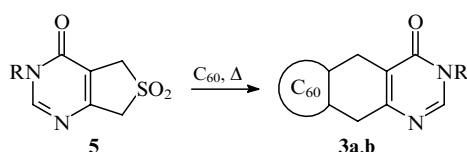
This reaction underlies the so-called 'reactive extraction' method, which permits recovery of higher fullerenes from fullerene soot.⁵⁴ The soot is first extracted with toluene and 1,2,4-trichlorobenzene and the residue is heated with quinodimethane precursor **1**.



This gives rise to a product soluble in conventional solvents and containing C_{60} – C_{400} clusters including multisubstituted ones. The ordinary extraction from commercial soot recovers 8.4% of fullerenes, whereas reactive extraction gives additionally 11.8%. Derivatives **2a,b** and **3a,b** result from reactions of C_{60} with sulfones **4**, **5**, which act as precursors of pyrimidine- and pyrimidonequinodimethanes.⁵⁵

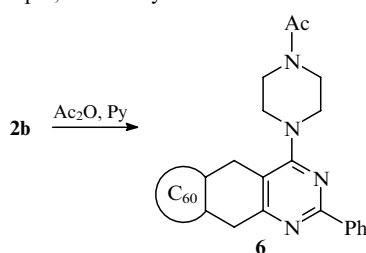


X = OMe (**a**, 77%), N(CH₂)₂NH (**b**, 95%).

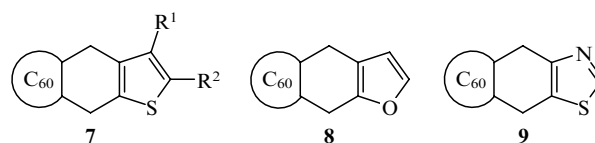


R = H (**a**, 82%), Me (**b**, 52%).

The biological activities of these derivatives can be assayed, if they have been transformed into water-soluble products, for example, into acetyl derivatives **6**.⁵⁵

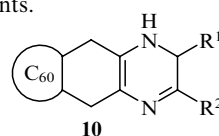


Fullerene derivatives **7–9** have been prepared by [4+2] cycloaddition to C_{60} of six-membered heterocyclic analogues of *o*-quinodimethane generated *in situ* from the corresponding thiophenes, furans and thiazoles.⁵⁶



$R^1 = R^2 = H$; $R^1 = H, R^2 = CO_2Me$; $R^1 - R^2 = (CH=CH)_2$.

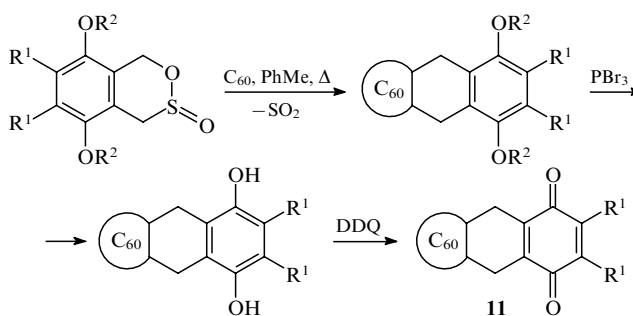
When the reactants are exposed to microwave radiation, the reaction time becomes shorter and the product yields increase. Thus microwave irradiation was used to synthesise compound **10** by the reaction of C_{60} with quinodimethanes prepared *in situ* from the corresponding *o*-bis(bromomethylated) quinoxaline and pyridine derivatives on treatment with NaI in the presence of a crown ether.⁵⁶ The use of microwave radiation for other Diels–Alder reactions and for 1,3-dipolar cycloaddition to C_{60} has also been proposed.⁵⁷ The reaction time decreases to several minutes, which makes it possible to avoid decomposition to the initial components.



$R^1 - R^2 = (CH=CH)_2$, ; $R^1 = R^2 = CN$.

The redox potentials for all newly synthesised organofullerenes were determined by voltammetry in solution.⁵⁶ The first reduction potentials for these compounds were found to undergo slight cathodic shifts with respect to that for C_{60} .

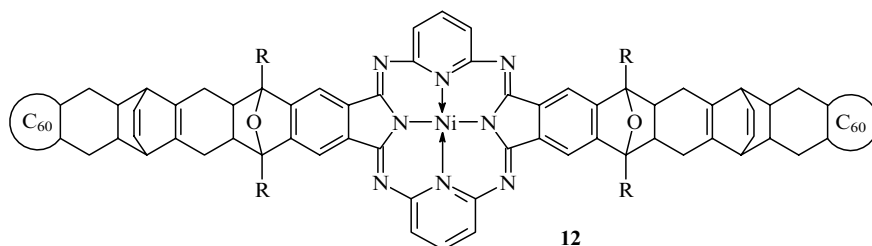
In another study,⁵⁸ sultines (prepared from commercially available ronalite) were used as the precursors of quinodimethanes. On heating in toluene in the presence of C_{60} , sultines eliminate SO_2 ; the resulting adducts are converted into quinones **11** on further modification.



$R^1 = H, R^2 = C_6H_{13}, Me$; $R^1 = Br, R^2 = Me$; $R^1 - R^1 = (CH=CH)_2$, $R^2 = Me$; DDQ is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

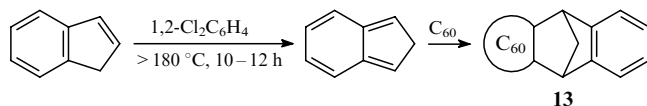
Quinodimethanes have also been used to prepare adducts of C_{60} with phthalocyanines and hemiporphyrins; electrochemical characteristics of these compounds have been determined.⁵⁹ In particular, triad **12**, containing two fullerene fragments was synthesised for the first time in the 1-chloronaphthalene medium (Scheme 1).

Scheme 1



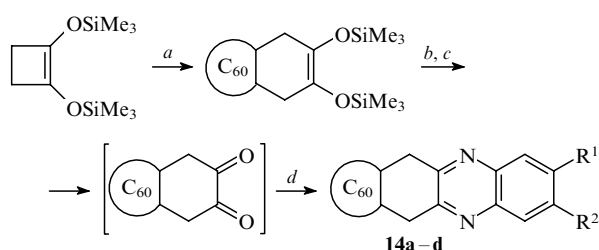
R = $CH_2OC_5H_{11}$.

Yet another example of functionalisation of C_{60} via [4+2] cycloaddition is its reaction with indene, which isomerises into isoidene under the reaction conditions. The yield of the reaction product **13** was 30%, while about 35% of the C_{60} recovered unchanged. The electron-withdrawing capacity of the adduct was somewhat lower than that of C_{60} (see Ref. 60).



The researchers cited⁶⁰ believe that the indene adducts might be useful for the development of new materials for optics and electronics.

The new method for the synthesis of 1,3-diazines fused to fullerene, described by Torres-Garcia *et al.*,⁶¹ can be extended to a large number of diamines. It should be noted that the last stage is carried out in an acid medium in order to prevent nucleophilic addition to fullerenes.



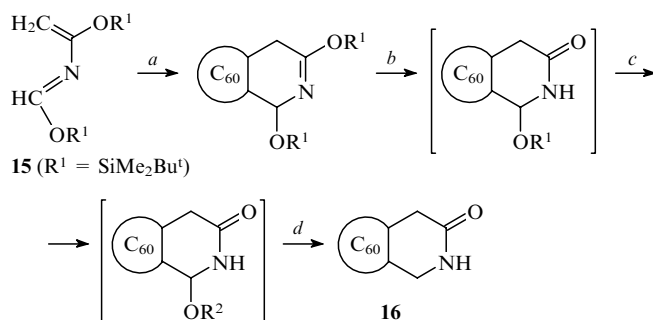
(a) C_{60} , 1,2- $Cl_2C_6H_4$, 180 °C, > 50%; (b) Br_2 , -77 °C; (c) $Et_3N \cdot 3HF$;

(d) R^1 , R^2 , 1,2- $Cl_2C_6H_4$, AcOH;

$R^1 = R^2 = H$ (**a**, 37%); $R^1 = H$; $R^2 = OMe$ (**b**, 29%);

$R^1 - R^2 = (CH=CH)_2$ (**c**, 32%), (**d**, 10%).

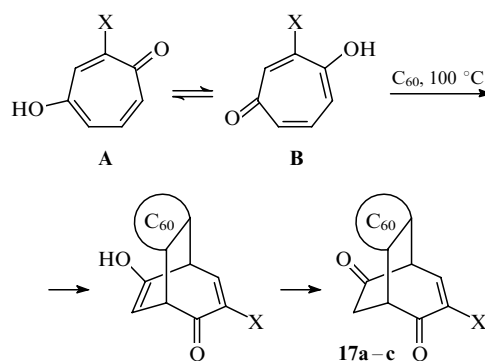
1,3-Bis(*tert*-butyldimethylsilyloxy)-2-azabuta-1,3-diene (**15**) adds to C_{60} fullerene at room temperature.⁶² Hydrolysis, replacement of the silyloxy group by an alkoxy group (in order to avoid the retro-reaction) and dealkoxylation yield a fullerene derivative of δ -valerolactam **16**, which is a very interesting starting compound for the synthesis of amino acids and polyamides containing a fullerene fragment. These derivatives can be prepared after opening the six-membered ring.



(a) C_{60} , PhH, 20 °C, Ar, 4 h; (b) 10% HCl (77%);

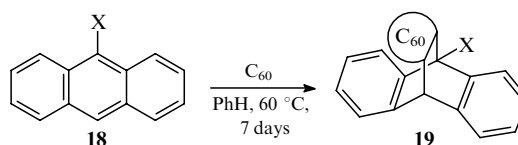
(c) conc. HCl, R^2OH , $CHCl_3$, Δ , 12 h; $R^2 = Et$ (100%), $(CH_2)_3OH$ (62%); (d) Et_3SiH , CF_3CO_2H , $CHCl_3$, Δ , 12 h (88%).

On prolonged heating, C_{60} adds 7-substituted 4-hydroxytropone.⁶³ The tropone moiety exists as two tautomeric forms, **A** and **B**. Since the reactivity of the sterically more hindered form **B** increases at elevated pressures, in most cases, the yields of reaction products **17a–c** increase when the reaction is carried out under a pressure of 300 MPa.



X = H (**a**), OMe (**b**), Cl (**c**).

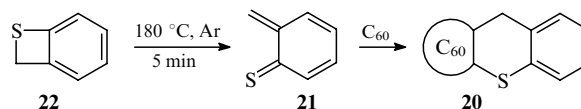
γ -(9-Anthryl)-7-oxaoctanoic acid **18** adds to C_{60} in a similar way.⁶⁴ Adduct **19** forms true Langmuir films on an aqueous phase; they can be transferred as monolayer and multilayer films onto substrates, quartz, Si[111] or calcium fluoride plates.⁶⁴



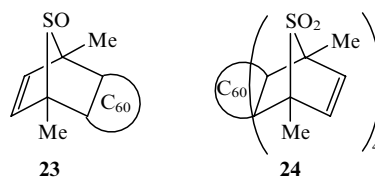
X = $CH_2O(CH_2)_5CO_2H$.

At 160–180 °C, fullerene C_{60} reacts with norbornadiene and its 7-spirocyclopropane derivatives (a 200- to 300-fold excess of the diene is used in the reaction) to give, depending on the substituent in the cyclopropane ring, [1+3]-, [1+4]- or [2+2]-type adducts, including polyaddition products.⁶⁵

The fullerene analogue of thiochroman **20** was obtained by the hetero-Diels–Alder reaction with thioquinonemethide (**21**),⁶⁶ formed *in situ* from benzothietane (**22**).

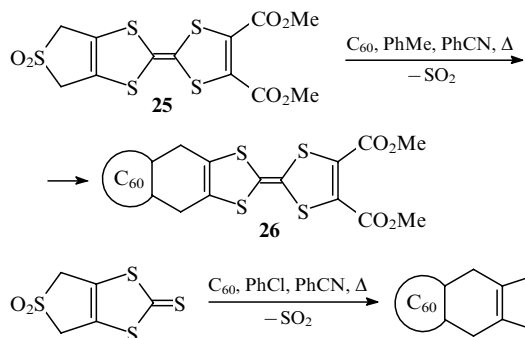


The bulky fullerene fragment does not prevent oxidation of compound **20** at the sulfur atom by *m*-chloroperbenzoic acid. This reaction at 20 °C gave a sulfoxide (yield 89%) and sulfone (yield 45%). At room temperature, C_{60} readily reacts with 2,5-dimethylthiophene *S*-oxide and with 2,5-dimethylthiophene *S,S*-dioxide; the reaction with the sulfoxide affords monoadduct **23**, and the reaction with the sulfone gives tetraadduct **24**.⁶⁷



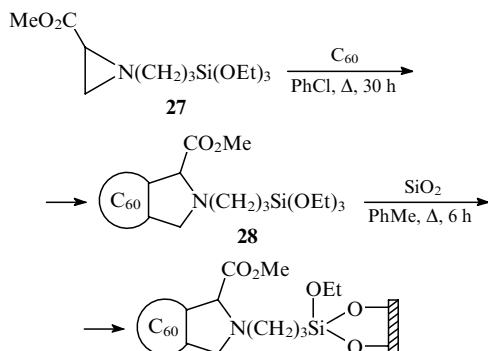
The goals of the synthesis of the adducts **23** and **24** were firstly, to carry out further functionalisation at the SO and SO_2 groups and, secondly, to study their biological activities, because cycloadducts with thiophene oxide fragments are used as biologically important reactive metabolites.

Llacay *et al.*⁶⁸ were the first to synthesise the fullerene adducts with organosulfur compounds containing a sulfonyl group capable of being eliminated, for example, with tetrathiofulvalene **25**.



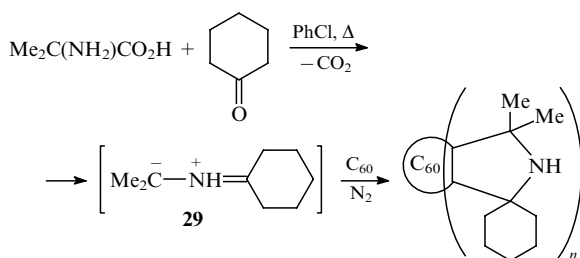
Thione **26** was isolated in 41% yield as a highly stable clathrate including 0.5 molecules of CS₂.

Fulleropyrrolidines, which are fairly promising compounds for the preparation of stationary phases for liquid chromatography of biological objects, have been synthesised by stereospecific thermal 1,3-dipolar cycloaddition of C₆₀ to *cis*- and *trans*-*N*-benzyl-1,2-diphenylaziridines.^{69, 70} Thermally induced cleavage of the aziridine ring in *N*-[3-(triethoxysilyl)propyl]-2-methoxycarbonylaziridine (**27**) in the presence of C₆₀ gives rise to fulleropyrrolidine **28**, which can be attached by a covalent bond to silica gel used for HPLC.



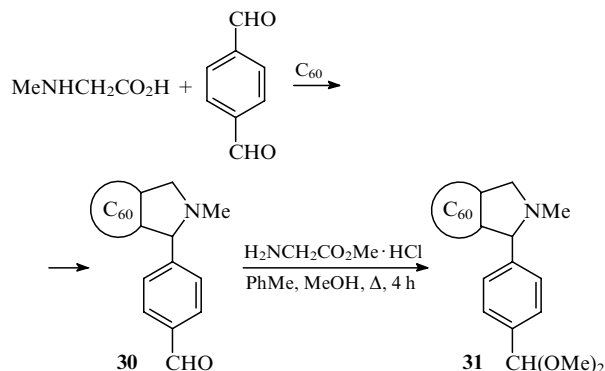
This new adsorbent with the immobilised fullerene-containing group displays an exceptionally high separating capacity with respect to cyclic oligomeric compounds, calixarenes or cyclodextrins in both organic and mixed aqueous-organic media.⁷⁰ Optically pure fulleropyrrolidines have also been synthesised.⁷¹ Stationary phases modified with chiral fullerenes can be used for separation of enantiomers.

When a mixture of α -amino acid, a carbonyl compound and C₆₀ fullerene is heated in chlorobenzene, fullerene undergoes a [2 + 3]-type cycloaddition to the intermediate azomethine ylide **29**, giving rise to oligoadducts containing one to three pyrrolidine fragments, depending on the reaction conditions.^{72–77}



$n = 1-3$.

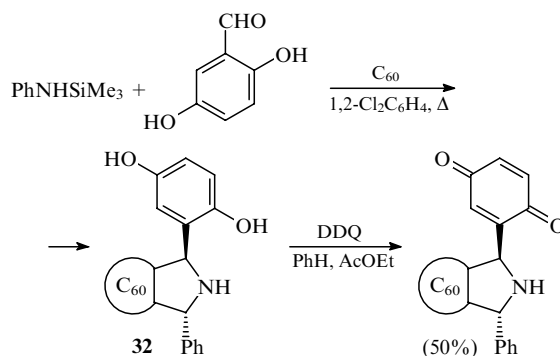
The reaction with methyl nonyl ketone follows a similar route.⁷² Heating of sarcosine, terephthalic aldehyde and C₆₀ in toluene (in this case, the intermediate ylide is stabilised by the phenyl group) gave compound **30**, which was converted into the amphiphilic 1-methyl-2-(4-dimethoxymethylphenyl)fulleropyrrolidine (**31**).⁷⁴



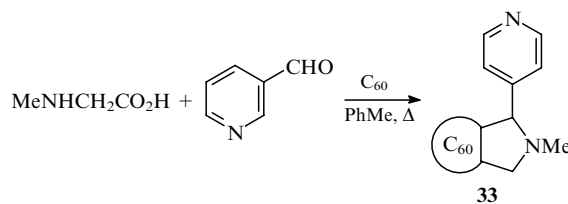
Compound **31** forms Langmuir–Blodgett films and monolayers on an air/water interface; these films are also formed when 22-tricosenoic acid is added. They possess good transparency and thermal stability.^{73, 74}

Fluorescence of aryl-substituted fulleropyrrolidines has an interesting feature, namely, its intensity is much higher than that of C₆₀, which is due to the decrease in the symmetry of the molecule. At the same time, the electron-withdrawing ability of the C₆₀ spheroid in these adducts is markedly lower than that of fullerene.⁷⁷

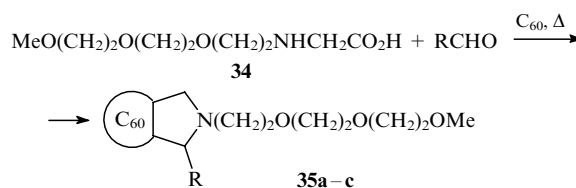
Silylamines can be used in this type of synthesis instead of the amino acid; the compound **32** obtained in this way has been oxidised to a quinone.⁷⁸



By varying the amino acid and the aldehyde used, one can prepare biologically active compounds. For example, a fullerene analogue of natural nicotine **33** has been prepared in order to estimate the influence of the fullerene fragment on the toxicity of nicotine.⁷⁹ However, the solubility of compound **33** in solvents miscible with water was found to be too low.



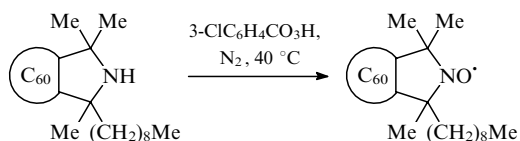
The amino acid was modified by an efficient solubilisation agent, triethylene glycol; this gave compound **34**, which reacted with aldehydes and C₆₀ fullerene to give fulleropyrrolidones **35** (including those containing a nicotine fragment) soluble in an H₂O–DMSO mixture.⁷⁹



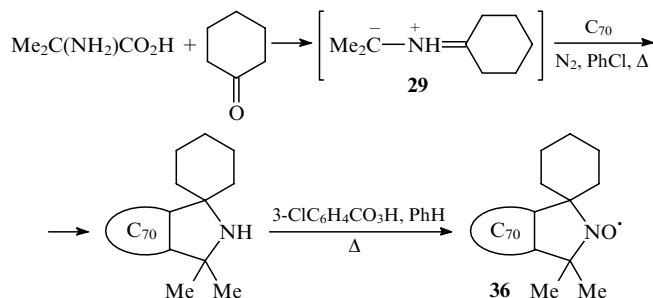
R = 3-Py (**a**), 4-Py (**b**), CH₂O(CH₂)₂O(CH₂)OMe (**c**).

Compound **35c** exhibits an antimicrobial activity including that with respect to a large number of pathogenic microorganisms.⁷⁹

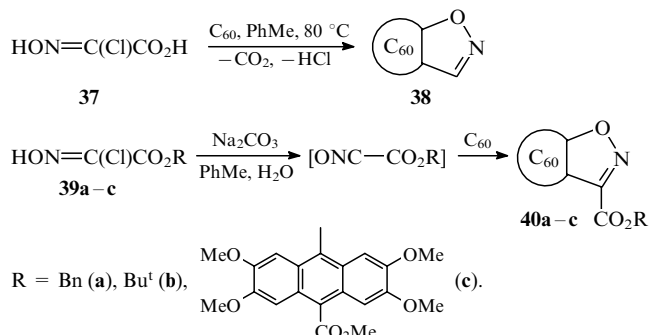
On oxidation with *m*-chloroperbenzoic acid, fulleropyrrolidines are converted into stable nitroxides possessing ferromagnetic properties.^{75, 76}



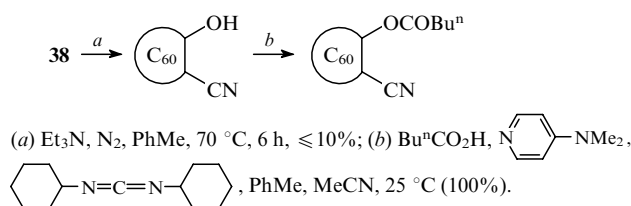
Paramagnetic nitroxide **36** with a spirocyclohexane fragment has been synthesised from C₇₀ fullerene.⁷⁶



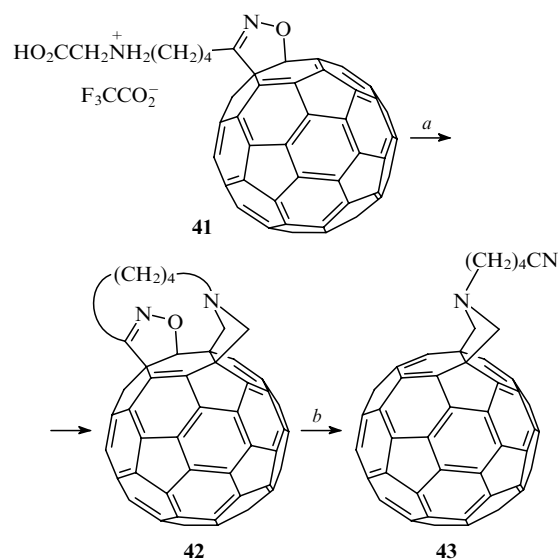
Nitrile oxides generated from oximes or in another way add to C₆₀ giving rise to fullerenoisoxazolines.^{77–84} Thus fulminic acid (**37**) is converted into fullerenoisoxazoline **38**, while its esters **39a–c** afford derivatives **40a–c** with retention of the alkoxy-carbonyl group.⁸⁰



The readily available fullerenoisoxazoline **38** is a convenient starting compound for the synthesis of diverse functional derivatives of fullerene.⁸¹

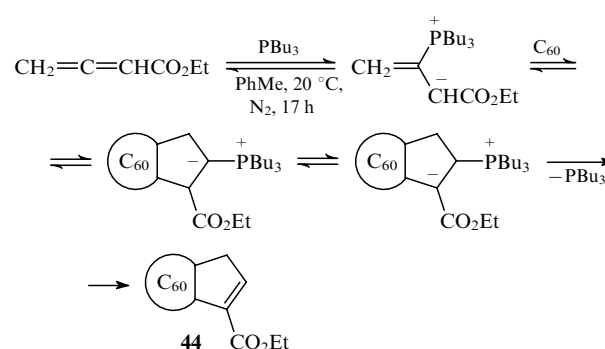


Fullerenoisoxazolines decompose under relatively mild conditions with quantitative regeneration of C₆₀. This process occurs on refluxing in chlorobenzene in the presence of Mo(CO)₆ or on treatment with excess diisobutylaluminium hydride in toluene at 20 °C.⁸² The decomposition of the isoxazoline fragment can be used either to control fullerene functionalisation or to perform further functionalisation. Thus treatment of substituted fullerenoisoxazoline **41** with formaldehyde yields tricyclic derivative **42**. When the latter compound is made to react with Mo(CO)₆, *N*-substituted fulleropyrrolidine **43** is produced.⁸²

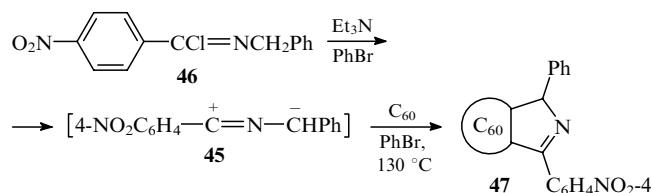


(a) CH₂O, PhMe, Δ, 67%; (b) Mo(CO)₆, PhCl, Δ.

The method for the synthesis of cyclopentenes based on cycloaddition of 2,3-dienoates or 2-ynoates to electron-deficient alkenes in the presence of phosphine has been employed successfully for the synthesis of fullerencyclopentenes. The driving force of this reaction is nucleophilic attack by a tertiary phosphine on a β-allene or acetylene carbon atom. A series of successive prototropic shifts is followed by β-elimination of phosphine giving rise to fullerencyclopentene **44**.^{85, 86}

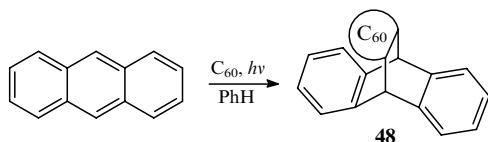


The first example of cycloaddition of ylide **45**, prepared from *N*-benzyl-1-(4-nitrophenyl)chloromethylideneamine (**46**), to C₆₀ fullerene was reported.⁸⁷



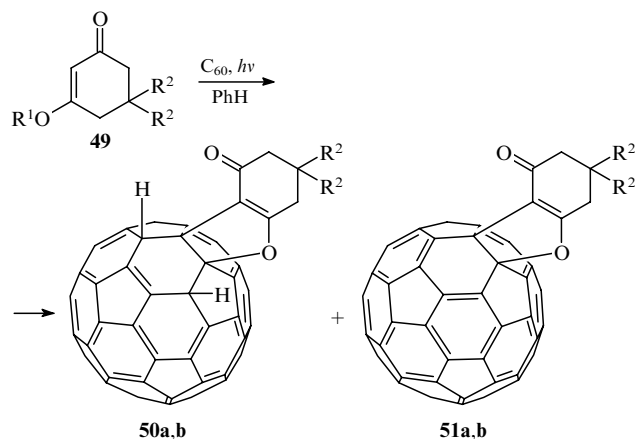
However, based on the ¹³C and ¹H NMR data, the authors suggest that, in addition to the normal [6-6]-adduct **47**, the reaction yields an approximately equal amount of a [5-6]-adduct with an open annulene structure as a mixture of two diastereoisomers.

It is known that photoexcited C₆₀ fullerene in the triplet state has stronger electron-withdrawing capacity than that in the ground state. Thus it is able to react with moderately electron-releasing reagents according to the [2+2]-cycloaddition pattern.^{88–90} For example, anthracene adds to C₆₀ on exposure to a laser radiation with λ ≥ 500 nm giving rise to adduct **48**.⁹¹



4-Propenylanisole does not react with C_{60} fullerene without light. On exposure to the light of a xenon lamp ($\lambda > 500$ nm) at 20 °C, both *cis*- and *trans*-isomers are converted into monoadducts (yield 40%, the *trans*-compound being the major product), which, however, decompose to the initial components under conditions of mass spectroscopy.⁸⁸ Studies of the isotope effects and the ^1H NMR spectra of the adducts formed in the reaction of C_{60} fullerene with *cis*-2-deuterio-1-(4-methoxyphenyl)propene made it possible to propose a two-step reaction mechanism involving a bipolar or biradical intermediate.⁸⁹

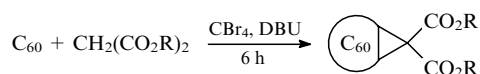
Jensen *et al.*⁹⁰ have studied the behaviour of C_{60} fullerene in the De Mayo reaction, *i.e.* [2 + 2] photocycloaddition of enolizable 1,3-diketones and 1,2-diketones to alkenes followed by opening of the cyclobutane ring giving rise to cyclooctadienones. The reactions of C_{60} with compounds **49** resulted in the synthesis of fused fullerene-furans, both chiral (**50a,b**) and achiral (**51a,b**).



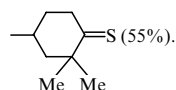
$R^1 = \text{H}, \text{Me}_3\text{Si}; R^2 = \text{H}$ (**a**), Me (**b**).

Presumably, the reaction involves either intermolecular oxidation by singlet oxygen of the cyclobutane intermediates formed initially or intramolecular oxidation of these intermediates by a triplet fullerene fragment.

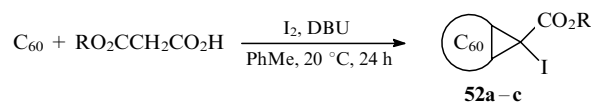
Synthesis of methanofullerenes using cycloaddition reactions is especially significant. Methanofullerenes can serve as the initial compounds for the preparation of functional derivatives of fullerene by introducing substituents into the side chains of the adducts. Routes to methanofullerenes are diverse. They include thermal addition of diazo compounds followed by thermolysis or photolysis, addition of carbenes, and reactions with ylides, which follow an addition–elimination mechanism. Cyclopropanation by diethyl bromomalonate (Bingel reaction⁹²) is among the best and most widely used cyclopropanation methods. Recently this reaction has been modified⁹³ in such a way that bromomalonates (which are difficult to prepare) are formed *in situ* during the cyclopropanation of fullerene. Fullerene is made to react with malonates in the presence of CBr_4 and diazabicyclo[5.4.1]undec-7-ene (DBU) at 20 °C in toluene; the reagents are taken in a 10-fold excess (DBU in a 20-fold excess) with respect to fullerene.



$R = 3,5\text{-(3-BnOC}_6\text{H}_4\text{CH}_2\text{O)}_2\text{C}_6\text{H}_3\text{CH}_2$ (29%), Et (57%), $\text{C}_{18}\text{H}_{37}$ (65%),

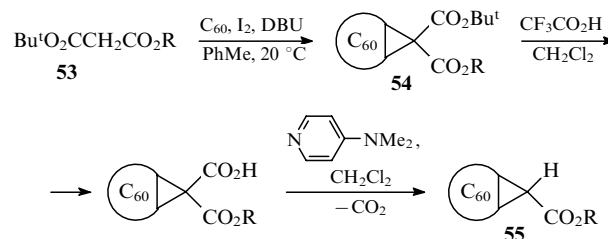


The reaction of monoesters of malonic acid, I_2 and DBU with C_{60} resulted unexpectedly in iodinated derivatives **52a–c**.⁹⁴



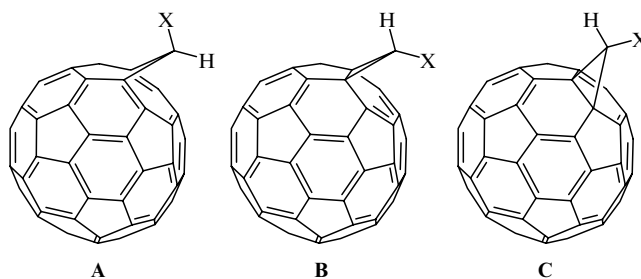
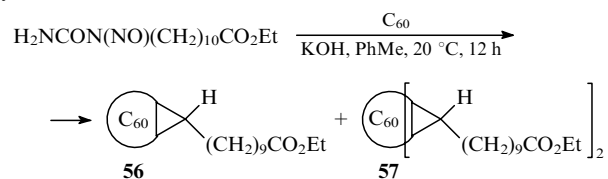
$R = \text{Bn}$ (**a**), $3,5\text{-(C}_{12}\text{H}_{25}\text{O)}_2\text{C}_6\text{H}_3\text{CH}_2$ (**b**), $(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OEt}$ (**c**).

Presumably, the carbanion arising at the first stage is not sufficiently nucleophilic to be converted into diiodomalonate; instead, it is decarboxylated to give $\text{RO}_2\text{CCH}_2\text{I}$, which adds to fullerene. The reaction with diester **53** yielded fullerene-cyclopropanedicarboxylate **54** and monoester **55**.



$R = 3,5\text{-(C}_{12}\text{H}_{25}\text{O)}_2\text{C}_6\text{H}_3\text{CH}_2$.

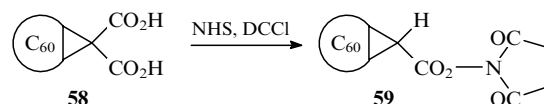
Amphiphilic C_{60} derivatives, **56** and **57**, containing an undecanoic acid fragment, have been synthesised (in 45% total yield); the purpose of the synthesis was to study the properties of thin films prepared from these compounds. The monoadduct **56** was resolved into isomers **A–C** using column elution chromatography.⁹⁵



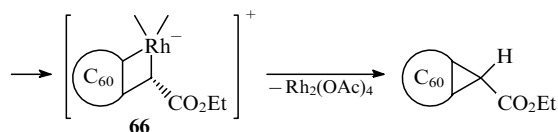
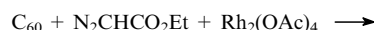
$X = (\text{CH}_2)_9\text{CO}_2\text{Et}$.

The side chain in methanofullerenes is often modified in order to obtain biologically active compounds. Mono- and di-carboxylic acids, especially 1,2-methanofullerene[60]-61-carboxylic (fulleromalonic) acid, are used most frequently as the starting compounds. Thus *N*-phenyl(1,2-methanofullerene[60])-61-formohydroxamic acid has been prepared from this acid.⁹⁶

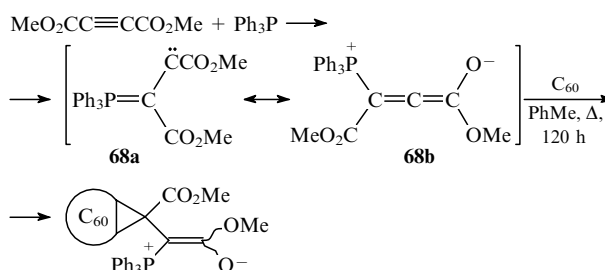
When 1,2-methanofullerene[60]-61,61-dicarboxylic acid (**58**) reacts with *N*-hydroxysuccinimide (NHS) and chloro-*N,N*-dicyclohexylcarbodiimide (DCC), it eliminates water and CO_2 being thus converted into compound **59**, which reacts with primary and secondary amines, 1-aza-12-crown-4 and 1,6-aza-homo[60]fullerene.⁹⁷



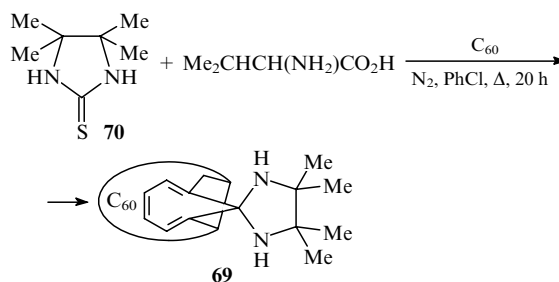
of a stoichiometric amount of dirhodium tetraacetate to give normal methanofullerenes, mainly, at a [6-6] bond.¹⁰¹ A mechanism including the formation of metallacycle **66** was proposed for the reaction.


$$\text{C}_{60} + \text{Me}_2\text{S}^+\text{CH}_2\text{R} \xrightarrow[\text{Bu}_4^+\text{NBr, PhMe, H}_2\text{O}]{\text{K}_2\text{CO}_3} \text{C}_{60}(\text{S}^+\text{CH}_2\text{R}) \quad \mathbf{67}$$

The reaction of C₆₀ with *tert*-butyl diazoacetate in benzene or toluene in the presence of dirhodium tetraacetate affords a new type of cycloadducts, tricyclic compounds **62a,b**, instead of the expected methanofullerenes. It is assumed that initially, cyclopropanation of the solvent gives norcaradiene **63**, and it is this product that reacts with fullerene.¹⁰⁰ Hydrolysis of the ester group yields acids **64a,b**, which are then converted into derivatives **65a,b** at the amino group of leucine.



Spiro derivative of C₆₀ fullerene, adduct **69**, containing an ‘open’ [5-6] bond has formed unexpectedly in the reaction of C₆₀ with 4,4,5,5-tetramethyl-1,3-diazolidine-2-thione (**70**) and DL-valine.¹⁰⁴



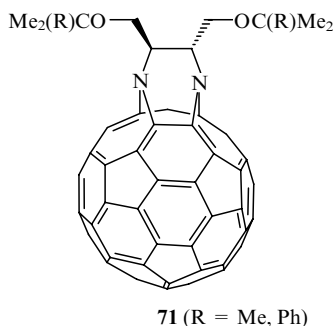
The mechanism assumed for this reaction includes the reaction of thione **70** with amino acid to give a carbene, which adds to fullerene.

Shen *et al.*¹⁰⁵ were the first to demonstrate that the reaction of C₆₀ fullerene with chiral 1,4-di-*tert*-alkoxy-2,3-bisazidobutanes gives rise to chiral bisazafulleroids. Enantiomeric pairs with the

R = H (**a**), Me (**b**); DCC is dicyclohexylcarbodiimide.

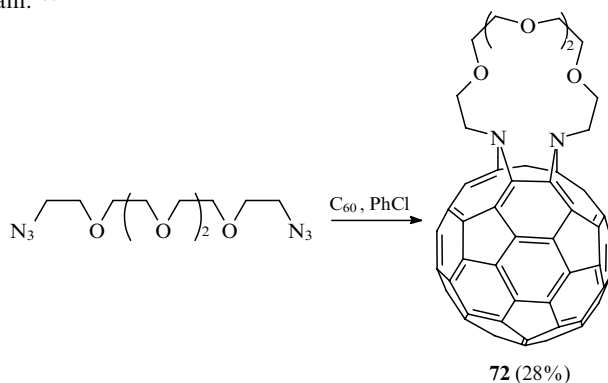
However, when 1-methylnaphthalene is used as the solvent, fullerene smoothly reacts with ethyl diazoacetate in the presence

(2*R*,3*R*) and (2*S*,3*S*) symmetry were obtained in ~51% yields. The enantiomers exhibit mirror image circular dichroism curves.



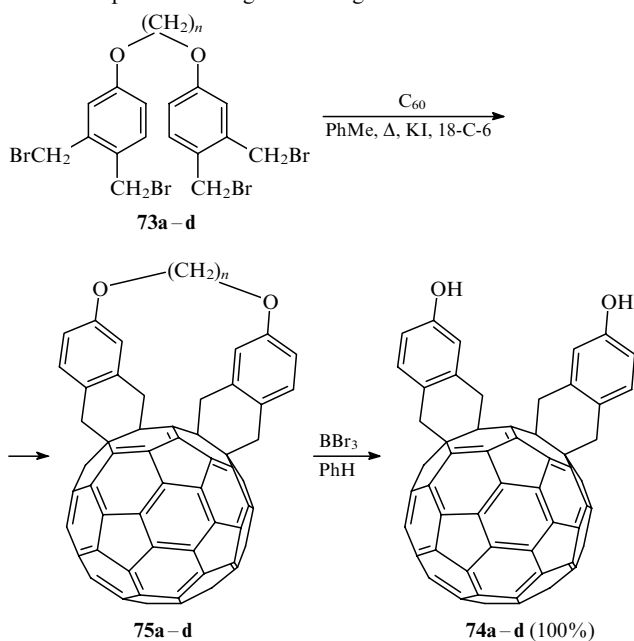
Apparently, removal of the *tert*-alkyl groups from compounds **71** would provide a route to water-soluble chiral fullerene derivatives, which is important for the investigation of their biological activities.

A bisazafulleroid fragment has been inserted in a crown-ether chain.¹⁰⁶



According to NMR data, the bisadduct **72** has a structure with 'open' [5-6] bonds. The fullerene-crowns are excellent agents for binding metals. Perhaps, new superconducting substances would be found among these complexes.¹⁰⁶

The reaction of fullerene with tetrabromides **73a-d** has resulted in selective multifunctionalisation of fullerene, the goal of which was to prepare disubstituted bisphenols with substituents located at particular rings in the cage.¹⁰⁷

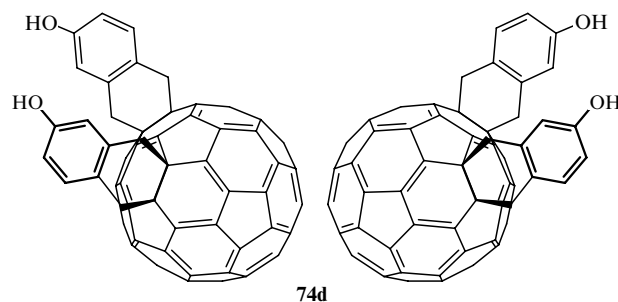


n = 2 (**a**), 3 (**b**), 4 (**c**), 5 (**d**).

The reaction is carried out under conditions of high dilution (10^{-4} mol litre⁻¹) and the guiding (CH₂)_{*n*} chain is subsequently split off.¹⁰⁷ When *n* = 2–5, the addition occurs selectively within one hemisphere of the C₆₀ cage. When *n* = 2, 3, only *cis*-2- and *cis*-3-isomers are formed and for *n* = 5, bisaddition yields the *e*-adduct. When *n* = 4, the reaction gives a complex mixture of bisadducts. For both the cyclic precursors and acyclic bisadducts, types of symmetry and the relationship between the symmetry and chirality were established by analysing the data of mass, NMR, UV and visible spectra (all adducts with *C*₁ and *C*₂ symmetry are chiral and those with *C*_s symmetry are achiral). The chiral *cis*-3- and *e*-adducts were resolved into enantiomers using HPLC with a chiral phase [cellulose tris(3,5-dimethylphenyl carbamate)-coated silica gel (CHIRAL CEL OD), hexane–isopropyl alcohol]. For example, for *n* = 2, the bisphenol **74a** was obtained.

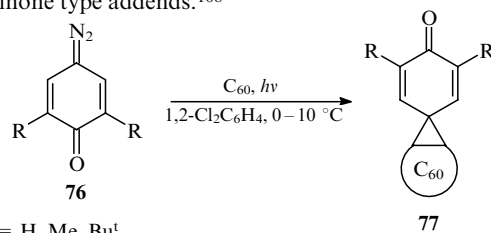
Both the precursor **75a** and the final diol **74a** are *cis*-2 isomers (this was observed for the first time for fullerene bisadducts) and are achiral; the compound **75a** corresponds to *C*_s symmetry.

The cyclic precursor **75d** and the bisphenol **74d** for *n* = 5 are *e*-isomers with *C*₁ symmetry; they are chiral and optically active. The total yield of the isomers at the final stage is 100%. The [α]_D values for the ethers **75a,d** (5.7×10^2 and -5.2×10^2) and the diols **74a,d** (4.4×10 and -7.4×10) were determined. The structures of optical isomers of the bisphenol **74d** are presented below.



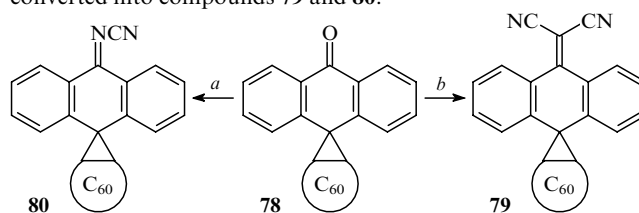
The compounds **74a-d** belong to the few examples of chiral derivatives with achiral substituents known in the chemistry of cage compounds, in particular, in the fullerene chemistry.

The reaction of C₆₀ fullerene with diazo compound **76** has resulted in the synthesis of spirane methanofullerenes **77** with quinone type addends.¹⁰⁸



R = H, Me, Bu^t.

Spiro[10-anthrone-9,61']methanofullerene (**78**) and spiro[cyclohexanone-4,61']methanofullerene (the latter as a mixture of [6-6] and [5-6] isomers) were prepared in a similar way. The conjugated dienone **78** exhibits stronger electron-withdrawing capacity than the initial C₆₀ fullerene. The anthrone **78** was converted into compounds **79** and **80**.¹⁰⁸



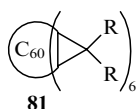
(a) Me₃SiN=C=NSiMe₃, TiCl₄, CHCl₃, Δ, 5 days (60%);

(b) CH₂(CN)₂, TiCl₄, Py, CHCl₃ (26%).

Chemical modification of more than two double bonds in the C_{60} molecule gives, as a rule, a mixture of regio- and stereo-isomers. Therefore, study of the possibility of synthesising a single isomer by multifunctionalisation of C_{60} is of interest. These molecules could serve as useful tools in the studies of functional catalysis and in the materials science; they could find application in bioorganic chemistry (for example, for reactions with DNA, enzyme inhibition, design of compounds for drug transport, and for other purposes¹⁰⁹).

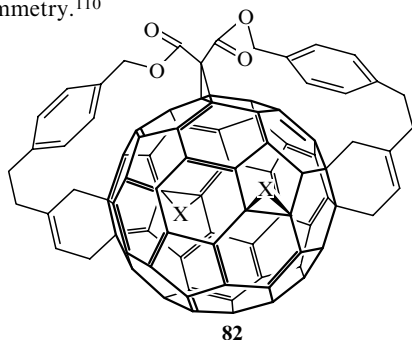
Hirsch has studied the regiochemistry and stereochemistry of multiple addition to the double bonds in C_{60} and has developed a theoretical substantiation of these reactions.^{13, 21}

Double (and multiple) cyclopropanation with dialkyl bromo-malonates according to the Bingel reaction pathway is used most often to prepare polysubstituted fullerenes.⁹² Thus C_{60} has been made to react⁹³ with the malonate and CBr_4 in the presence of DBU on the addition of 10 equiv. of 9,10-dimethylanthracene and at longer reaction times; under these conditions, symmetrical hexakis(adducts) **81** were obtained in good yields.



$R = CO_2CH_2Me, CO_2(CH_2)_{16}Me$.

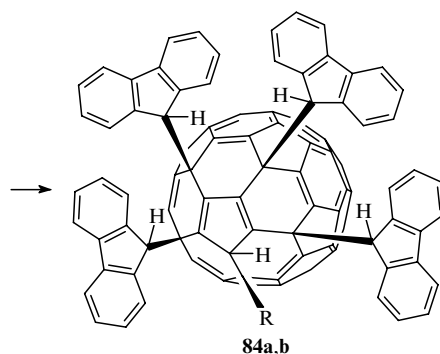
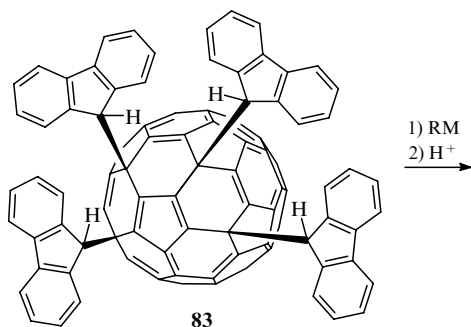
When pentakis(adducts) **82** with C_{2v} symmetry are again treated with diazomethane, heptakis- and octakis-adducts with C_s symmetry, pyrazoline derivatives, are formed with high regioselectivity. These products are converted into methanofullerenes by thermally induced abstraction of nitrogen. The direction of nitrogen abstraction was assumed to be controlled by orbital symmetry.¹¹⁰



$X = C(CO_2Et)_2, C(CO_2CH_2CO_2Et)_2$.

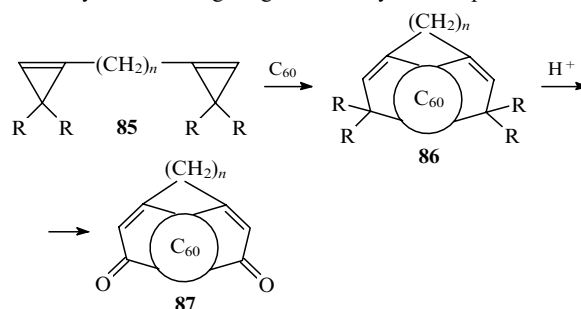
The tetrakis(adduct) **83** contains a fulvene π -subsystem located on the spheroid surface. This compound is prepared from a mixture of C_{60} , fluorenylpotassium and fluorene in THF. The mixture is kept under an argon atmosphere in the presence of traces of oxygen for 72 h and the adduct is then isolated by preparative chromatography.¹¹¹

The tetrakis(adduct) **83** adds nucleophiles, which is typical of a fulvene π -system. Thus it reacts with 1-octynyllithium in THF or with NaCN in a DMF–chlorobenzene mixture to give pentakis(adducts) **84a,b** in 63% and 68% yields, respectively.



$RM = C_6H_{13}C\equiv CLi$ (**a**, 63%), $NaCN$ (**b**, 68%).

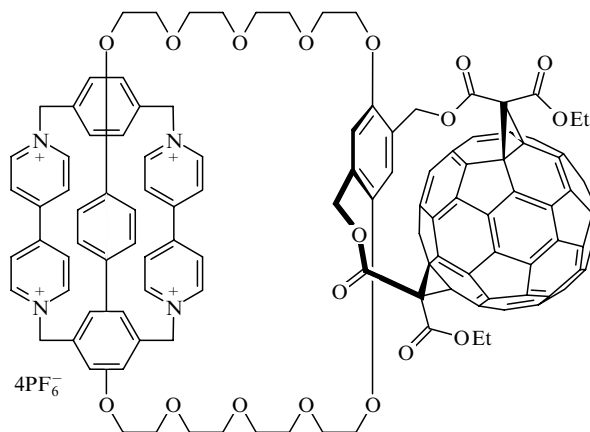
Long-term heating of C_{60} with compounds **85** in anhydrous 1,2-dichlorobenzene in the presence of 4 Å molecular sieves results in double cycloaddition giving rise to tricyclic compounds **86**.¹⁰⁹



$R-R = OCM_2O$; $n = 3, 4, 6$.

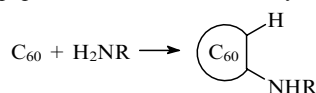
Acid hydrolysis affords quantitatively the corresponding diketones **87**.

A [2]catenane containing the C_{60} bishomofullerene fragment was synthesised for the first time using a sequence of two modified Bingel reactions (yield 18%).¹¹²



2. Nucleophilic, electrophilic and radical addition

Nucleophilic addition to C_{60} fullerene gives, as a rule, mono-adducts; for example, C_{60} adds one amino acid molecule.¹¹³ Dipeptides react in a similar way.¹¹⁴



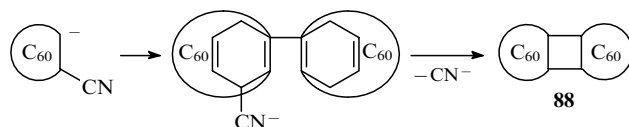
R is an amino acid or dipeptide residue.

Fullerene dipeptide derivatives are soluble in water owing to association with amino acid residues.¹¹⁴ These adducts penetrate

inside the liposomes, they exhibit adjuvant[‡] properties and antiviral activity.^{113, 115, 116}

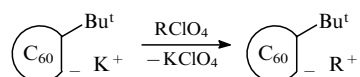
The reaction of C₆₀ in 1,2-dichlorobenzene with NaCN in DMF affords not only the [C₆₀(CN)][−] anion but also the [C₆₀(CN)]^{2−} and [C₆₀(CN)]^{3−} anions, although the monoion predominates (as shown by negative-ion mass spectrometry).¹¹⁷

Mechanochemical activation (mixing of solid reactants in a vibratory mill¹¹⁸) can be used for functionalisation of fullerenes. The reaction of C₆₀ with NaCN carried out in this way gave the dimer C₁₂₀ **88**, in which two spheroids are linked *via* a cyclobutane ring. The fact that the reaction pathway differs from that observed in solutions is due to the unique ability of the cyanide ion to serve as both a nucleophile and a leaving group.



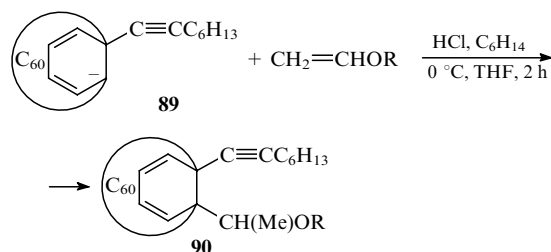
The reactivity of the dimer **88** does not differ much from that of C₆₀. For instance, it enters into the Bingel reaction with diethyl bromomalonate and DBU (in equimolar amounts) to give a mixture of isomeric monoadducts (at least, three compounds) in 44% total yield.¹¹⁸

Tanaka *et al.*¹¹⁹ made use of the fact that the fullerene spheroid readily forms anions and synthesised an unusual class of compounds, hydrocarbon salts.



R⁺ is tris[1-(5-isopropyl-3,8-dimethylazulenyl)]cyclopropenylum.

Vinyl ethers add to the stable 2-(1-octynyl)-1,2-dihydrofulleren[60]-1-ide ion (**89**) in the presence of HCl; this affords [6-6] bisadducts **90**, which are promising monomers for cationic polymerisation.¹²⁰

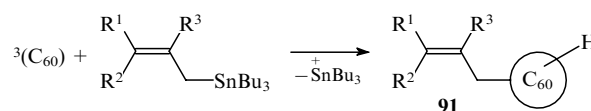


R = CH₂Prⁱ, (CH₂)₂OAc.

The fullerene C₆₀ adds Grignard reagents ClMgCH₂SiR₃ (R = Alk, Ar, AlkO) yielding mainly compounds C₆₀(H)CH₂SiR₃ in THF and only products of the formula C₆₀(CH₂SiR₃)₂ in toluene.¹²¹

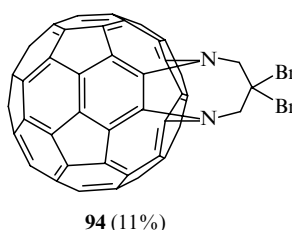
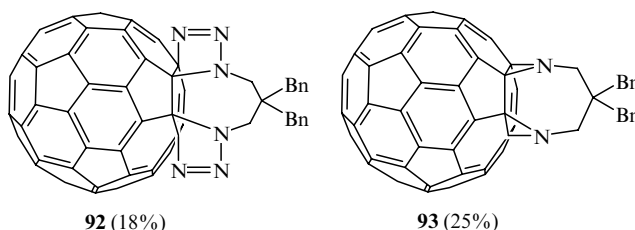
Fullerenylmethylsilanes such as C₆₀(H)CH₂SiMe₂Cl, C₆₀(H)CH₂SiMe_n(OR)_{3−n} and C₆₀[CH₂SiMe_n(OR)_{3−n}]₂, where R = Alk, n = 0, 1, are used to modify silica gel. The products thus formed are used as sorbents for HPLC, as heterogeneous photosensitisers and in catalysis.¹²¹

Irradiation of C₆₀ and allylstannanes in a benzene or toluene solution results in the regioselective formation of fullerene mono-allylation products. The process is inhibited by oxygen or benzonitrile.¹²² Fullerene derivatives **91** have been synthesised in this way. This reaction occurs by a mechanism involving triplet C₆₀ and single-electron transfer.¹²²

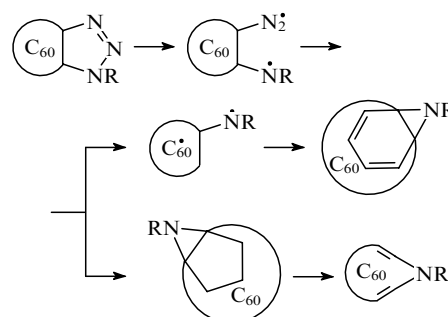


R¹, R², R³ = H, Me.

Mixed adducts **92–94** were directly synthesised for the first time from C₆₀ and 2,2-dibenzyl-1,3-diazidopropane¹²³ by refluxing the reactants in chlorobenzene.



Bistriazolines are precursors of bisdiazolines and can be converted into the latter by thermolysis in chlorobenzene. Thermolysis of the bistriazoline **92** afforded the compound **94**. The formation of the adducts **93** and **94** was interpreted¹²³ in terms of a radical mechanism, similar to the mechanism of triazoline thermolysis.



3. The addition of hydrogen and the properties of hydrides

All attempts to prepare completely hydrogenated fullerene C₆₀H₆₀ failed. This compound appears to be highly unstable due to the enormous strain which arises upon the formation of twenty planar cyclohexane rings and numerous shielding H–H interactions.¹³ By 1997, hydrides with the compositions C₆₀H_x (x = 2, 4, 18, 32, 36, 36–50, 42–44) and C₇₀H_x (x = 2, 4, 8, 10, 34–36, 36–38, 36–44) were known.^{124, 125}

The methods used to prepare fullerene hydrides have all been considered in detail;^{11, 125} they include Birch reduction, hydroboration, hydrozirconation, solid-phase and liquid-phase hydrogenation with hydrogen, electrochemical reduction, reduction with diimide or with chromium acetate, photoinitiated electron transfer and reduction with metal hydrides.

Despite the fact that fullerenes could be promising catalysts for activation of the C–H bonds in hydrocarbons *via* the formation of fullerene hydrides, as was convincingly demonstrated in a comprehensive review,¹¹ this aspect has not yet received adequate attention. Studies are mainly concerned with the structure^{124, 125} and spectral and photophysical properties of fullerene hydrides.^{124–128} It is assumed that the solid hydride C₆₀H₃₆ corresponds to *T* symmetry and contains four isolated

[‡] Adjuvants are compounds stimulating an increase in the number of antibodies.

benzenoid rings, located in tetrahedral positions on the surface of the closed shell of the molecule.

A preparative synthesis of fullerene hydrides was carried out by treatment of fullerenes with metals and water serving as a source of protons;¹²⁵ although the number of possible isomers is enormous, only a few of them are formed. For instance, heating of a solution of C₆₀ fullerene in toluene with a Zn(Cu) mixture (freshly prepared Zn dust is employed) gives rise to a mixture of hydrides, which are isolated by preparative liquid chromatography. Depending on the temperature, reaction time and the ratio of the metals, the compounds C₆₀H₂, C₆₀H₄ and C₆₀H₆ (two isomers) can be obtained in 66%, 45% and 38% yields, respectively. Reduction of C₇₀ fullerene afforded C₇₀H₈ and C₇₀H₁₀ (three isomers) in a total yield of 62%. The hydrides C₇₀H_n are all unstable in air and during storage.

Fullerene hydrides and deuterides containing up to 24 hydrogen atoms per fullerene molecule have been obtained upon hydrogenation (with either hydrogen or deuterium) at 1–2.5 MPa and 573–673 K of a mixture of fullerite (83% of C₆₀, 15% of C₇₀ and 2% of higher fullerenes) and powdered intermetallic compounds LaNi₅, LaNi_{14.65} and CeO₃.¹²⁹ At 800 K, fullerene hydrides (deuterides) decompose with evolution of gaseous hydrogen (or deuterium); at 1000 K, the reaction of fullerite with intermetallic compounds is accompanied by evolution of the corresponding 3d metal.¹²⁹ The hydrides prepared in this way can serve as sources of high-purity hydrogen. When fullerite (78% of C₆₀ and 22% of C₇₀) is deuterated in the presence of Pd clusters (Pd powder and Pd/C), the maximum content of deuterium corresponds to [C₆₀ + C₇₀]D₂₆ and is attained after ten repetitions of the heating–cooling cycle (673–293 K) at 2.5 MPa.¹³⁰

Fullerene dihydride C₆₀H₂ has been synthesised by ultrasonic treatment of C₆₀ fullerene in decalin for 2–4 h in a sealed vessel under argon.¹³¹ The hydrogen needed to hydrogenate fullerene is formed upon sonolysis of the solvent.

The dehydrating capacity of C₆₀ fullerene may be useful in the studies of biological objects. Thus C₆₀ dehydrates the Hantsch ester (the reaction simulates the action of dihydronicotinamide-adeninedinucleotide) at 100 °C under anaerobic conditions to give diethyl 2,6-dimethylpyridine-3,5-dicarboxylate; in this reaction, fullerene is converted into mixed hydrides C₆₀H_n (*n* = 2, 4, 6).¹³² It is of interest that this dehydrogenation can be carried out by leaving the reaction mixture in the light at 20 °C; in this case, C₆₀ acts as a catalyst because it is recovered unchanged.¹³²

On irradiation in the presence of sensitisers such as 9,10-dicyanoanthracene (and diphenyl as a co-sensitiser), the radical cation C₆₀^{•+} is generated from C₆₀. The radical cation reacts with hydrogen donors, for example, with *tert*-butyl methyl ether, propionaldehyde and alcohols giving rise to 1-substituted 1,2-dihydro[60]fullerenes.¹³³

The hydride 1,2-C₆₀H₂ has been prepared in 70% yield by the reaction of photoexcited C₆₀ fullerene with 10-methyl-9,10-dihydroacridine.¹³⁴

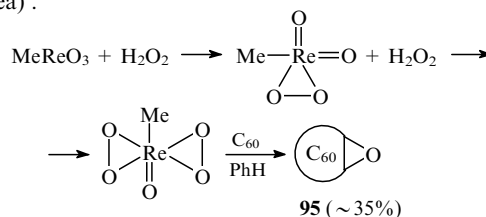
The proton at the 4-position of stable 1-*tert*-butyl-1,4-dihydro[60]fullerene undergoes base-catalysed migration to give a thermodynamically more favoured isomer, 1-*tert*-butyl-1,2-dihydro[60]fullerene.¹³⁵

4. Oxidation

The electronegative fullerene molecules can be easily reduced but cannot be readily oxidised; however, the reaction of fullerene with oxygen on exposure to UV light (in hexane) or heating of fullerene in the presence of oxygen results in vigorous oxidation accompanied by fragmentation, *i.e.* rupture of the C=C bonds in the cage.¹³ Upon irradiation, C₆₀ passes initially into the triplet state; the transfer of energy from this species affords singlet oxygen, which oxidises the fullerene.⁹

Oxygen derivatives of fullerenes receive little attention yet. The monoxide, namely, 1,2-epoxy[60]fullerene (**95**), is prepared by reactions with various oxidants including systems with cyto-

chrome P450;¹³⁶ however, the yields are relatively low. A preparative pathway to 1,2-epoxy[60]fullerene (**95**) has been described¹³⁷ in which fullerene is treated with the system 'methyltrioxorhenium–hydrogen peroxide (as a complex with urea)'.



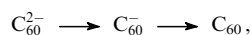
Interestingly, either component of this oxidative system taken alone give virtually no target product.

The epoxide C₇₀O, which is fairly difficult to obtain, has been isolated in ~0.5% yield upon the use of an arc-discharge reactor with a rotating cathode and an anode made of carbon plates (the reactor operation time was 24 h).¹³⁸ Study by ¹³C NMR spectroscopy showed the presence of two isomers, 1,2-epoxy-C₇₀ and 5,6-epoxy-C₇₀ in 47:57 ratio. The predominance of the [5-6] isomer was interpreted¹³⁸ as being due to the lower strain in its molecule.

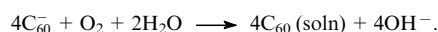
The compound C₁₂₀O (its synthesis has been reported¹³⁹) disproportionates at 400 °C to give 60% of C₆₀, 15% of C₁₂₀O₂, and a mixture containing oligomeric (C₆₀)_nO_m oxides (*n* = 3, 5; *m* = 3–9).¹⁴⁰

The dioxide C₁₂₀O₂ is stable at room temperature both in a pure state and in solutions. After thermolysis of C₁₂₀O at 550–560 °C, product C₁₁₉ containing two C₅₈ cages was isolated from the reaction mixture in 2% yield. The cages are connected by a bridge comprising three *sp*³-hybridised carbons, two of which are equivalent.¹⁴¹

Oxidation of C₆₀[−] permits the preparation of an aqueous colloidal solution of C₆₀ fullerene.¹⁴² The C₆₀[−] anion is formed when a solution of C₆₀ in THF is treated successively with an Ni–Al alloy and an aqueous solution of sodium hydroxide; C₆₀^{2−} can be prepared in a similar way except that DMSO is used in place of THF. The anions are inert with respect to water but highly sensitive to oxygen. Oxidation occurs *via* consecutive steps



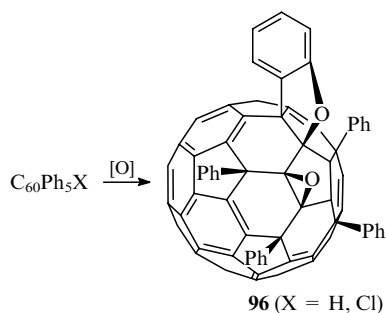
the overall reaction being written as



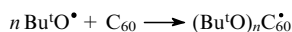
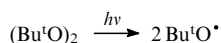
If the oxidation is performed in an aqueous medium, C₆₀ forms a colloidal solution containing non-crystalline and quite homogeneous particles with a dimension of ~10 nm (as established by electron microscopy); in an anhydrous organic solvent, C₆₀ precipitates as a black powder.

Electrochemical reduction of C₆₀O affords an electrochemically active film; a different active film is formed upon the reduction of C₆₀ to the dianion in the presence of O₂.¹⁴³ Films of conducting polymers, which are deposited on the electrodes upon electrochemical reduction of C₆₀O, are promising for the design of important materials for engineering (*e.g.*, for microelectronics).¹⁴⁴

An interesting feature of pentaphenyl-substituted fullerenes has been discovered.¹⁴⁵ The compound C₆₀Ph₅Cl was kept for two weeks in air and in the light, and C₆₀Ph₅H was stored for a year. Both substances were spontaneously oxidised yielding complex mixtures of products. In both cases, a compound with the composition C₆₀Ph₄C₆H₄O₂ was isolated from the mixture in 60% yield. Relying on NMR and mass spectroscopy, it was established that elimination of hydrogen or chlorine atoms linked to the cage and an *ortho*-hydrogen atom of the neighbouring phenyl group followed by oxidation gives rise to fullereno-benzo[*b*]furan **96**. The mechanism of this reaction is not yet entirely clear.



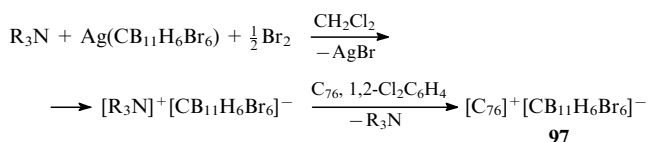
The radicals generated in the reaction of fullerene with *tert*-butyl peroxide on irradiation are highly stable under a nitrogen atmosphere and react only slowly with oxygen, water and with radical traps such as nitrobenzene.¹⁴⁶



$n \geq 1$.

Fullerenols eliminate active oxygen radicals including superacidic radical anions formed in biological systems,¹⁴⁷ which opens up the way for using them in biochemistry and pharmacology.

No compounds containing the C_{60}^+ cation have been obtained. However, the salt **97**, containing the C_{76}^+ cation, which has a much lower electrochemical oxidation potential, has been synthesised.¹⁴⁸



$\text{R} = 2,4\text{-Br}_2\text{C}_6\text{H}_3$.

The salt **97** can be stored for several weeks under a nitrogen atmosphere. Apparently, this is the first compound with a carbocation consisting only of carbon.

5. Halogenation

It was shown back in 1991–1992 that C_{60} fullerene reacts with gaseous chlorine and fluorine and with liquid bromine giving complex mixtures of addition products.¹³ Subsequently, these studies have not progressed greatly due to the difficulties in the isolation of individual compounds and in controlling halogenation reactions.

It had been considered⁹ that iodine does not react with fullerene; however, later,^{40,41} CTC involving iodine and C_{60} were prepared.

The C_{60} fullerene readily reacts with chlorine under free radical reaction conditions to give $\text{C}_{60}\text{Cl}_{40}$ (see Ref. 149). This compound can be used as an intermediate in the further fullerene functionalisation, namely, synthesis of polyfullerol and polyfluorofullerene.

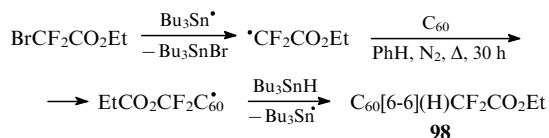
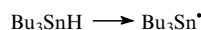
The reaction of C_{60} with excess iodine chloride (toluene, 20 °C) gives rise to an individual compound, C_{60}Cl_6 ; the reaction with liquid bromine affords C_{60}Br_2 , while the reaction in CS_2 solvent results in C_{60}Br_5 (see Ref. 9).

Fluorination of fullerenes is receiving somewhat more attention because fluorinated derivatives might be of interest for materials science.¹⁵⁰

Thus fluorofullerenes containing up to 60 fluorine atoms per molecule, including $\text{C}_{60}\text{F}_{48}$,¹⁵¹ can be prepared by fluorination with fluorine gas, while hyperfluorofullerenes $\text{C}_{60}\text{F}_{76}$ can be synthesised on treatment with fluorine with exposure to UV radiation; this reaction is accompanied by cleavage of the spheroidal cage.¹⁴⁹ When C_{60} is treated with MnF_3 at 330 °C (24 h), $\text{C}_{60}\text{F}_{36}$ is formed.¹⁵² Judging by the mass spectrometric data, the mixture of fluorinated derivatives resulting from the reaction of C_{60} with KrF_2 in anhydrous HF contains mainly

$\text{C}_{60}\text{F}_{44}$ and $\text{C}_{60}\text{F}_{46}$ (see Ref. 150). Treatment of $\text{C}_{60}/\text{C}_{70}$ with vapours of the fluorides WF_6 , TaF_5 , NbF_5 and TiF_4 results in the preparation of fluorides $\text{MF}_n \cdot \text{C}_{60}$ (the $\text{MF}_n:\text{C}_{60}$ ratio is $< 1:2$).¹⁵³

A preparative route to fullerene derivatives with organofluorine substituents (for instance, derivative **98**) involves the reaction of C_{60} with haloalkanes and tributyltin hydride under free-radical reaction conditions.¹⁵⁴



When $n\text{-C}_6\text{F}_{13}\text{I}$, BrCF_2Br , $n\text{-C}_{12}\text{F}_{25}\text{I}$ and $\text{I}(\text{CF}_2)_6\text{I}$ are used, initiation of the reaction requires the addition of azoisobutyronitrile. The hydrogen atom in the C_{60} ring in the resulting compounds is highly acidic and can be replaced by other functional groups in a weakly alkaline medium.¹⁵⁴

V. Fullerenes in polymerisation reactions

When C_{60} fullerene pellets are exposed to a pressure of 1.2 GPa at 600 K for 5 h, $[2+2]$ cycloaddition occurs to give polymers including linear polymers in which the C_{60} fragments are linked by cyclobutane rings.¹⁵⁵ The C_{70} fullerene is more difficult to polymerise,¹⁵⁶ which has been explained by steric hindrance to the $[2+2]$ cycloaddition involving the double bonds in the equatorial region of the ellipsoidal cage. Judging by spectroscopic data,¹⁵⁶ heating solid C_{70} fullerene at 750 °C under a pressure of at least 7.5 GPa affords dimers.

Shvartsburg *et al.*¹⁵⁷ have designed a setup permitting generation of the $\text{C}_{120}^{+/-}$, $\text{C}_{130}^{+/-}$ and $\text{C}_{140}^{+/-}$ ions, which are formed upon laser-induced desorption of crude C_{60} films, and measured their mobility and the trajectories. The trajectories of these ions were in satisfactory agreement with those calculated for the dimers produced upon $[2+2]$ cycloaddition. This study is the first experimental proof of the structure of fullerene dimers.¹⁵⁷

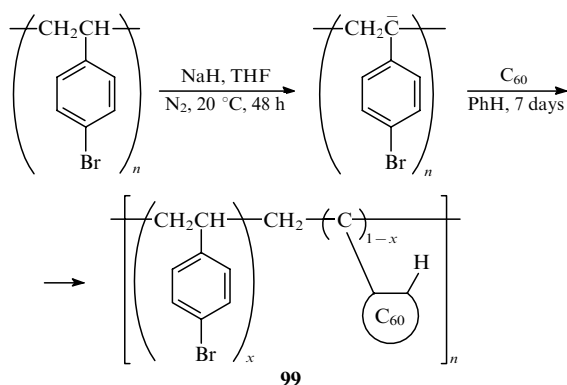
Simultaneous laser-induced vaporisation of C_{60} and graphite at a low helium pressure and a temperature of 400–500 °C or 1900–2400 °C gives rise to polymers of the composition $\text{C}_{60}(\text{CC}_{60})_{n-1}$ ($n = 2\text{--}7$), the dimer C_{121} being the predominant species.¹⁵⁸ When the laser radiation intensity is low, polymers dissociate to give the monomeric components, whereas high radiation intensity results in the elimination of C_2 .

During polymerisation of ordinary monomers, C_{60} can be introduced both in the backbone and in the side chain of the polymer formed.

The chain growth reaction during polymerisation of polystyrene in the presence of C_{60} yields stable free radical (polystyrene) C_{60} (see Ref. 159). The C_{60} and C_{70} fullerenes copolymerise with styrene by a standard free radical mechanism both in block and in aromatic solvents;¹⁶⁰ this affords dark-brown polymers soluble in the same solvents as polystyrene and fluorescing more intensely than polystyrene (fluorescence is shifted to the blue region).

High-pressure (0.1 to 1.5 GPa) polymerisation of styrene in the presence of C_{60} gives rise to a mixture containing products both soluble and insoluble in chloroform.¹⁶¹ An insoluble polystyrene with the chains cross-linked by fullerene molecules was isolated from this mixture.

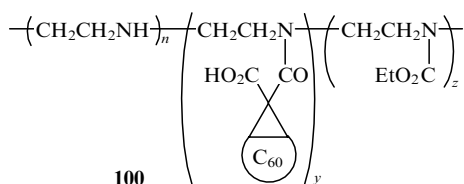
Modification of polymers by C_{60} fullerene fragments changes markedly their physicochemical properties and, in some cases, substantially increases the solubility. A new method for the synthesis of soluble fullerenedated polymers by the reaction of carbanionic polymeric intermediates with C_{60} has been developed.¹⁶²



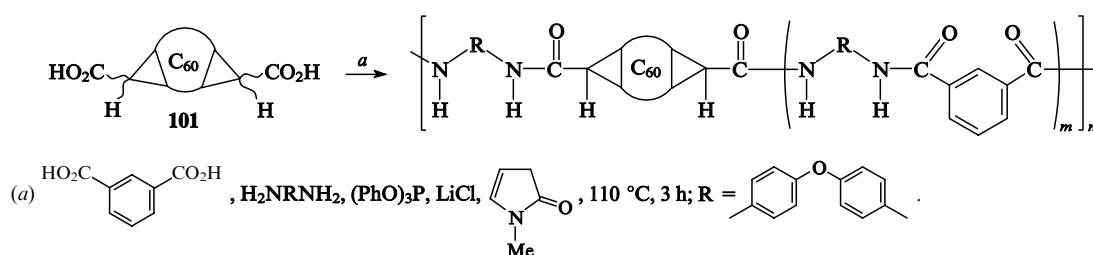
Poly-4-bromostyrene **99** with pendant fullerenes is readily soluble in most common organic solvents (CCl_4 , CHCl_3 , PhH, THF). Poly(vinylbenzyl chloride) modified with C_{60} fullerene and soluble in organic solvents has been prepared in a similar way.¹⁶³ It was found^{164, 165} that C_{60} fullerene substantially inhibits free-radical polymerisation of vinyl monomers in the presence of AIBN by reacting with the initiator and/or by terminating the chain growth.^{164, 165} This is true for copolymerisation with methyl acrylate, methyl methacrylate, acrylonitrile, vinyl acetate and *N*-vinylpyrrolidine.¹⁶⁴ Only with highly reactive monomers such as cyanoethyl acrylate and cyanovinyl acetate, does C_{60} give copolymers (yields 53% and 65%, respectively). Free-radical copolymerisation of 4-vinylbenzoic acid and 2- or 4-vinylpyridine with C_{60} results in polyelectrolytes.¹⁶⁶ Apparently, in addition to non-linear copolymers, the process yields homopolymers and microparticles, which can be separated from copolymers only using microporous filters.

When styrene or methyl methacrylate is subjected to radical polymerisation in the presence of C_{60} (1 mass % in the reaction mixture), fullerene reacts at early steps of the process. This gives rise to branched structures; the proportion of the linear polymer increases with time. Physicochemical properties of these polymers have been characterised in detail.¹⁶⁷

As noted above, the synthesis of water-soluble fullerene derivatives, in particular water-soluble polymers, is important regarding the investigation of the biological properties of fullerenes. Derivatives of this type have been prepared by covalent attachment of hydrophilic linear polymers to the fullerene fragment.¹⁶⁸ Thus the poly(propionylethyleneimine–ethyleneimine) copolymer is added to methano[60]fullerenedicarboxylic acid in the presence of 1-ethyl-3-(dimethylaminopropionyl)carbodiimide. The reaction is carried out in chloroform at 0 °C. This gives water-soluble polymer **100** with pendant C_{60} groups (molecular mass 49 000) in about 15% yield.



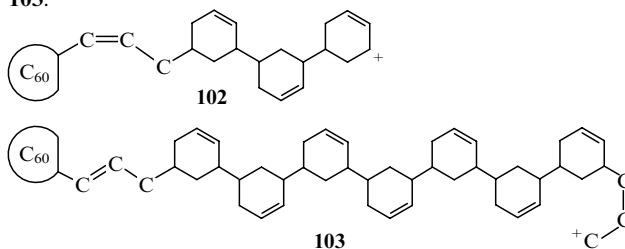
The high solubility of this polymer is due to the presence of the *N,N*-diethylenepropioamide fragment, which is structurally



related to *N,N*-dimethylformamide and *N,N*-dimethylacetamide, miscible with water.

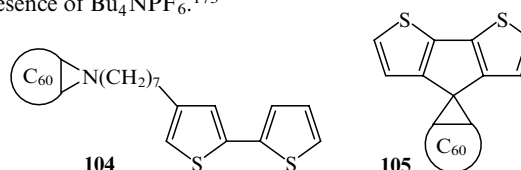
New copolyamides containing dimethanofullerene fragments in the backbone have been synthesised¹⁶⁹ using [60]fullerene-bismethanocarboxylic acid (**101**) (Scheme 2). The polymer forms a brown brittle film capable of coating glass.

Cationic polymerisation involving C_{60} fullerene has been studied.¹⁷⁰ Multicharged cations derived from C_{60} (they are generated¹⁷¹ using a special ion source) are highly reactive in the gas phase. Dications and trications initiate cyclochain polymerisation of allene or propyne under these conditions.¹⁷⁰ More than sixteen allene molecules add to the C_{60}^{2+} dication, odd-numbered adducts reacting approximately 10 times faster than even-numbered ones. It is assumed that multiaddition occurs during the chain growth; the alternation of the reaction rates is attributed to the difference between charge distribution and stability due to the formation of either acyclic or cyclic cation, for example, **102** or **103**.



Studies dealing with the development of conducting and semiconducting polymeric systems involving C_{60} are in progress. One method for the synthesis of conducting polymeric composites is polymerisation on a supporting template.¹⁷² The template is a cross-linked fullerenol–polyurethane elastomer. It is impregnated with aniline; this gives a film, which is brought in contact with an oxidising aqueous solution containing LiCl , $(\text{NH}_4)_2\text{S}_2\text{O}_8$ and HCl at -15 °C and is thus converted into a new elastomer with inserted polyaniline. This product is characterised by much higher conductance than the initial ‘prepolymer’ without losing the elasticity and tensile properties. The presence of the template hampers migration of the conducting species, which is a significant reason for deterioration of the physical properties of the material.

The bisthiophene derivative **104**, functionalised with fullerene, polymerises at the electrode during voltammetry in CH_2Cl_2 in the presence of $\text{Bu}_4^+\text{NPF}_6^-$.¹⁷³



An electrically conducting polymer of the ‘necklace with a pendant’ type was prepared for the first time by anodic oxidation of the bisthiophene derivative containing a fullerene fragment **105**.¹⁷⁴

The change in the photophysical and optical properties of conducting polymers upon the formation of composites with C_{60} fullerene is due to complex formation (resulting in the change in

Scheme 2

the polymer conformation¹⁷⁵) and, what is more important, to the transfer of electrons from the polymer to C₆₀ (see Ref. 176). The spectrum of the film prepared from a mixture of C₆₀ with poly(3-hexylthiophene) exhibits a substantial shift in the UV and visible region.¹⁷⁵ Doping of poly(3-octadecylthiophene) with C₆₀ causes quenching of the polymer photoluminescence.¹⁷⁶ The poly-2-methoxy-5-(2'-ethylhexyloxy)-1,4-phenylvinylene film doped with C₆₀ fullerene is promising for the manufacture of holographic recording materials.¹⁷⁷

VI. Fullerenes in catalysis

Fullerene C₆₀ participates in catalysed processes as either a part of the catalyst and/or a substrate which modifies the action of the catalyst.

The complex $\eta^2\text{-C}_{60}\text{Pd}(\text{PPh}_3)_2$ has been used as the catalyst in the homogeneous (in toluene) and heterogeneous (supported on Sibunit) hydrogenation of 3,7-dimethyloct-6-en-1-yn-3-ol (dehydrolinolool).¹⁷⁸ The process occurs almost selectively (99.5%) as hydrogenation of the triple bond to a double bond; the catalyst activity in the heterogeneous process is maximal and is an order of magnitude higher than that of the traditional catalyst, namely, Pd supported on Sibunit.¹⁷⁸

The tetralin extract of carbon was subjected to hydrocracking in petroleum ether with the addition of a dispersed C₆₀/C₇₀ mixture (90 : 10) and without this mixture. Fullerenes exerted no noticeable effect on the course of hydrocracking.¹⁷⁹

The complex $\text{C}_{60}[\text{Pd}(\text{OAc})_2(\text{PPh}_3)]_3$ was reduced with hydrogen on heating to give a Pd–C₆₀ complex. Phenylacetylene, diphenylacetylene, cyclohexene and hex-1-ene were hydrogenated in the presence of 1 mol. % of this catalyst.¹⁸⁰ Alkenes were completely reduced. The yields were comparable to those attained in the hydrogenation over Pd/C but the reaction occurred faster. The mechanism of the catalytic influence of the C₆₀ substrate is unknown; however, it is assumed that metal fragments form active sites on the C₆₀ spheroid.¹⁸⁰

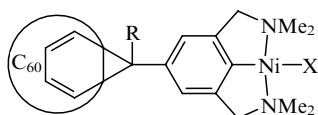
Photochemical oxidation of alkenes in the presence of silica gel modified with C₆₀(H)CH₂SiMe₂(OPrⁱ) has been carried out.¹²¹

In order to prepare new film-forming materials including those promising as semiconducting films (for example, for the manufacture of diodes), polyaddition of benzene to fullerene in the presence of Kovacic catalyst (CuCl₂ + AlCl₃) has been carried out.¹⁸¹ This gave the compound C₆₀Ph₁₉H₁₉, which might have resulted from the reaction of protonated C₆₀ with benzene. At 400 °C, this compound eliminates hydrogen to give C₆₀Ph₁₉. Both compounds form films from toluene solutions and C₆₀Ph₁₉ exhibits clear-cut luminescence in the blue-green region.

The structure and catalytic properties of ruthenium on the C₆₀ substrate (as well as on crude and extracted fullerene black and on the fullerene cathodic deposit) have been studied.^{182, 183} Highly dispersed amorphous Ru was prepared from Ru₃(CO)₂ by the impregnation/activation method. This system serves as an active catalyst for hydrogenation of CO and 2-cyclohexanone under atmospheric pressure.

The molecular sieve MCM-41 is used to prepare catalysts with high surface areas for reactions with bulky molecules. The addition of C₆₀ changes substantially the behaviour of the sieves during their dehydroxylation on heating, due to the abstraction of the hydroxy groups from the silanol fragments of the sieve to give C–H and C–OH groups followed by condensation of the C–OH groups or combination of C–OH with C–H.¹⁸⁴

Precursors of fullerene-containing chelates of the type



R = H, Me; X = H, Br,

have been synthesised;¹⁸⁵ these compounds may find application as supported catalysts and in homogeneous catalysis.

VII. Prospects for the practical use of fullerenes

Extensive practical use of fullerenes would be largely determined by their availability. According to the data for 1995,¹³ fullerenes were supplied by the Hoechst AG (Germany), SES Research (USA) and MER (USA) companies. The price of C₆₀ fullerene was about \$500 per kg in 1997.¹⁸⁶ Back in 1995 the MER company developed a contact arc process which provided a daily output equal to 30 kg of carbon soot with a high fullerene content. Methanofullerene[60]-61-carboxylic acid is also commercially available (Fluka, Switzerland).

According to the data of MER,¹⁸⁶ attention is attracted first of all by the possibility of using fullerenes for the production of rechargeable galvanic cells, with electrodes made of C₆₀/C₇₀ films applied onto various substrates and for the storage of hydrogen, in particular, in the fuel cells of electric cars, and the storage of adsorbed oxygen (which may be useful in medicine and in military engineering). Fullerenes have been patented as precursors of diamonds and diamond coatings, production of which from fullerenes is energetically more favourable than that from graphite. The use of fullerenes for strengthening metal surfaces upon insertion of carbide particles into a metal matrix is also promising. Films of compounds containing fullerene fragments could be used in nonlinear optics, optical computerisation and in sensor technology as solid sensors.

Molecular donor–acceptor charge transfer complexes can present considerable interest as the initial compounds for the manufacture of new materials,¹⁸⁷ for example, superconductors^{43, 153, 188} (superconductivity transitions up to 40 K have been observed).¹⁸⁸

Nitroxides with a fullerene fragment and various fullerene-pyrrolidines can find use in the synthesis of organic ferromagnets.^{75, 76} Films possessing valuable properties have been prepared based on fullerene-pyrrolidines.^{73, 74} Methano- and pyrrolidino-fullerenes are efficient photosensitisers for the generation of singlet oxygen.¹⁰² The formation of C₆₀ and C₇₀ fullerene adducts with porphyrins of phthalocyanines increases the photoinitiated electrical conductivity of the latter (see Ref. 53 and references therein). Nitrogen-containing fullerene derivatives immobilised on silica gel make it possible to develop new adsorbents.⁷⁰

The potential use of fullerenes as biologically active compounds has stimulated vigorous development of the chemistry of functional derivatives of fullerene, especially after 1993, when it was shown¹⁸⁹ that water-soluble fullerene derivatives with methane bridges inhibit HIV enzymes, namely, protease and reverse transcriptase; data on the biological properties of fullerene derivatives have been published.^{190, 191}

For biological assays, it is necessary to prepare functional derivatives soluble in water or in polar media with a stabilising fragment linked to the fullerene by a covalent bond. Nakamura *et al.*¹⁹¹ have classified the biologically active fullerene derivatives into two types: the detergent type (in which the side chain is modified by, for example, attachment of carboxylic acid residues *via* organic binding groups) and the spherical type, in which there are polar groups distributed over the fullerene sphere (this class includes fullerenols and amino adducts).

VIII. Conclusion

In recent years, exohedral addition and, especially, cycloaddition has remained the main line of functionalisation of fullerenes. These reactions have been employed to prepare a large number of new oxygen- and nitrogen-containing derivatives such as quinones, pyridones, nitrile oxides and pyrrolidine derivatives. The photophysical and photochemical properties of these compounds (fluorescence, phosphorescence) and the redox potentials of these derivatives depend on the degree of functionalisation and posi-

tions of functional groups in fullerene fragments. Fullerene derivatives containing heteroatoms can be used to model the photosensitisation and photosynthesis processes, including those involving singlet oxygen, which is important for the research into biological systems. An important aspect in the studies is development of the methods for selective multifunctionalisation, which would direct the addend to a particular site of the carbon cage.

Among the fundamental studies devoted to the properties of fullerenes, the syntheses of a catenane with a fullerene fragment, the preparation of hydrocarbon salts and the generation of the carbocation consisting of only carbon atoms deserve attention. While Kroto, one of the fullerene discoverers, was amazed by the ability of pure carbon to be dissolved in organic solvents, the preparation of an aqueous colloidal solution of C₆₀ seems even more remarkable.

The potential practical application of fullerenes and their functional derivatives is being studied along several paths. In the case of C₆₀ fullerene, this is mainly production of films deposited on various substrates including diamond-like ones, sensitisers and adsorbents for gases. The synthesis of new complexes and incarcenanes (fullerenes containing an element incorporated in the cage) is aimed at the preparation of new superconductors, dielectrics and ferromagnets. Numerous publications have been devoted to the synthesis of C₆₀ adducts in order to use them as the starting compounds in the synthesis of biologically active products.

The preparation of fullerene-based catalysts and catalytic systems and the synthesis of fullerene-containing polymers have been less developed. The progress along these lines might be expected in the future.

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Stable tellurols and their metal derivatives

I D Sadekov, A V Zakharov

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Abstract. Data on the synthesis, reactions and structures of stable aromatic tellurols and sterically hindered tellurols containing E–TeH bonds (E = C, Si or Ge) are systematised and generalised. Methods for the preparation of various metal derivatives of tellurols as well as applications of these derivatives in the low-temperature synthesis of metal tellurides are considered. The bibliography includes 90 references.

I. Introduction

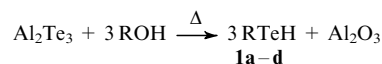
Tellurium analogues of alcohols and phenols, *viz.*, tellurols (RTeH), belong to a class of organotellurium compounds which are rather poorly studied. First representatives of these compounds, *viz.*, alkanetellurols, were synthesised back in 1926,¹ while rather stable aromatic tellurols, *viz.*, 2,4,6-trialkylbenzenetellurols and tris(trimethylsilyl)silanetellurols, were prepared only in 1991.² Based on these compounds and their analogues and derivatives, a wide range of tellurolates of various metals have been synthesised in recent years. Tellurolates of sterically hindered organoelement tellurols (Me₃Si)₃ETeH (E = C, Si or Ge) are of particular interest because these compounds can be used in the pyrolytic synthesis of metal tellurides. Since these compounds contain E–Te–H bonds (E = Si or Ge), they do not formally belong to tellurols. However, it is reasonable to consider here methods of their preparation, reactions and spectral characteristics, because these derivatives possess unusual properties, in particular, enhanced stability in the crystalline state and in solutions compared to true tellurols. In addition, tellurolates based on the above-mentioned compounds allow one to prepare metal tellurides at relatively low temperatures.^{3–7}

II. Synthesis, reactions and structures of tellurols

1. Synthesis and reactions of tellurols

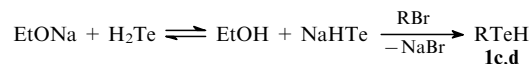
The first alkanetellurol, *viz.*, ethanetellurol **1a**, was prepared by high-temperature alcoholysis of Al₂Te₃ at 250 °C.¹ Later on, this method was modified by Baroni.⁸ Oxidation of the resulting alkanetellurols can be prevented if the process is performed

under an atmosphere of hydrogen. Apparently, the overall reaction is described by the following equation:



R = Et (**a**), Me (**b**), Pr (**c**), Bu (**d**).

Alkanetellurols **1c,d** were also prepared by the reactions of the corresponding alkyl halides with a solution of sodium ethoxide saturated with hydrogen telluride at low temperature.⁸ However, attempts at synthesising methane- and ethanetellurols **1a,b** according to this procedure have failed.



R = Pr (**c**), Bu (**d**).

The method which is most generally used for the preparation of different types of tellurols involves the reactions of their lithium and sodium salts (methods for their synthesis are discussed in Section III.1) with protic acids. Thus treatment of sodium methanetellurolate, which has been prepared from dimethyl ditelluride upon cleavage of the Te–Te bond with sodium in liquid ammonia, afforded methanetellurol **1b**.^{9–11} Trideuteriomethanetellurol **1e** was prepared analogously.¹¹



R = Me (**b**), CD₃ (**e**); HX = H₂SO₄, H₃PO₄.

The acid H₃PO₄ is a protonating agent of choice¹¹ because the use of even dilute H₂SO₄ leads to partial oxidation of tellurol **1b** to dimethyl ditelluride.

Alkanetellurols **1** are liquids with an unpleasant odour. The yellowish colour of these compounds is caused by the presence of dialkyl ditellurides, which were formed either upon thermal decomposition of tellurols or upon their oxidation with atmospheric oxygen.^{9–11} Tellurols can be stored at the temperature of liquid nitrogen with exclusion of air because they readily decompose at room temperature.¹¹

Decomposition of methanetellurol under UV irradiation occurs in two stages. First, dimethyl ditelluride and hydrogen are formed and then more profound decomposition occurs to form methane, higher hydrocarbons and tellurium.¹¹

Attempts to synthesise benzene- and thiophene-2-tellurols by protonation of their lithium salts with trifluoroacetic acid in THF or of their sodium salts in an ethanol–ethyl acetate mixture have been unsuccessful.¹² Attempts to prepare benzenetellurol upon

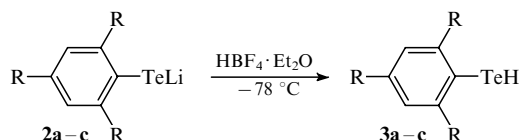
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methanolysis of (phenyltelluro)trimethylsilane have also failed.^{13–15} However, benzenetellurol^{12, 14, 15} and thiophene-2-tellurol,¹² which are prepared according to the above-described methods *in situ*, are efficient reducing agents for organic compounds.^{12, 15} In the presence of ZnI₂, they are used for converting carbonyl compounds into asymmetrical ethers.¹⁴

Arenetellurols were synthesised by protonolysis of suspensions of sterically hindered lithium arenetellurolates **2** (prepared by reducing the corresponding diaryl ditellurides with lithium triethylborohydride) with HBF₄ etherate in light petroleum. Compounds **3** were obtained in nearly quantitative yields.²

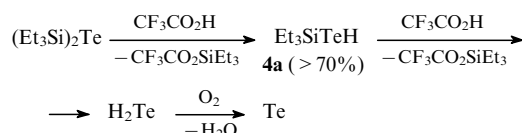


R = Me (**a**), Prⁱ(**b**), Bu^t (**c**).

Arenetellurols **3** are colourless crystalline compounds, which can be recrystallised from light petroleum at $-110\text{ }^{\circ}\text{C}$. However, these compounds are light-sensitive and begin to decompose at -40 to $-30\text{ }^{\circ}\text{C}$ to form metallic tellurium.² The thermal stability of arenetellurols **3** is independent of the bulkiness of the substituents. In particular, tellurol **3a** is more stable than **3c**.²

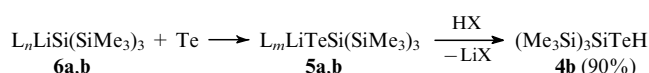
The most stable tellurols are organoelement tellurols (Me₃Si)₃ETeH (E = C, Si or Ge). Due to the presence of bulky substituents, metal tellurolates prepared from these tellurols are readily soluble in nonpolar organic solvents and exist as monomers or weakly associated aggregates. These properties together with the volatility and high thermal stability allow one to use salts of organoelement tellurols in the pyrolytic synthesis of metal tellurides (see Section III).

The first tellurol containing the Si–TeH bond to be synthesised was triethylsilanetellurol **4a**.¹⁶ This compound was prepared by treatment of bis(triethylsilyl) telluride with an equimolar amount of trifluoroacetic acid at $20\text{ }^{\circ}\text{C}$ and was isolated by vacuum distillation.



Under the action of an excess of CF₃CO₂H, the Si–Te bond in the tellurol **4a** was cleaved and triethylsilyl trifluoroacetate and elemental tellurium were formed as the final reaction products.¹⁶ Apparently, the latter was formed upon oxidation of intermediate H₂Te.

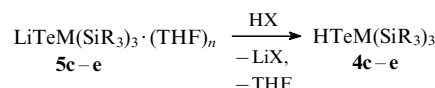
Sterically hindered tris(trimethylsilyl)silanetellurol (**4b**) was synthesised by protonolysis of lithium salts **5a**^{17–19} or **5b**²⁰ with trifluoroacetic acid in hexane^{17–19} or with HCl in toluene.²⁰ The salts **5a**²¹ and **5b**²² were prepared according to a standard procedure for the synthesis of these salts, which involves the insertion of the Te atom at the Si–Li bond in the complexes of tris(trimethylsilyl)silyllithium with THF (**6a**)²¹ or with dioxethane (DME) (**6b**).²²



L = THF: $n = 3$ (**6a**), $m = 2$ (**5a**); L = DME: $n = 1.5$ (**6b**), $m = 1$ (**5b**); HX = HCl, CF₃CO₂H.

Colourless crystalline tellurol **4b** is stable under an argon atmosphere in the dark for at least several days. In sunlight, solid tellurol **4b** turns dark but the spectral characteristics remain unchanged. In solutions, the tellurol **4b** rapidly decomposes under exposure to light to form a tellurium mirror.^{17, 18}

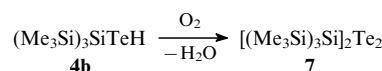
Protonolysis of lithium tris(trimethylsilyl)methanetellurolate (**5c**),²³ tris(trimethylsilyl)germanetellurolate (**5d**)¹⁹ and tris(triphenylsilyl)silanetellurolate (**5e**),²⁴ which have been preliminarily isolated and purified, with trifluoromethanesulfonic acid in ether^{17–19} or with trifluoroacetic acid in hexane²⁴ afforded tellurols **4c–e** in 57%–81% yields. Protonolysis of lithium salts **5e** in diethyl ether, which is more polar than hexane, was accompanied by partial decomposition of the tellurol **4e** resulting also in bis(triphenylsilyl) telluride and H₂Te.²⁴



M = C, R = Me, $n = 2$ (**5c**); M = Ge, R = Me, $n = 3$ (**5d**); M = Si, R = Ph, $n = 3$ (**5e**).

Tellurols **4c–e** are crystalline compounds the colour of which varies from yellow to orange. These compounds melt at temperatures above $120\text{ }^{\circ}\text{C}$. Compounds **4c,d**, like tellurol **4b**, were isolated and purified by sublimation under high vacuum, while tellurol **4e** was purified by recrystallisation from hexane at low temperature. The stability of tellurols **4c,d** is similar to that of tellurol **4b**,¹⁹ whereas tellurol **4e** is more sensitive to atmospheric oxygen.²⁴

The reactions of tellurols governed by the presence of the hydrotelluride function are poorly studied. Oxidation of the tellurol **4b** with oxygen afforded ditelluride **7**. Compound **7** can be more easily synthesised by the oxidation of the tellurolate **5a** with oxygen or CuCl^{17, 18} or by the oxidation of the tellurolate **5b** with iodine, because these procedures exclude the stages of isolation and purification of the tellurol.²⁰



The pK_a values of tellurols **4b–d** and of a number of related thiols and selenols were determined (photometrically, for solutions in isobutyl methyl ketone).¹⁹ The following values were obtained: 7.3 for HTeSi(SiMe₃)₃ (**4b**), 9.3 for HTeC(SiMe₃)₃ (**4c**), 7.4 for HTeGe(SiMe₃)₃ (**4d**), 8.3 for HSe(SiMe₃)₃, 10.7 for HSSi(SiMe₃)₃ (the synthesis was described in Ref. 25) and 10.8 for HSeC(SiMe₃)₃ (the synthesis was described in Ref. 26).

The acid strengths of silane- and germanetellurols **4b,d** are approximately 100 times higher than that of their carbon analogue **4c**. This is also true for the corresponding selenium derivatives. This tendency for the change in the pK_a values was attributed¹⁹ to the lower electronegativity of Si (1.9) and Ge (2.0) compared to C (2.5). For compounds HM(SiMe₃)₃ (M = S, Se or Te), the pK_a values increase in the series Te > Se > S.¹⁹ Thus the tellurol **4b** is a stronger acid than the corresponding selenol and thiol by a factor of 10 and 1000, respectively. The same tendency for the change in the acidity is typical of inorganic hydrides of the corresponding elements.²⁷

2. X-Ray diffraction analysis and ¹H and ¹²⁵Te NMR spectra of tellurols

The molecular and crystal structure of tris(triphenylsilyl)silanetellurol **4e** was established by X-ray diffraction analysis.²⁴ The Te–Si bond length is 2.511 Å and the Te–Si–C angles are in the range of 106.0–109.6°. Unlike Ph₃SiOH, which exists in the crystal as an H-bound tetramer,²⁸ the tellurol **4e** exists as a monomer (like triphenylsilanethiol Ph₃SiSH²⁹). In the crystal, there are no shortened or specific intermolecular contacts smaller than the sum of the van der Waals radii of the elements. Thus the Te···Te distances are 4.64 Å (the sum of the van der Waals radii is 4.40 Å).³⁰ Evidently, hydrogen bonds in the crystal of the tellurol **4e** are absent due to the low electronegativity of the tellurium atom.

The ¹H and ¹²⁵Te NMR spectroscopic data are given in Table 1.

Table 1. Data of ^1H and ^{125}Te NMR spectroscopy of tellurols **2** (CDCl_3 , -20°C), tellurols **4** (PhH , 20°C) and their analogues.

Compound	^1H NMR δ (see ^a)	^{125}Te NMR δ (see ^b)	$J_{\text{Te-H}}$ Hz	Ref.
2,4,6- $\text{Me}_3\text{C}_6\text{H}_2\text{TeH}$ (2a)	-2.68	-91.4	63	2
2,4,6- $\text{Pr}^i_3\text{C}_6\text{H}_2\text{TeH}$ (2b)	-2.95	-134.8	48.6	2
2,4,6- $\text{Bu}^t_3\text{C}_6\text{H}_2\text{TeH}$ (2c)	-1.25	153.8	51.9	2
$(\text{Me}_3\text{Si})_3\text{SiTeH}$ (4b)	-8.82	-955	74	17–19
	-8.83	-955.1	74.6	20
$(\text{Me}_3\text{Si})_3\text{CTeH}$ (4c)	-5.1	-63	101	19
$(\text{Me}_3\text{Si})_3\text{GeTeH}$	-9.02	-940	95	19
Ph_3SiTeH	-6.45	-684	27.4	24
H_3SiTeH^c	-7.46	—	58	31
H_3GeTeH^c	-7.44	—	52	31

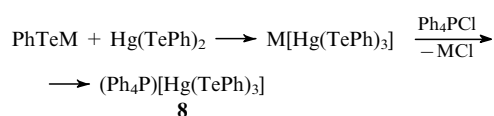
^a The chemical shifts of the protons bound to the Te atoms are given; ^b the chemical shifts relative to Me_2Te ; ^c the spectra were recorded in CDCl_3 at 20°C .³¹

The signals for the protons bound to the Te atoms in the tellurols **4b–e** containing the trimethylsilyl group are observed at substantially higher field (at δ from -6.45 to -8.82) than the analogous signals in the ^1H NMR spectra of the aromatic tellurols **2a–c** (at δ from -1.25 to -2.95). A comparison of the chemical shifts of the protons bound to the chalcogen atoms in the ^1H NMR spectra of tris(trimethylsilyl)silanechalcogenols $(\text{Me}_3\text{Si})_3\text{EH}$ ($\text{E} = \text{S}, \text{Se}$ or Te) are indicative of successive downfield shifts of these signals in the series $\text{Te} < \text{Se} < \text{S}$.¹⁹

The resonance signals for the ^{125}Te nuclei are observed as doublets in a very broad region (more than 1100 ppm), viz., from δ 153.8 for the aromatic tellurol **2c** (see Ref. 2) to δ -955 for tris(trimethylsilyl)silane tellurol **4b**.^{17–20} A substantial upfield shift for the compound **4b** was related to the lower electronegativity of the silyl substituents compared to that of aromatic substituents.¹⁸

III. Synthesis, reactions and structures of metal tellurolates

Until recently, alkane- or arenetellurolates of alkali metals, viz., of lithium, sodium, and, to a lesser degree, of potassium, were the best studied representatives of metal tellurolates. These compounds were prepared either by reduction of the corresponding ditellurides or by insertion of the tellurium atom at the C–Li bond of organolithium derivatives.^{32–36} However, they are unstable and are readily oxidised; therefore, none of these tellurolates was isolated in the individual form and structurally characterised. These compounds prepared *in situ* find wide use in the synthesis of various classes of organotellurium compounds and primarily of ditellurides and tellurides. Mercury(II) tellurolates $\text{Hg}(\text{TePh})_2$,^{37,38} $\text{Hg}(\text{TeC}_6\text{H}_4\text{Me-4})_2$,³⁸ $\text{Hg}(\text{TeC}_6\text{H}_4\text{-OEt-4})_2$,³⁹ $\text{Hg}(\text{TeBu}^n)_2$,⁴⁰ $\text{Hg}(\text{TeBu}^n)_2$,⁴¹ $\text{Hg}(\text{TeC}_2\text{F}_5)_2$ (see Ref. 42) and $\text{Hg}(\text{TeCF}_3)_2$ (see Ref. 43) were isolated in the individual state. However, these compounds in the solid state exist as polymers, which precluded their studies by X-ray diffraction analysis. Only the structure of a complex mercury tellurolate **8** was established by this method⁴⁵ (the synthesis was described in Ref. 44).



$\text{M} = \text{Na}, \text{K}$.

Mercury tellurolates are soluble in coordinating solvents such as 1,2-bis(diethylphosphino)ethane (DEPE) or 1,2-bis(dimethylphosphino)methane (DMPE).⁴¹ When the tellurolate and the

solvent were taken in a ratio of 1:2 or 1:1, coordination polymers or dimeric compounds of the $[\text{Hg}(\text{TePh})_2(\text{DEPE})]_2$ type, respectively, were formed.⁴¹ The structure of the latter compound was established by X-ray diffraction analysis.⁴¹ When heated in the solid state, the complexes of this type decompose to form mercury telluride, phosphine and the corresponding diorganyl ditelluride.⁴¹ The dimeric complexes decompose upon heating in solution.

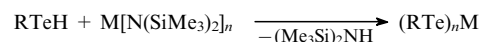
Rather stable tellurols containing bulky organic radicals have been synthesised recently, which made it possible to carry out systematic studies of their reactivities and the properties of the respective metal tellurolates (these data were most completely surveyed in a review⁴).

In this section, we consider methods for the synthesis, reactions and crystal structures of metal tellurolates containing bulky organic radicals. We restrict ourselves to consideration of tellurolates in which metal atoms are bound only to tellurium atoms. Tellurolates of other types, for example, tellurolates of metal cyclopentadienyl derivatives are not considered in detail (the data on these compounds were reported in the review⁴).

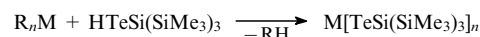
1. General methods for the synthesis of metal tellurolates

Presently, four major procedures for the preparation of metal tellurolates are known. These tellurolates were isolated in the individual state and in some cases were characterised by X-ray diffraction analysis.

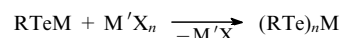
1. Tellurololysis of the M–N bond in metal *N*-trimethylsilylamides with stable free tellurols (most widely used).



This method was used for the preparation of tellurolates of Li,^{18,19} Na,¹⁸ K,¹⁸ Ca,^{46–48} Sr,^{46,47} Ba,^{46,47} Zn,^{17,49,50} Cd,^{2,49} Hg,^{49,51} Mn(II),^{52,53} Sn(II),⁵⁴ Pb(II),⁵⁴ Fe(II),⁵² divalent lanthanides (Eu,⁵⁵ Sm⁵⁵ and Yb⁵⁵) and trivalent lanthanides (La⁵⁶ and Ce⁵⁶) as well as of Al(III),⁵⁷ Sb(III)⁵⁷ $\{\text{Sb}(\text{NMe}_2)_3$ was used in the synthesis of $\text{Sb}[\text{TeSi}(\text{SiMe}_3)_3]_3$ and Bi(III).⁵⁷ Tellurolates of Mg,^{46,47} Zn,¹⁷ In(III),⁵⁷ Tl(I),⁵⁷ Zr(IV)⁵⁸ and Hf(IV)⁵⁸ were prepared by tellurololysis of the M–C bonds in metal alkyls or metal cyclopentadienyl derivatives with the use of tris(trimethylsilyl)silane tellurol **4b**.



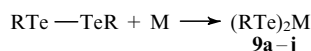
2. Exchange reactions of metal tellurolates (most often, of lithium derivatives) with metal halides. These reactions are of a rather general character as well.



$\text{M} = \text{Li}, \text{Na}; \text{X} = \text{Cl}, \text{Br}$.

This method was used for the preparation of tellurolates of Cu(I),⁵⁹ Au(I),⁶⁰ Cd,⁶¹ Hg,^{49,51} Mn(II),⁵² Fe(II),⁵² Co(I),⁵² Cr(II),⁵² Ga(III)⁵⁷ and In(I).⁵⁷ Sodium tellurolates were used in the synthesis of Zn and Cd tellurolates.⁶² Tellurolates of divalent lanthanides (Yb, Sm and Eu,^{63,64}) were synthesised with the use of potassium derivatives of sterically hindered tellurols because it is impossible to separate lanthanide tellurolates from lithium or sodium halides formed in the exchange reactions with the use of lithium or sodium salts.

3. Reduction of the corresponding ditellurides with lithium triethylborohydride,^{61,65} sodium amalgam,^{18,61,66} potassium amalgam¹⁸ or potassium tris(*sec*-butyl)borohydride^{61,66} allows one to synthesise alkali metal tellurolates with sterically hindered ligands. The insertion of some metals (Hg,^{37–39,41–43,51} Cd⁴³ or Yb⁶⁷) at the Te–Te bond of tellurides also belongs to reduction reactions. This method was used primarily for the preparation of metal tellurolates **9a–f, i, j** containing not-very-bulky substituents at the tellurium atom. However, tellurolates **9g, h, j** were also synthesised by this method.⁵¹



Compound 9	M	R	Ref.
a	Hg	Ph	37, 38
b	Hg	4-MeC ₆ H ₄	38
c	Hg	4-EtOC ₆ H ₄	39
d	Hg	Bu	41
e	Hg	C ₂ F ₅	42
f	Hg	CF ₃	43
g	Hg	2,4,6-Me ₃ C ₆ H ₂	51
h	Hg	2,4,6-Pr ₃ C ₆ H ₂	51
i	Cd	CF ₃	43
j	Yb	Ph	67

It should be noted that dimesityl ditelluride readily reacts with metallic mercury in toluene at room temperature without a solvent to form mercury mesitylenetelluroate **9g**,⁵¹ while the reaction of bis(2,4,6-triisopropylphenyl) ditelluride is performed in a polar solvent, such as methanol, at room temperature. The latter reaction is reversible and the telluroate **9h** decomposes to the corresponding ditelluride and metallic mercury upon heating in methanol or upon recrystallisation from nonpolar solvents. Attempts to prepare mercury bis(2,4,6-tri-*tert*-butylphenyl)telluroate by the reaction of the corresponding ditelluride with metallic mercury have been unsuccessful.⁵¹

Ytterbium di(benzenetelluroate) was synthesised in liquid ammonia. After evaporation of the solvent and extraction with pyridine, the complex with composition (PhTe)₂Yb(Py)₅ was isolated.⁶⁷ Attempts to prepare Yb(III) telluroate by the reaction of Yb(III) chloride with sodium benzenetelluroate have failed because Yb(III) was reduced to Yb(II) and the same complex of divalent Yb, *viz.*, (PhTe)₂Yb(Py)₅, has been obtained as the only product.⁶⁷

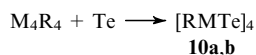
The only copper(I) telluroate prepared by insertion of the copper atom at the Te–Te bond was Cu(I) trifluoromethane-telluroate.⁴³



Boiling of diaryl ditellurides with a copper powder in dioxane resulted in elimination of one tellurium atom to form diaryl tellurides in virtually quantitative yields.^{35, 36}

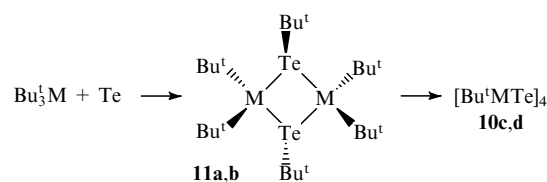
4. Insertion of the tellurium atom at the C–Li bond of the corresponding lithium derivatives was used for the preparation of lithium derivatives of some sterically hindered telluroles.^{17–20, 23, 61, 68}

Thus the reactions of organic derivatives of Al(I)⁶⁹ and In(I)⁷⁰ with elemental tellurium in toluene or hexane gave compounds **10a, b** in yields of > 80%. The structures of both compounds contain distorted heterocubane molecular cores M₄Te₄ (M = Al or In) (data from X-ray diffraction analysis).^{69, 70}



M = Al, R = C₅Me₅ (**a**); M = In, R = (Me₃Si)₃C (**b**).

The insertion of the Te atom at the M–C bond of tris(*tert*-butyl)gallium^{71, 72} or -aluminium⁷¹ occurs on stirring of a mixture of the reagents in toluene at room temperature. In this case, telluroates **11a, b** were obtained in ~ 60% yields. In boiling toluene, compounds **10c, d** were formed. These compounds were also formed upon heating of dimers **11a, b**.⁷² The structure of aluminium telluroate **11b** was established by X-ray diffraction analysis.⁷¹

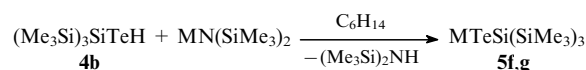


M = Ga (**10c, 11a**), Al (**10d, 11b**).

The two latter methods are less common because they allow one to prepare telluroates of only a limited number of metals.

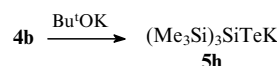
2. Alkali metal telluroates

Alkali metal telluroates were synthesised according to methods 1, 3 and 4 (primarily, according to methods 3 and 4). Tellurolysis of lithium and sodium bis(trimethylsilyl)amides with tris(trimethylsilyl)silanetelluroate **4b** afforded lithium telluroate **5f**¹⁸ and sodium telluroate **5g**.¹⁸ The reactions performed in hexane yielded alkali metal telluroates, which are not coordinated by solvent molecules or donor ligands.

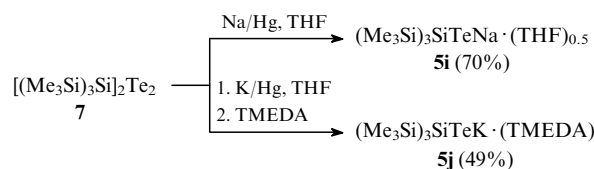


M = Li (**f**, 54%), Na (**g**, 61%).

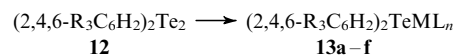
Potassium telluroate **5h** was prepared by the reaction of the telluroate **4b** with Bu^tOK.¹⁸



Alkali metal telluroates containing the bulky tris(trimethylsilyl)silyl or aryl substituents were prepared by reducing the corresponding ditellurides (method 3). The reactions are generally carried out in THF at room temperature. The resulting telluroates are isolated as complexes with THF or with other donor ligands. Thus reduction of the ditelluride **7** with potassium or sodium amalgam gave telluroates **5i, j** as complexes with THF or tetramethylethylenediamine (TMEDA).¹⁸



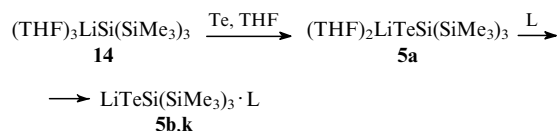
The reactions of ditellurides **12** (R = Me or Prⁱ) with lithium triethylborohydride in THF,⁶¹ with sodium amalgam in the presence of TMEDA^{61, 66} or DME⁶¹ as well as with potassium tris(*sec*-butyl)borohydride either in THF⁶¹ or followed by treatment with crown ether (18-C-6)⁶⁶ afforded complexes of telluroates **13a–f**.



Compound 13	Reducing agent	R	M	L	n	Yield (%)
a	LiBEt ₃ H	Me	Li	THF	1.5	80
b	LiBEt ₃ H	Pr ⁱ	Li	THF	2.5	48
c	Na/Hg	Me	Na	TMEDA	2	80
d	Na/Hg	Pr ⁱ	Na	DME	1	64
e	KBu ₃ BH	Pr ⁱ	K	THF	1.33	40
f	KBu ₃ BH	Pr ⁱ	K	18-C-6	1	47

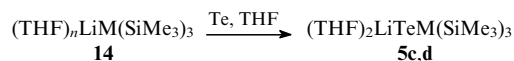
Complexes of lithium telluroates were also prepared by the reactions of elementary tellurium with organolithium compounds.

Complexes **5b, k** were synthesised by the reaction of powdered tellurium with organolithium compound **14**.¹⁸

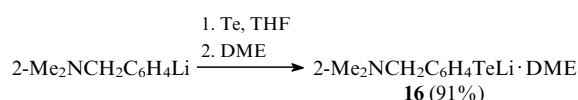
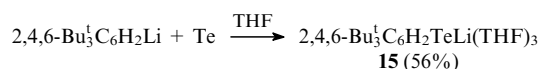


L = DME (**5b**, 82%), 12-C-4 (**k**, 79%).

The reaction of the lithium derivative **14** with Te in DME gave the complex **5b** in 72% yield.²⁰ Complexes of tellurolates **5c,d**,¹⁹ **15**^{61,68} and **16**⁶¹ were synthesised analogously.



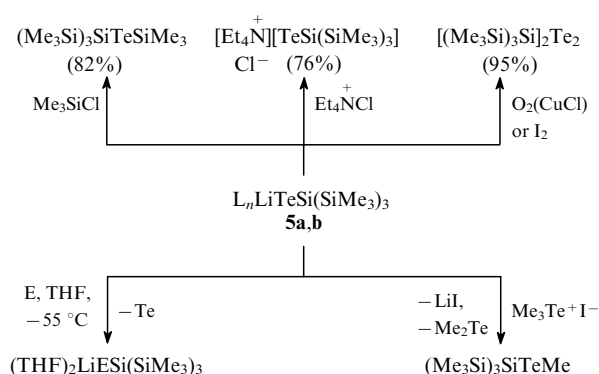
M = C (**c**, 56%), Ge (**d**, 48%).



Complexes of alkali metal tellurolates containing bulky substituents are thermally stable at room temperature and can be stored without decomposition under an inert atmosphere for a long period of time. However, these compounds are readily oxidised in the solid state and in solution with atmospheric oxygen to give the corresponding ditellurides. As can be seen from the above-considered reactions, THF in the complexes is readily replaced by stronger donor ligands such as DME, TMEDA, 18-C-6 or 12-C-4.

Some reactions which were studied using alkali metal tellurolates **5a**^{17–19} and **5b**²⁰ as examples are shown in Scheme 1.

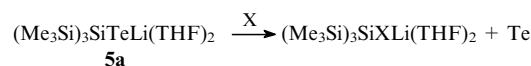
Scheme 1



E = Se (93%), S (90%).

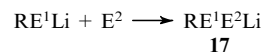
It is known³⁶ that lithium and sodium alkane- and arenetellurolates are oxidised to the corresponding ditellurides. In this respect, the behaviour of lithium tris(trimethylsilyl)silane-tellurolate (**5e**) is unusual.²⁴ Its oxidation with atmospheric oxygen or the reaction with CuCl afforded only $(\text{Ph}_3\text{Si})_2\text{Te}$.²⁴

The exchange reactions of tellurium atoms in diaryl ditellurides³⁶ and in some tellurium-containing heterocycles⁷³ for sulfur or selenium atoms have long been known. These reactions proceed at high temperature. The tellurolate **5a** reacts with S or Se at -55°C . Based on this fact, Bonasia *et al.*¹⁹ considered the reactions of the tellurolate **5a** with selenium and sulfur (metathesis) yielding lithium tris(trimethylsilyl)silaneselenolate and -thiolate to be a new type of reactions in the chemistry of chalcogens.



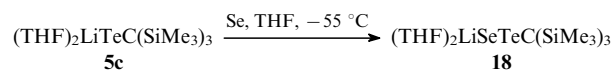
X = Se, S.

Reactions of the tellurolate **5a** with chalcogens occur as the replacement of tellurium by a lighter chalcogen. It is known that in the reactions of lithium alkane- and arenetellurolates, lighter chalcogens are inserted into the bond between heavier chalcogen and lithium atoms to form lithium chalcogenylchalcogenolates **17**.⁷⁴

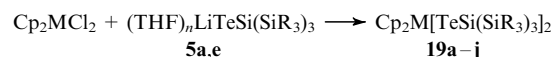


E¹ = Te; E² = Se, S; E¹ = Se, E² = S.

Unlike with lithium tris(trimethylsilyl)silane-tellurolate **5a**, the reaction of the carbon analogue of this compound, *viz.*, lithium tris(trimethylsilyl)methanetellurolate **5c**, with selenium at -55°C resulted in a dark-red solution containing, according to the ¹²⁵Te NMR spectrum, lithium tellurenylselenolate **18**. Attempts at isolating this compound in the solid state have led to its decomposition into a mixture of nonidentified compounds.¹⁹



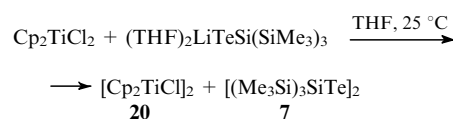
The exchange reactions of tellurolates **5a** and **5e** with cyclopentadienyl complexes of Ti, Zr and Hf made it possible to synthesise new tellurium-containing complexes **19a–j**.^{24,75} The structures of the compounds **19d**, **g**⁷⁵ and **19f**²⁴ were established by X-ray diffraction analysis.



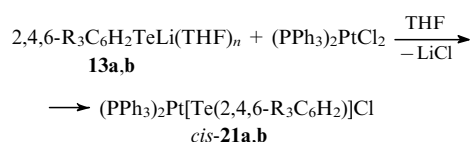
Compound 19	Cp	M	R	Yield (%)
a	C ₅ H ₅	Ti	Ph	75
b	C ₅ Me ₅	Ti	Ph	55
c	C ₅ H ₅	Ti	Me	86
d	C ₅ Me ₅	Ti	Me	70
e	C ₅ H ₅	Zr	Ph	71
f	C ₅ H ₄ Bu ^t	Zr	Ph	74
g	C ₅ H ₅	Zr	Me	75
h	C ₅ H ₅	Hf	Ph	67
i	C ₅ H ₄ Bu ^t	Hf	Ph	33
j	C ₅ H ₅	Hf	Me	72

Compounds of the type **19** were also formed in the reactions of lithium tellurolate **5c** with metal complexes.⁷⁵ However, the resulting products rapidly decomposed to give eventually Te, HC(SiMe₃)₃ and a mixture of nonidentified metal-containing compounds.

In the reactions of Ti, Zr and Hf cyclopentadienyl complexes with the tellurolate **5a**, the nature of the solvent is of considerable importance. Thus the reactions in hexane afforded tellurolates **19**, while the reaction of the compound **5a** with titanium complex in THF yielded the dimeric complex **20** and the ditelluride **7**.⁷⁵



The reactions of tellurolates **13a,b** with *cis*-bis(triphenylphosphine)platinum dichloride resulted in displacement of one chloride ligand to form tellurium-containing platinum complexes **21a,b**. The structure of the complex **21b** was established by X-ray diffraction analysis.⁶¹



R = Me (a), Prⁱ (b).

The structures of many complexes of alkali metal tellurolates with Lewis bases were established by X-ray diffraction analysis. Below are considered the characteristic structural features of these compounds. In the crystal, lithium tellurolate (THF)₂LiTe–Si(SiMe₃)₃ (**5a**) exists as dimers and contains the Li₂Te₂ core. The Te–Li bond lengths in the ring (2.82 and 2.88 Å) are close to the values predicted based on the ionic radii (Li⁺, 0.73 Å; Te^{2–}, 2.07 Å).⁷⁶ The Te–Si and Li–O bond lengths are 2.48 and 1.90 Å, respectively. The Li–Te–Li and Te–Li–Te bond angles are 90.4 and 89.6°, respectively.¹⁸

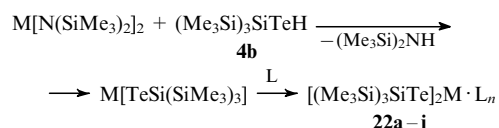
In lithium tellurolate **16**, the Li atom is tetrahedrally coordinated by two oxygen atoms of DME, the nitrogen atom and the tellurium atom.⁶¹ The Te–Li distance in this compound (2.717 Å) is smaller than that in the tellurolate **5a**. The Te–C bond length (2.142 Å) has the standard value.⁷⁷ The Te–Li–O bond angles are 125.8 and 118.2° and the Te–Li–N angle is 99.6°. However, it remains unclear whether this molecule retains N→Te coordination, which has been observed in analogous compounds with tellurium-containing substituents in the *ortho* position with respect to the CH(R)NMe₂ group (R = H or Me) in the aromatic rings [the N→Te bond lengths are 2.366⁷⁸ and 2.406 Å⁷⁹ in 2-iodotellurenylbenzyl dimethylamine and 2-(1-dimethylaminoethyl)benzenetellurium trichloride, respectively, which are substantially smaller than the sum of the van der Waals radii of Te and N (3.70 Å)³⁰].

In the complex **15**⁶¹ containing a bulky aryl substituent, the C–Te–Li angle is 99.1°, whereas the corresponding angles in the structurally similar sodium tellurolate **13c**⁶⁶ and potassium tellurolate **13f**⁶⁶ are 102.2° and 77.7°, respectively. The aryl ligand in the tellurolate **15** is planar. The Te atom deviates from the plane by 0.56 Å. The Te–Li bond length (2.82 Å) is close to the corresponding bond length in the tellurolate **5a**. The Te–C and Li–O bond lengths are 2.184 and 1.95 Å, respectively. The Te–Li–O angles are in the range of 108.8–115.2°.

In the crystal, potassium tellurolate **13f** exists as monomers. The Te–K distance (3.499 Å) is indicative of a weak interaction between the alkali metal atom and the tellurolate anion.⁶⁶ The Te–C distance is 2.15 Å and the C–Te–K angle is 77.68°. The average K–O bond length is 2.849 Å.

3. Alkaline-earth metal tellurolates

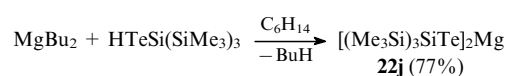
The major method for the preparation of alkaline-earth metal tellurolates **22** involves tellurololysis of di[bis(trimethylsilyl)amides] of the corresponding metals with tris(trimethylsilyl)silanetellurol **4b** in hexane at room temperature (the amide:tellurolol ratio is 1:2). In most cases, the resulting tellurolates were isolated as adducts with different Lewis bases.^{46,47}



Compound 22	M	L	<i>n</i>	Yield (%)
a	Mg	THF	2	68
b	Mg	Py	2	73
c	Mg	12-C-4	2	50
d	Ca	THF	4	46
e	Ca	Py	4	66
f	Sr	THF	4	25
g	Sr	Py	4	75
h	Ba	THF	4	52
i	Ba	Py	5	73

The reaction performed in toluene afforded compound **22d** in 85% yield.⁴⁸

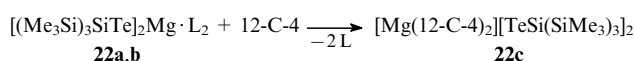
Magnesium tellurolate **22j**, which does not contain coordinating solvents, was synthesised by tellurololysis of the Mg–C bond of dibutylmagnesium.^{46,47}



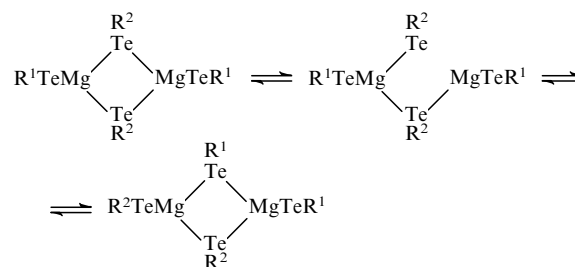
A complex of magnesium **22a** with tetrahydrofuran was prepared⁴⁷ by the reaction of mercury bis[tris(trimethylsilyl)silanetellurolate]⁴⁹ with an excess of powdered Mg in THF (the yield was 44%).

Tellurolates **22a–j** are yellow crystalline compounds, which are readily soluble in hydrocarbons and ether. These compounds are sensitive to atmospheric oxygen and moisture but can be stored under an inert atmosphere at room temperature for a long period of time. The reactions of tellurolates **22** with oxygen afforded ditelluride **7** and the reactions with water yielded the tellurol **4b**.

The tetrahydrofuran complexes slowly lose coordinated solvent molecules at room temperature and are readily converted into the pyridine complexes upon recrystallisation from pyridine.^{46,47} Treatment of magnesium tellurolates **22a, b** with 12-crown-4 resulted in replacement of both the coordinated solvent molecules (pyridine or THF) and the tellurolate ligands to form the ionic complex **22c**.^{46,47}



The ¹H NMR spectra of magnesium tellurolate **22j** in toluene-*d*₈ are indicative of the stereochemical flexibility of the latter in solutions.⁴⁷ At 20 °C, the ¹H NMR spectrum has a singlet signal, which is broadened as the temperature is decreased and is split into two peaks at –90 °C.⁴⁷ Apparently, this is due to a slow (within the NMR time scale) intramolecular exchange of the bridging and terminal ligands in the dimeric structure of the tellurolate at low temperature.⁴⁷



In the ¹²⁵Te NMR spectra of pyridine adducts **22b, e, g, i**, the signals for the ¹²⁵Te nuclei are observed in a rather narrow region from δ –1578 to –1405^{46,47} (Table 2).

The molecular and crystal structures of the tellurolates **22a**,^{46,47} **22d**^{46–48} and **22i**⁴⁷ were established by X-ray diffraction analysis.

In magnesium tellurolate **22a**, the Mg atom is tetrahedrally coordinated by two oxygen atoms of two THF molecules and two tellurium atoms.^{46,47} The Mg–Te bond lengths have similar values (2.720 and 2.714 Å), the Mg–O bond lengths are in the range of 2.035–2.038 Å and the Te–Mg–Te and O–Mg–O angles are 135.48 and 94.8°, respectively. The Te–Mg–O angles are nonequivalent, one angle at each tellurium atom being large (111.77 and 144.37°) and one angle being small (96.37 and 94.79°). This may be due to steric repulsions from the lone electron pairs of the tellurium atoms although a crystal packing effect is not ruled out.^{46,47}

The results of two independent crystallographic studies^{46,48} of calcium tellurolate **22d** agree with each other. The coordination polyhedron about the Ca atom is a distorted octahedron. The Ca–Te distance is 3.19 Å and the Ca–O distances are 2.36 and

Table 2. Data of ^{125}Te NMR spectroscopy of metal tellurolates.^a

Compound	Solvent	δ	Ref.
$(\text{Me}_3\text{Si})_3\text{SiTeLi}(\text{THF})_2$ (5a)	C_6D_6	−1622	18, 19
$(\text{Me}_3\text{Si})_3\text{SiTeLi}(\text{THF})$	C_7D_8	−1578	19
$(\text{Me}_3\text{Si})_3\text{SiTeLi}(\text{DME})$ (5b)	C_6D_6	−1641	20
$(\text{Ph}_3\text{Si})_2\text{TeLi}(\text{THF})_3$ (5e)	C_6D_6	−1337	24
$(\text{Me}_3\text{Si})_3\text{CTeLi}(\text{THF})_2$ (5c)	C_7D_8	−287	19
$(\text{Me}_3\text{Si})_3\text{GeTeLi}(\text{THF})_2$ (5d)	C_6D_6	−1515	19
$2,4,6\text{-Me}_3\text{C}_6\text{H}_2\text{TeLi}(\text{THF})_{1.5}$ (13a)	THF	−383.7	2
$2,4,6\text{-Pr}_3\text{C}_6\text{H}_2\text{TeLi}(\text{THF})_{2.5}$ (13b)	THF	−478.5	2
$2,4,6\text{-Bu}_3\text{C}_6\text{H}_2\text{TeLi}(\text{THF})_3$ (15)	THF	9.2	2
$2,4,6\text{-Me}_3\text{C}_6\text{H}_2\text{TeK}(\text{THF})_{1.3}$	THF- d_8	−296	63
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_2\text{Mg}(\text{Py})_2$ (22b)	C_6D_6	−1578	46, 47
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_2\text{Ca}(\text{Py})_4$ (22e)	C_6D_6	−1458	46, 47
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_2\text{Ca}(\text{THF})_4$ (22d)	THF- d_8	−2204	48
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_2\text{Sr}(\text{Py})_4$ (22g)	C_6D_6	−1482	46, 47
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_2\text{Ba}(\text{Py})_5$ (22i)	C_6D_6	−1405	46, 47
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_3\text{Sb}$ (23d)	C_6D_6	−584	57
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_3\text{Bi}$ (23c)	C_6D_6	−627	57
$\{[(\text{Me}_3\text{Si})_3\text{SiTe}]_2\text{Zn}\}_2$ (22k)	C_7D_8	−783, −1215	49
$\{[(\text{Me}_3\text{Si})_3\text{SiTe}]_2\text{Cd}\}_2$ (22l)	C_7D_8	−933, ^b −1338 ^c	49
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_2\text{Hg}$ (22m)	C_7D_8	−850	49
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_2\text{Zn}(\text{Py})_2$ (31a)	CDCl_3	−1469	49
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_2\text{Cd}(\text{DMPE})$ (31d)	CD_2Cl_2	−1565 ^d	49
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_2\text{Sn}(\text{DMPE})_2$ (33b)	C_7D_8	−1175 ^e	54
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_2\text{Sn}(\text{PMe}_3)$ (33a)	C_7D_8	−1165 ^f	54
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_2\text{Fe}(\text{DMPE})_2$ (34c)	C_6D_6	−1189 ^g	52
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_2\text{Fe}(\text{Cl})(\text{DMPE})$ (36)	C_6D_6	−1350 ^h	52
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_4\text{Zr}$ (46a)	see ⁱ	459	4
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_4\text{Hf}$ (46b)	see ⁱ	193	4
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_4\text{Zr}(\text{NCC}_6\text{H}_3\text{Me}_{2-2,6})_2$ (48a)	see ⁱ	203	4
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_4\text{Hf}(\text{NCC}_6\text{H}_3\text{Me}_{2-2,6})_2$ (48b)	see ⁱ	−14	4
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_4\text{Zr}(\text{DMPE})$ (49a)	see ⁱ	151, −116	4
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_4\text{Hf}(\text{DMPE})_2$ (49b)	see ⁱ	128, −349	4
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_2\text{Te} = \text{Zr}(\text{DMPE})_2$ (50a)	see ⁱ	−706, −1173, ^j −1197	4
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_2\text{Te} = \text{Hf}(\text{DMPE})_2$ (50b)	see ⁱ	−701, −1212, ^k −1250	4
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_3\text{Au}$ (41b)	C_6D_6	−1112	60
$[(\text{Me}_3\text{Si})_3\text{GeTe}]_3\text{Au}$ (41c)	C_6D_6	−1093	60
$[(\text{Me}_3\text{Si})_3\text{CTe}]_4\text{Au}_4$ (41a)	C_6D_6	−302	60
$[(\text{Me}_3\text{Si})_3\text{CTe}]_3\text{Au}(\text{PPh}_3)$ (42a)	C_6D_6	−148	60
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_2\text{Yb}(\text{TMEDA})_2$ (55a)	C_6D_6	610	55
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_2\text{Sm}(\text{TMEDA})_2$ (55b)	C_6D_6	3243	55
$(2,4,6\text{-Me}_3\text{C}_6\text{H}_2\text{Te})_2\text{Yb}(\text{THF})_2$ (54a)	THF- d_8	−280	64
$(2,4,6\text{-Me}_3\text{C}_6\text{H}_2\text{Te})_2\text{Yb}(\text{THF})_3$ (54a)	THF- d_8	−270	63
$(2,4,6\text{-Me}_3\text{C}_6\text{H}_2\text{Te})_2\text{Yb}(\text{diglym})_2$ (54d)	THF- d_8	−260	64
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_3\text{La}$ (58a)	C_7D_8	1018	56
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_3\text{La}(\text{DMPE})_2$ (59a)	C_7D_8	−894, −1074	56
$[(\text{Me}_3\text{Si})_3\text{SiTe}]_2$ (7)	C_6D_6	−678	18
$(\text{Ph}_3\text{Si})_2\text{Te}$	C_6D_6	−851	24
$(\text{Me}_3\text{Si})_3\text{SiTeSiMe}_3$ (44)	C_6D_6	−1081	18
$(\text{Me}_3\text{Si})_3\text{SiTeMe}$	C_6D_6	−637.7	18

^a The chemical shifts are given relative to Me_2Te ; ^b $J_{\text{Te}-\text{Cd}} = 1059$ Hz;^c $J_{\text{Te}-\text{Cd}} = 1821$ Hz; ^d $J_{\text{Te}-\text{Cd}} = 744$ Hz, $J_{\text{Te}-\text{P}} = 137$ Hz;^e $J_{\text{Te}-\text{P}} = 64$ Hz; ^f $J_{\text{Te}-\text{P}} = 79$ Hz; ^g $J_{\text{Te}-\text{P}} = 80$ Hz; ^h $J_{\text{Te}-\text{P}} = 78$ Hz;ⁱ the solvent is not mentioned; ^j t, $J_{\text{Te}-\text{P}} = 166$ Hz; ^k t, $J_{\text{Te}-\text{P}} = 190$ Hz.

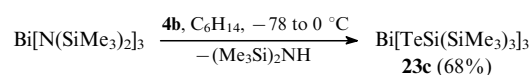
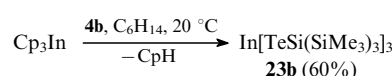
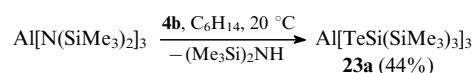
2.41 Å. The tellurium ligands are in *trans* positions. The Ca—Te—Si angle is 128.5°.

In barium tellurolate **22i**, the five pyridine ligands are located in the equatorial plane and the two tellurium ligands are in axial positions. The Ba—Te distances are 3.38 Å, the Ba—N distance (average value) is 2.888 Å and the Ba—Te—Ba angle is 171.9°.⁴⁷

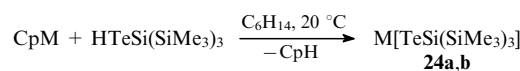
4. Aluminium, gallium, indium, antimony and bismuth tellurolates

In this section, we discuss methods for the synthesis of aluminium, gallium and indium tellurolates containing bulky substituents at the tellurium atom.

Tellurolates of Group IIIA elements were synthesised by tellurololysis of the N—M and C—M bonds with the tellurol **4b** (method 1).⁵⁷ This procedure was used for the preparation of tellurolates of Al **23a**, In(III) **23b** and Bi(III) **23c**.

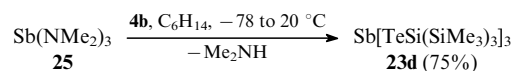


Tellurololysis of the C—M bonds afforded tellurolates of In(I) **24a** and Tl(I) **24b**. Compound **24b** was isolated as a solvate with composition $\text{Tl}[\text{TeSi}(\text{SiMe}_3)_3](\text{C}_6\text{H}_{14})_{0.125}$.

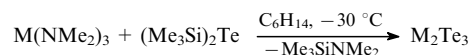


M = In (**a**, 43%), Tl (**b**, 80%).

The synthesis of Sb(III) tellurolate **23d** was performed by the tellurololysis of tris(dimethylamino)antimony (**25**) instead of the antimony trimethylsilylamide derivative.⁵⁷

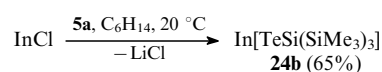
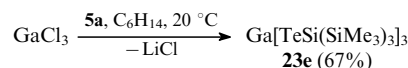


It should be noted that tris(dimethylamino) derivatives of Sb and Bi are convenient starting compounds in the low-temperature synthesis of tellurides of the corresponding elements. Thus polycrystalline Sb_2Te_3 and Bi_2Te_3 were prepared in high yields by the reactions of $(\text{Me}_2\text{N})_3\text{M}$ (M = Sb and Bi, respectively) with bis(trimethylsilyl) telluride.⁸⁰

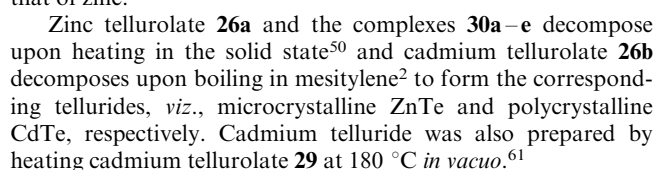


M = Sb, Bi.

Method 2 consisting in the exchange reaction of metal tellurolates with metal halides is of lesser importance due to lower yields and lesser purity of the compounds formed. Thus tellurolates of Ga(III) **23e** and In(I) **24b** were synthesised by the reactions of the corresponding chlorides with lithium tris(trimethylsilyl)silanetellurolate **5a**.⁵⁷



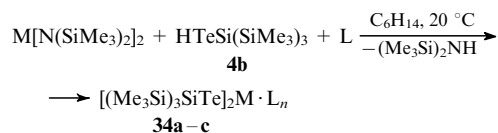
Attempts to prepare Tl(III) tellurolate by the exchange reaction have been unsuccessful because the tellurolate **5a** was oxidised to the ditelluride **7** in the course of the reaction.⁵⁷



The tellurolate **22n** forms analogous adducts with a number of other monodentate phosphorus-containing ligands, *viz.*, with Me_2PPh , Et_3P and $(\text{cyclo-C}_6\text{H}_{11})_3\text{P}$. However, these adducts were not isolated in the individual state. Their formation was judged from the presence of high-field signals in the ^{31}P NMR spectra of solutions. Weak Lewis bases, such as Ph_3P and $(\text{MeO})_3\text{P}$, do not form complexes with **22n**.⁵⁴

Pyrolysis of the tellurolates **22n,o** under a stream of nitrogen at 250 °C afforded cubic tellurides SnTe and PbTe . However, these compounds contained admixtures of small amounts of carbon and hydrogen.⁵⁴ Thermolysis of the tellurolates **22n,o** can be performed by heating them in aromatic hydrocarbons. Thus PbTe was prepared by heating the tellurolate **22o** in toluene at 100 °C for 22 h. The addition of Lewis bases to solutions of the tellurolates **22n,o** promotes their decomposition to form metal tellurides. Thus the tellurolate **22o** was quantitatively converted into PbTe upon addition of an excess of MeCN to an ethereal solution.

Like silylamides of other metals, Fe(II) and Mn(II) di[bis(trimethylsilyl)amides] reacted with the tellurol **4b** in hexane at room temperature. However, attempts to purify the resulting tellurolates failed because of their very high solubility.⁵² Tellurolysis of Fe(II) and Mn(II) silylamides in the presence of Lewis bases afforded stable crystalline adducts **34a–c**.⁵²

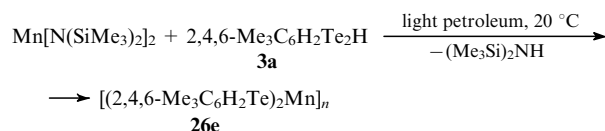


$\text{M} = \text{Mn}$; $n = 1$, $\text{L} = \text{DMPE}$ (**34a**, 79%);

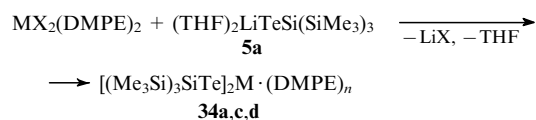
$n = 2$, $\text{L} = \text{Bu}^t\text{-C}_6\text{H}_4\text{N}$ (**34b**, 81%);

$\text{M} = \text{Fe}$, $n = 2$, $\text{L} = \text{DMPE}$ (**34c**, 71%).

The reaction of manganese silylamide with the sterically hindered arenetellurol **3a** was performed in the usual fashion and gave Mn(II) arenetellurolate **26e** in 95% yield.⁵³

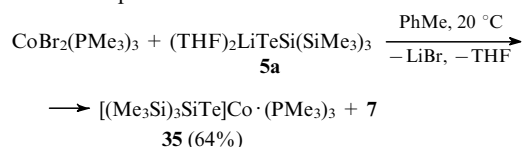


Fe(II) , Mn(II) and Cr(II) tellurolates **34a, c, d** were also prepared by the exchange reactions.⁵² Since the reactions of dihalides of these elements with lithium tellurolate **5a** afford the ditelluride **7** and insoluble pyrophoric products with unidentified structures, the exchange reactions are carried out either in the presence of Lewis bases or starting from adducts of metal halides with DMPE .⁵²



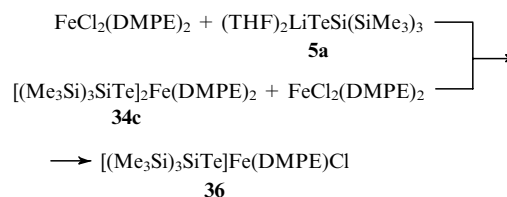
$\text{X} = \text{Cl, I}$; $\text{M} = \text{Mn}$, $n = 1$ (**34a**, 80%); $\text{M} = \text{Fe}$, $n = 2$ (**34c**, 79%); $\text{M} = \text{Cr}$, $n = 2$ (**34d**, 74%).

The reaction of lithium tellurolate **5a** with CoBr_2 yielded Co(I) tellurolate **35** as the final product due to strong reducing properties of the compound **5a**.⁵²

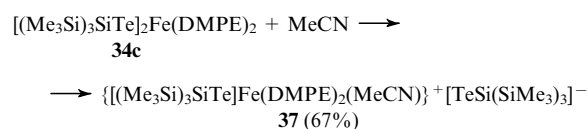


The reaction of the adduct $\text{FeCl}_2(\text{DMPE})_2$ with the tellurolate **5a** (taken in an equimolar ratio) afforded tellurolate **36** with mixed

ligands (the yield was 88%).⁵² This compound was also prepared in 82% yield by ligand exchange between the tellurolate **34c** and $\text{FeCl}_2(\text{DMPE})_2$.



The Fe(II) tellurolate complex **34c** differs from other tellurolates and their complexes in the lability of the tellurolate ligands. This is evidenced by the above-considered ligand exchange reaction as well as by the data on the conductivity of a solution of the compound **34c** in MeCN .⁵² The molar conductivity of the solution ($182 \Omega^{-1} \text{cm}^2 \text{mol}^{-1}$) corresponds to that of an 1:1 electrolyte. Recrystallisation of the complex **34c** from MeCN afforded a salt-like complex **37**.⁵²



The complexes **34a–c** are coloured crystalline compounds, which are readily soluble in hydrocarbons. These compounds are air- and moisture-sensitive but are stable under nitrogen at room temperature. Among them, Mn(II) complexes **34a, b** are the most air-sensitive (they are oxidised in a few seconds). The complexes **34a–c** cannot be sublimed because they decompose on heating ($100\text{--}200^\circ\text{C}$, 10^{-3} Torr).⁵²

The complexes **34a, b, d** are paramagnetic. The magnetic moments are $2.7\text{--}5.9 \mu_B$.⁵² In the ^1H NMR spectra, the signals for the $\text{Si}(\text{SiMe}_3)_3$ groups are broad and are shifted downfield by 2–4 ppm compared to the signals for the analogous groups in diamagnetic compounds. Unlike silane complexes **34a, b**, Mn(II) arenetellurolate complex **26e** is soluble only in coordinating solvents like other polymeric complexes. The complex **26e** is extremely air-sensitive and does not sublime.⁵³ The reaction of the tellurolate **26e** with bipyridine gave the complex $[(2,4,6\text{-Me}_3\text{C}_6\text{H}_2\text{Te})_2\text{Mn}]_2(\text{bipy})_3$, which is substantially more soluble than the initial tellurolate.

The molecular and crystal structures of Sn(II) tellurolate **22n**⁵⁴ and of tellurolate complexes of Sn **33a**,⁵⁴ Mn **34a**,⁵² Fe (**34c** and **36b**)⁵² and Co **35**⁵² were established by X-ray diffraction analysis.

In the crystal, the tellurolate **22n** has the dimeric structure.⁵⁴ The Sn_2Te_2 core is nonplanar. The $\text{Sn} - \text{Te} - \text{Sn}$ and $\text{Te} - \text{Sn} - \text{Te}$ angles are 91.65° and 78.71° , respectively. The ligands are in *cis* positions. Thus, the fact that the metal atom bears a lone electron pair is the reason for the formation of a structure which differs from that of $\{\text{Zn}[\text{TeSi}(\text{SiMe}_3)_3]_2\}_2$ (**22k**).⁴⁹ In the compound **22k**, the tellurolate ligands are in *trans* positions. The bridging $\text{Sn} - \text{Te}$ bonds (2.946 and 2.956 Å) are substantially longer than the $\text{Sn} - \text{Te}_{\text{termin}}$ bonds (2.800 Å).

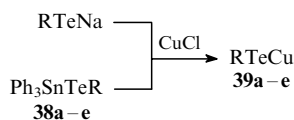
The $\text{Te} - \text{Si}$ bond length is 2.531 Å. The average $\text{Te}_{\text{bridg}} - \text{Sn} - \text{Te}_{\text{termin}}$ and $\text{Sn} - \text{Te}_{\text{bridg}} - \text{Si}$ angles are 89.27° and 107.22° , respectively.

In the complex **33a**, the geometry of the bonds about the tin atom is trigonal-bipyramidal.⁵⁴ The $\text{Te} - \text{Sn} - \text{Te}$ angle (98.86°) is somewhat larger than that in the initial tellurolate. The $\text{Te} - \text{Sn}$ bonds (2.834 and 2.849 Å) are somewhat longer than the $\text{Sn} - \text{Te}_{\text{termin}}$ bonds in the compound **22n**.

7. Copper, silver and gold tellurolates

Of copper, silver and gold tellurolates, only Cu(I) tellurolates which do not contain bulky organic radicals at the Te atom have been described previously. These compounds were prepared by the exchange reactions of sodium tellurolates with CuCl ^{84,85} or by the reactions of CuCl with triphenylstannyl tellurides **38a–c**.^{85,86}

The latter method is a procedure of choice because it allows one to obtain analytically pure tellurolates **39a–e** in higher yields.

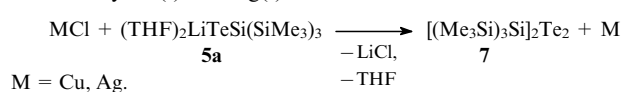


R = Et (**a**), Bu (**b**), C₅H₁₁ (**c**), Ph (**d**), 4-EtOC₆H₄ (**e**).

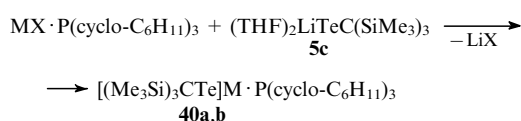
The synthesis of Cu(I) benzenetellurolate **39d** was performed with the use of the corresponding germanium and lead derivatives, *viz.*, Ph₃GeTePh and Ph₃PbTePh, instead of Ph₃SnTePh.⁸⁷

The tellurolates **39a–d** are brown insoluble powders, which have apparently the polymeric structures.^{85, 86}

Attempts to prepare Cu(I) and Ag(I) tellurolates with bulky organic radicals by the exchange reactions of metal chlorides with lithium tellurolate **5a** have been unsuccessful.⁵⁹ Since tris(trimethylsilyl)silanetellurolate **5a** is a stronger reducing agent than the usual lithium and sodium tellurolates, it is readily oxidised by Cu(I) and Ag(I) chlorides to the ditelluride **7**.

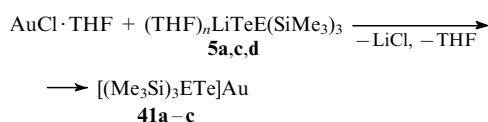


However, the reactions with the use of a weaker reducing agent, *viz.*, lithium [tris(trimethylsilyl)]methanetellurolate (**5c**), instead of the tellurolate **5a** afforded Cu and Ag tellurolates **40a, b** with the bulky organic substituent at the tellurium atom.⁵⁹ The tellurolates **40a, b** were synthesised by the reactions of the tellurolate **5c** with tricyclohexylphosphine complexes of metal halides in toluene at room temperature and were isolated as the complexes with P(cyclo-C₆H₁₁)₃.⁵⁹



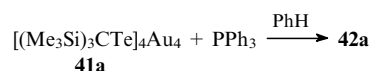
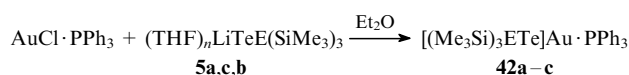
M = Cu, X = BF₄ (**a**, 51%); M = Ag, X = Br (**b**).

The synthesis of Au(I) tellurolates with sterically hindered radicals was carried out only by the exchange reactions.⁶⁰ Thus free Au tellurolates **41a–c** were prepared by the reactions of AuCl·THF with lithium tellurolates **5a, c, d**. The conditions for the preparation of Au(I) tellurolates are determined by the stability of the resulting compounds. Alkane-type tellurolate **41a** was synthesised in benzene at room temperature, while thermally unstable analogues, *viz.*, silane analogue **41b** and germane analogue **41c**, were prepared in ether at –78 °C. The latter two tellurolates were contaminated by LiCl. Attempts to purify these compounds led to their decomposition.



E = C (**41a**, 42%), Si (**41b**), Ge (**41c**).

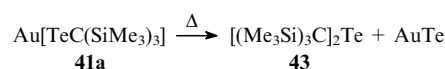
Complexes of tellurolates **41a–c** with Ph₃P were synthesised by the exchange reactions between tellurolates **5a, c, d** and the AuCl triphenylphosphine complex.⁶⁰ The reactions were carried out under conditions identical with those used in the reactions with free tellurolates. The difference was that alkanetellurolate complex **42a** was also prepared in ether. The complex **42a** was synthesised by the reaction of the tellurolate **41a** with Ph₃P in benzene.⁶⁰



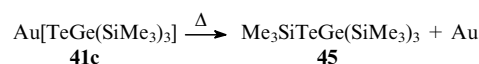
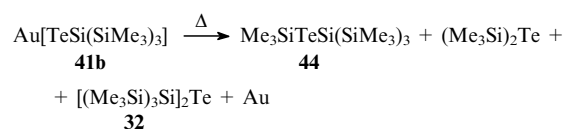
E = C (**42a**, 65%), Si (**42b**), Ge (**42c**).

The tellurolates **41a–c** are crystalline compounds, which differ substantially in thermal stabilities. Of these compounds, Au(I) alkanetellurolate **41a** is most stable, it decomposes only on melting and is resistant to water and air. Tellurolates **41b, c** decompose in solution even at –40 °C, which precludes their recrystallisation and purification. In the solid state, these compounds are resistant to water and air for at least 1–3 h.⁶⁰

The nature of the element bound to three trimethylsilyl groups affects the composition of thermal decomposition products of Au(I) tellurolates and their triphenylphosphine complexes. Only alkanetellurolate **41a** decomposes analogously to tellurolates of other metals containing the bulky (Me₃Si)₃SiTe group [Zn, Cd,⁸³ Sn, Pb,⁵⁴ lanthanides(II),⁵⁵ lanthanides(III)⁵⁶ and Zr⁵⁸] to form bis[tris(trimethylsilyl)methyl] telluride **43** and, apparently, gold telluride.



Decomposition of silane- and germanetellurolates proceeded in a different manner. Thus the tellurolate **41b** gave compound **44** as the major product. The analogous mixed germyl silyl telluride **45** was obtained from the tellurolate **41c**.



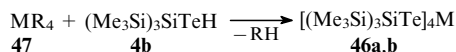
In the ¹²⁵Te NMR spectra of the tellurolates **41a–c** (see Table 2), the signals are substantially shifted upfield on going from alkanetellurolate **41a** (δ –302) to silanetellurolate **41b** (δ –1112) and germanetellurolate **41c** (δ –1093). Bonasia *et al.*⁶⁰ attributed this fact to stronger shielding of the tellurium atom in the compounds **41b, c**.

The molecular and crystal structures of the tellurolate **41a**⁶⁰ and its complex with triphenylphosphine **42a**⁶⁰ were established by X-ray diffraction analysis. The structure of the tellurolate **41a** comprises a nonplanar-square Au₄Te₄ core. The tellurium atoms occupy the vertices, each Te atom being bound to two Au atoms. The Au₄Te₄ core adopts a butterfly conformation with both wings of the butterfly being nearly coplanar. One wing comprising Te(1), Au(1), Te(2), Au(4) and Te(4) is coplanar to within 0.04 Å, while the second half consisting of Te(3), Au(2), Te(2), Au(3) and Te(4) is coplanar to within 0.09 Å.⁶⁰ The dihedral angle between these two mean planes is 144.98(6)°. All Au–Te bond lengths are 2.56 Å (average values). The Te–Au–Te fragments are almost linear; the Te–Au–Te angle is 175° (the average value). The Au–Te–Au angles vary in the range of 87–90°. The Te–C bond length in the tellurolate **41a** (2.23 Å) is virtually equal to that in the triphenylphosphine complex **42a** (2.224 Å).⁶⁰

In the complex **42a**, the Te–Au–P fragment is almost linear. The Te–Au–P and Au–Te–C angles are 174.3 and 104.1°, respectively. The Au–Te bond length (2.566 Å) is equal to that in the tellurolate **41a**. The intermolecular Au–Te contacts (3.74 Å) virtually coincide with the sum of the van der Waals radii of the elements (3.72 Å).

8. Zirconium and hafnium tellurolates

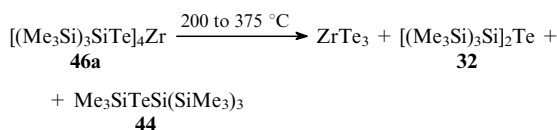
Zirconium tellurolate **46a** and hafnium tellurolate **46b** were prepared in 70%–85% yields by tellurolysis of the M–C bonds of metal tetraalkyl derivatives **47** with the tellurol **4b**.⁵⁸



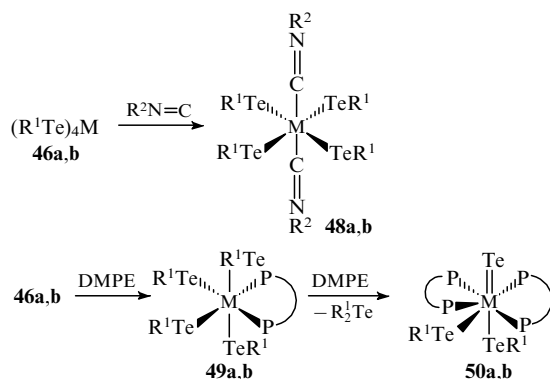
R = Bn, Bu^tCH₂; M = Zr (a), Hf (b).

The tellurolates **46a,b** are high-melting crystalline compounds (**46a** is green and **46b** is red), which can be recrystallised from hexane. These compounds readily react with water and oxygen to give the tellurol **4b** and the ditelluride **7**.⁵⁸

Heating of zirconium tellurolate **46a** *in vacuo* from 200 to 375 °C afforded zirconium telluride ZrTe₃ contaminated by admixtures of carbon and hydrogen. In this case, volatile organic thermolysis products, *viz.*, bis[tris(trimethylsilyl)silyl] telluride (**32**) and tris(trimethylsilyl)silyl trimethylsilyl telluride (**44**), as well as nonidentified compounds containing the SiMe₃ group were obtained.⁵⁸



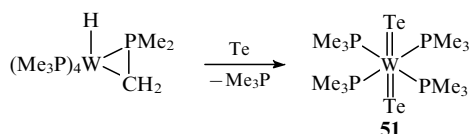
The reactions with Lewis bases are typical of the compounds **46a,b**, as of other tellurolates. Thus the reactions with 2,6-dimethylphenyl isocyanide afforded six-coordinate complexes **48a,b** of 1 : 2 composition.⁵⁸ The reactions with the bidentate DMPE ligand gave complexes **49a,b** of 1 : 1 composition.⁵⁸



R¹ = (Me₃Si)₃Si, R² = 2,6-Me₂C₆H₃; M = Zr (a), Hf (b).

Treatment of the complexes **49a,b** with 1 equiv. of DMPE afforded seven-coordinate complexes **50a,b** in 50%–80% yields as well as the telluride **32**.⁵⁸

An analogous tungsten complex **51** containing the terminal W = Te bonds was synthesised.⁸⁷



Later, complexes containing the Nb = Te,⁸⁸ Ta = Te⁸⁹ and Ge = Te⁹⁰ bonds were synthesised.

The complexes **50a,b** are red-brown crystalline air-sensitive compounds.⁵⁸ In solutions, these compounds are stereochemically fluxional. The ¹H and ³¹P NMR spectra recorded in toluene at –85 °C have sharp singlets. The signals for the SiMe₃ groups are broadened as the temperature is increased to 20 °C and coalesce at a temperature above 40 °C. The ¹²⁵Te NMR spectrum of the compound **50a** (see Table 2) has three signals at δ –706, –1173 and –1197. The high-field signals were assigned to two non-equivalent TeSi(SiMe₃)₃ groups and the low-field signal was assigned to the tellurium atom of the Zr = Te bond.

The structures of the tellurolate **46a** and the telluride **50a**⁵⁸ were established by X-ray diffraction analysis. The zirconium

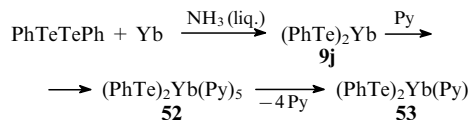
atom in the molecule of the compound **46a** is bound to four tellurium atoms and has a pseudotetrahedral coordination environment. The Te–Zr bond lengths are in the range of 2.724–2.751 Å and the Te–Zr–Te angles vary in a rather wide range from 101.6 to 115.9°, which is apparently due to repulsions between the bulky (Me₃Si)₃SiTe groups.⁵⁸

In the complex **50a**, the coordination polyhedron about the zirconium atom is a distorted pentagonal bipyramid. Two DMPE ligands and one [tris(trimethylsilyl)]siletellurolate ligand lie in the equatorial plane. The second (Me₃Si)₃SiTe ligand and the tellurium atom of the Zr = Te bond occupy axial positions. The Zr–TeSi(SiMe₃)₃ bond lengths (2.939 and 3.028 Å for the axial and equatorial ligands, respectively) are substantially larger than those in the tellurolate **46a**, while the Zr = Te bond is substantially shorter (2.650 Å).⁵⁸

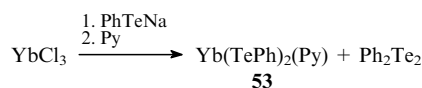
9. Lanthanide tellurolates

Recently, considerable attention has been focused on the synthesis of lanthanide tellurolates because these compounds can serve as precursors of lanthanide tellurides, which are of interest from the viewpoint of magnetic and luminescent properties.⁶⁴ The synthesis of lanthanide tellurides from elements is performed at high temperatures and is accompanied by formation of substantial amounts of admixtures due to the high oxophilicity of rare-earth elements. In this connection, the low-temperature synthesis of lanthanide tellurides from the corresponding tellurolates, which can be readily purified according to different procedures, is of particular interest.

One of the simplest tellurolates of this type, *viz.*, Yb(II) tellurolate **9j**, was synthesised by the reaction of diphenyl ditelluride with Yb in liquid ammonia.⁶⁷ Since the tellurolate **9j** is insoluble in usual organic solvents, it was isolated as a complex **52** after evaporation of ammonia and extraction of the residue with pyridine. The complex **52** is unstable and eliminates pyridine yielding the complex **53**.⁶⁷

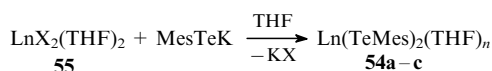


An attempt to prepare Yb(III) tellurolate by the exchange reaction of YbCl₃ with sodium benzenetellurolate led only to Yb(II) derivative **53**.



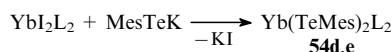
The structure of the complex **52** was established by X-ray diffraction analysis.⁶⁷ The coordination polyhedron about the Yb atom is a pentagonal bipyramid. The equatorial positions are occupied by five pyridine ligands and the axial positions are occupied by two benzenetellurolate ligands. The Te–Yb–Te and Yb–Te–C angles are 175.5 and 103.6°, respectively. The average Yb–Te, Te–C and Yb–N bond lengths are 3.282, 2.192 and 2.618 Å, respectively.

Lanthanide(II) tellurolates **54a–c** containing the bulky mesitylenetellurolate residue were synthesised by the exchange reactions of lanthanide(II) halides **55** with potassium 2,4,6-trimethylbenzenetellurolate.^{63,64} When the reactions are carried out with the use of sodium or lithium tellurolates, lithium and sodium halides formed in the reactions cannot be completely separated from the major reaction products. Potassium bromide and iodide are readily precipitated from the reaction mixtures because they are less soluble in THF than the corresponding lithium and sodium halides.⁶⁴



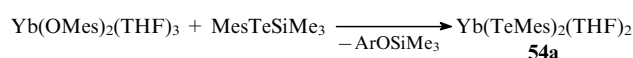
Ln = Yb, $n = 2–3$ (**54a**, 85%–93%); Ln = Sm, $n = 2$ (**54b**, 67%); Ln = Eu, $n = 2$, (**54c**, 71%), X = Br, I.

The complexes of Yb(II) tellurolate with diglyme and DME (**54d,e**, respectively) were prepared analogously.⁶⁴



L = diglyme (**d**), DME (**e**).

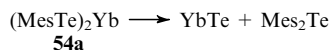
An alternative approach to the synthesis of lanthanide tellurolates, which makes it possible to prevent the formation of alkali metal halides, involves the reactions of lanthanide alkoxides (aryloxides) with mesityl trimethylsilyl telluride. The driving force for these reactions is the formation of Si–O bonds. For example, this procedure was used for the preparation of the tellurolate **54a**.⁶⁴



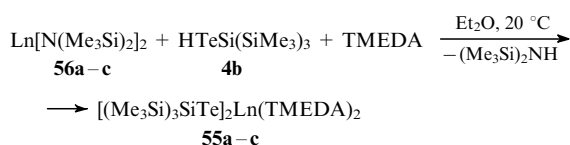
The preparative usefulness of this procedure is impaired because the resulting trimethylsilyl ethers cocrystallise with, or coordinate, tellurolates **54** and are removed with difficulty.

The tellurolates **54a–e** are coloured crystalline compounds (**54a, b, d** are orange and **54c** is dark-green). These compounds are very air- and moisture-sensitive; Yb tellurolate **54a** is diamagnetic and the tellurolates **54c, d** are paramagnetic. The effective magnetic moments are 3.06 and 6.95 μ_B , respectively.⁶⁴

Pyrolysis of the complex **54a** in boiling toluene at 250–300 °C *in vacuo* afforded dimesityl telluride and a black insoluble precipitate. Annealing of the precipitate at 900 °C for 24 h gave cubic YbTe.⁶³

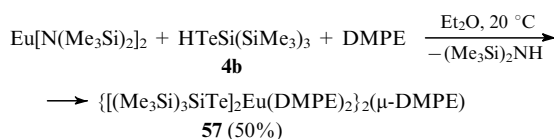


Representatives of lanthanide(II) tellurolates of yet another type, *viz.*, bis[tris(trimethylsilyl)silane]tellurolates **55a–c**, were synthesised by a slightly modified procedure of tellurololysis of silylamides of the corresponding metals **56a–c**. The reaction in diethyl ether in the presence of an excess of TMEDA afforded six-coordinate complexes **55a–c** in 40%–63% yields.⁵⁵



Ln = Yb (**a**), Sm (**b**), Eu (**c**).

The reaction performed with DMPE as a Lewis base yielded a seven-coordinate dimer **57**⁵⁵ containing the bridging DMPE ligand. The formation of the Eu(II) complex with the coordination number as large as seven is a consequence of the longer Eu–P bond compared to the Eu–N bond.⁵⁵

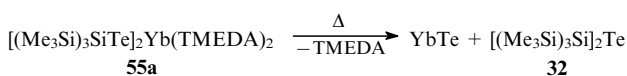


In the reaction with Eu(III) silylamide, the tellurol **4b**, which is a strong reducing agent, converted Eu(III) into Eu(II). The tellurol **4b** also reduced Yb(III) and Sm(III) silylamides.⁵⁵

The tellurolates **55a–c** are deeply coloured air- and moisture-sensitive crystalline compounds. After storage under nitrogen at room temperature for 12 h, these compounds begin to decompose. At –40 °C, these compounds remain unchanged within

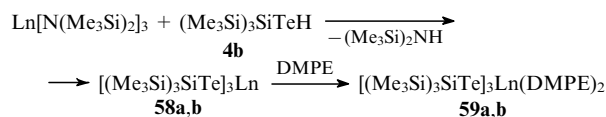
several weeks.⁵⁵ The large magnetic moments of the complexes **55c** and **57** ($\sim 8.0 \mu_B$) preclude the use of NMR spectroscopy.

Like most of trimethylsilanetellurolates of other metals, the tellurolate **55a** decomposes upon heating (150–200 °C, 10^{-2} Torr) to form the telluride **32** and YbTe contaminated by a carbon admixture.⁵⁵



The molecular and crystal structure of the tellurolate **57** was established by X-ray diffraction analysis.⁵⁵

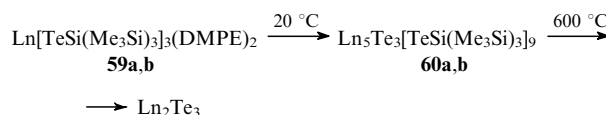
Unlike ytterbium, samarium and europium tris[di(trimethylsilyl)amides], which gave lanthanide(II) derivatives upon tellurololysis,⁵⁵ La(III) and Ce(III) silylamides were converted into lanthanide(III) tellurolates upon treatment with 3 equiv. of the tellurol **4b**⁵⁶ as evidenced by the data of ¹H and ¹²⁵Te NMR spectroscopy of the reaction mixtures. However, free La(III) and Ce(III) tellurolates **58a, b** are thermally unstable. Because of this, these compounds are isolated as complexes with DMPE **59a, b**, which are formed upon addition of an excess of the ligand to the reaction mixture. The yields of the complexes **59a, b** were no higher than 75%.⁵⁶



Ln = La (**a**), Ce (**b**).

Crystalline complexes **59** are coloured, *viz.*, **59a** is yellow and **59b** is orange. The complex **59a** is diamagnetic and the complex **59b** is paramagnetic ($\mu_{\text{eff}} = 2.28 \mu_B$). The data of dynamic multinuclear spectroscopy (¹H, ¹³C, ³¹P and ¹²⁵Te) are indicative of the stereochemical fluxionality of the compounds **59a, b** in solutions. Thus the ¹H NMR spectrum of the complex **59a** at 23 °C has a broad singlet of three equivalent tellurolate ligands and broad peaks of the methyl and methylene groups of the phosphorus-containing ligands. When the temperature is decreased to –84 °C, the tellurolate ligands give two peaks with the intensity ratio of 2:1 and the methyl groups of DMPE give two broad peaks with equal intensities. The ¹²⁵Te NMR spectra at –70 °C have two signals with the intensity ratio of 2:1. An analogous temperature dependence is also typical of the ¹³C and ³¹P NMR spectra.⁵⁶

As mentioned above, lanthanide(III) tellurolates in the absence of donor ligands decomposed to form bis[tris(trimethylsilyl)silyl] telluride **32** and a complex mixture of products from which compounds **60a, b** were isolated in low yields. The metal–tellurium clusters **60a, b** were considered⁵⁶ as intermediates in the pyrolytic conversions of the tellurolates **59a, b** into lanthanide tellurides. Pyrolysis of the compounds **59a, b** and **60a, b** *in vacuo* at 600 °C afforded lanthanide tellurides.⁵⁶



The structures of the compounds **59a** and **60b** were established by X-ray diffraction analysis.⁵⁶ The La atom in the complex **59a** has a pseudopentagonal-bipyramidal environment. Both phosphine ligands and one tellurolate ligand lie in the equatorial plane and two other tellurolate ligands are located in the axial plane. The La–Te_{eq} bond length is 3.141 Å and the La–Te_{ax} bond lengths are 3.168 and 3.170 Å, respectively. The Te_{ax}–La–Te_{ax} angle is 145.7°. Steric interactions between the equatorial tellurolate and phosphine ligands result in the difference in the La–P bond lengths (3.127, 3.143 Å and 3.208, 3.216 Å).

The molecule of the compound **60b** contains a six-membered $-\text{Te}-\text{Ce}-$ ring with the μ_3 -bridging $\text{Ce}(\text{TeR})_3$ fragments located above and below this ring. The $\text{Ce}-\text{Te}_{\text{termin}}$ bond lengths are smaller (3.026 Å) than the $\text{Ce}-\text{Te}_{\text{bridg}}$ bond lengths (3.183 and 3.235 Å). The Ce_3Te_3 bond lengths vary from 3.124 to 3.278 Å.

IV. Conclusion

As is evident from the present review, the synthesis of new metal tellurolates and their pyrolysis to the corresponding tellurides are of prime interest. It is in this field that the progress should be expected. Yet another line of investigation involves the synthesis of new stable tellurols. The stability of aromatic tellurols is determined by steric factors. Two-coordinate tellurium derivatives can be stabilised also by introducing substituents, such as COR, CH=N or N=N, which can form intramolecular coordination bonds with the tellurium atom, at the *ortho* position with respect to the tellurium-containing function. This method has not been applied in the chemistry of tellurols so far. Apparently, the synthesis of stable tellurols and intracomplex metal compounds based on these tellurols will be developed and will be the subject of further studies.

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Current problems of the electrochemistry of titanium and boron. Synthesis of titanium diboride and titanium intermetallic compounds in ionic melts

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Abstract. The current state of research into the titanium and boron electrochemistry and high-temperature electrochemical synthesis of titanium diboride and titanium intermetallic compounds with the iron triad metals is analysed. The prospects for the development of these studies are discussed. Primary attention is paid to the electrochemical properties and stability of halide systems containing titanium in various oxidation states together with boron. The bibliography includes 81 references.

I. Introduction

Studies on the electrochemical properties of titanium and boron and the processes of joint electroreduction of two or more components from ionic melts present interest for both theoretical and practical purposes. On the one hand, the results of these studies help one to understand characteristic features of multi-electron processes and to follow the development of high-temperature electrochemical synthesis; on the other hand, they underlie the development of new technologies for the production of nontraditional materials with unique properties.^{1–3} Despite the numerous publications devoted to the electrochemistry of titanium and boron as well as titanium diboride, data on the forms of their existence, the mechanisms of joint and separate electroreduction in ionic melts (especially chloride and fluoride melts) are quite scarce and contradictory. These processes serve as the basis for the technology of the electrochemical production of titanium, boron, titanium diboride and titanium intermetallic compounds; therefore, studies in this field are topical for the development of modern high-temperature electrochemistry.

II. Electrochemical behaviour of titanium

Electrolysis of titanium melts is a promising method for the production of metallic titanium and the synthesis of high-melting compounds (carbides, borides, silicides, intermetallic compounds) based on it. However, the complex pattern of the behaviour of

titanium-containing melts accounts for the stringent requirements in the process engineering and selection of the salt systems. Thus it is necessary to study systematically and comprehensively the electrochemical and chemical properties of titanium in various oxidation states in molten electrolytes.

1. Electrolysis of titanium-containing melts

Titanium metal is mainly produced either by electrolysis of the melts of titanium oxygen compounds, fluorides or chlorides or by electrolytic refinement of crude titanium and its compounds.

Electrolysis of oxygen compounds of titanium has several advantages over electrolysis of other compounds, first of all, ready availability and low cost of the raw materials, namely, titanium dioxide and alkali metal titanates. These advantages also include simplicity of the equipment and the environmental safety of the process. Numerous publications have been devoted to the electrolysis of TiO_2 in melts of alkali metal chlorides or fluorides or potassium (sodium) hexafluorotitanate. The low solubility of titanium dioxide in various melts (0.02%–0.07%) precludes its use for the production of titanium. In addition, during electrolysis of the NaCl – K_2TiF_6 melt containing titanium dioxide, the dioxide is reduced at the cathode to Ti_2O_3 . This is accompanied by the formation of a non-decomposing precipitate near the cathode. Electrolytic preparation of pure titanium in this system is impossible because of the formation of titanium monoxide at the cathode.

Study of a similar system based on calcium chloride showed that in this case, titanium metal is formed in a secondary process, namely, reduction of TiO_2 at the cathode by calcium produced in electrochemical processes. Normal operation of the electrolytic cell requires a low concentration of TiO_2 in the electrolyte, its continuous feed to the cell and replacement of the electrolyte after it has been saturated with CaO . Electrolysis of TiO_2 dissolved in molten alkali metal borates or phosphates has been considered.^{4,5} The researchers point to the necessity of additional purification of the resulting metal from oxygen.

Thus, the use of oxygen compounds for the electrolytic preparation of titanium and the synthesis of its derivatives is hardly promising, because lower titanium oxides, which contaminate the product, are formed at the cathode.

Calculations and experimental results show that electrolysis in molten salts of oxygen-containing acids, alkalis, oxides or many other melts does not ensure the preparation of pure titanium. The range of molten media is mainly limited to metal halides. However, these compounds, too, are not all suitable for electrolysis. Indeed, metals of Group IV and of subsequent Groups of the

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Periodic Table are usually much more electropositive than titanium; hence, halides of these metals are, most often, thermally unstable or possess low electrical conductivity. Alkali and alkaline earth metal chlorides and fluorides are best suited for this purpose.

Numerous studies have been devoted to the development of a method for the production of titanium by electrolysis of fluoride melts. Potassium and sodium fluorotitanates are recognised as the most promising titanium raw materials.^{5–9} It is not expedient to subject pure hexafluorotitanate to electrolysis. During electrolysis, it is reduced to K_2TiF_5 and, after that, the electrodes become passivated.

The system subjected to electrolysis is usually K_2TiF_6 dissolved in molten salts. An electrolyte consisting of potassium, lithium and sodium fluorides has been proposed as the medium for the electrolytic production of titanium.⁶ However, a process carried out in a purely fluoride melt can result in passivation of the anode by a gas film (anodic effect). In addition, since this melt is highly corrosive, the equipment soon goes out of service. Therefore, a mixture of alkali metal chlorides and potassium fluorotitanate has been proposed as the electrolyte for the electrolysis of titanium fluoride derivatives.^{5–9} When titanium metal reacts with a chloride–fluoride melt, a black crust insoluble in a mixture of alkali metal chlorides and fluorides is formed gradually on its surface. The existence of a fluoride complex of divalent titanium, $M_2[TiF_4]$, has been reported.⁸ Insoluble compounds formed at the cathode contaminate the cathodic product, which casts doubt on the expediency of using chloride–fluoride–fluorotitanate melts for producing pure titanium.

Preparation of titanium from titanium chlorides presents substantial interest. Titanium, having a variable valence, forms several chlorides, namely, $TiCl_4$, $TiCl_3$ and $TiCl_2$. The most readily available compound is $TiCl_4$; the production and purification of this compound on an industrial scale is now a routine practice. In the electrolysis of alkali or alkaline earth metal chlorides, $TiCl_4$ is either supplied onto the electrolyte surface or bubbled through the electrolyte, either neat or with a flow of an inert gas (see, for example, Refs 10, 11). Titanium tetrachloride is poorly soluble in molten alkali metal chlorides (the solubility is up to 2% at 1073 K); therefore, this technology does not provide high output. If the current density at the cathode is high, the alkali metal will be evolved together with titanium. It has been proposed to make use of this phenomenon, *i.e.* to carry out electrolysis at current densities sufficient for the evolution of the alkali metal. In this case, titanium tetrachloride is partially reduced by the reducing metal.

The solubility of titanium chlorides in which the metal oxidation number is less than four is substantially higher than the solubility of titanium tetrachloride. This fact has been taken into account in the development of a method for the preparation of titanium by electrolysis of its lower chlorides dissolved in chloride melts.¹⁰ Salts used in this process should be relatively pure as regards oxygen and elements that are more electropositive than titanium. Lower titanium chlorides can easily be prepared from titanium tetrachloride; they are readily soluble in molten salts and fairly stable at temperatures of electrolysis. These compounds possess high electrical conductivities and relatively low volatilities; however, they are chemically reactive. Under conditions of electrolysis, lower titanium chlorides react with almost any standard refractory lining material; evidently, the rate of such a reaction would depend substantially on the presence of oxygen in the cell.

A method has been proposed¹⁰ for continuous production of titanium by electrolysis of $TiCl_3$ and $TiCl_2$, which are formed in a separate reactor upon the reaction of titanium tetrachloride with hydrogen. To simplify this method, the synthesis of lower titanium chlorides and electrolysis can be carried out in one vessel. In this case, electrolysis occurs in two stages, namely, reduction of $TiCl_4$ to $TiCl_2$ and $TiCl_3$ at an auxiliary cathode and reduction of lower titanium chlorides to the metal on the main cathode.¹¹

It has been considered until recently that the cathodic process is a secondary reaction, consisting in the reduction of titanium by the alkali metal, which was evolved at the cathode. However, recent studies demonstrated that, under certain conditions, direct electrochemical discharge of the titanium ions occurs at the cathode. For this discharge to be possible, it is required, first of all, that the concentration of titanium ions in low oxidation states in the near-cathode layer be sufficiently high.

Electrolysis of titanium chlorides is carried out under the atmosphere of an inert gas (argon, helium). For rough purification of the electrolyte from moisture and occluded gases, the electrolytic cell is usually evacuated at 400–650 °C to a residual pressure of 10–20 mm Hg. Preliminary electrolysis at an auxiliary cathode with a voltage on the cell terminals equal to 1.8–2.0 V is also employed for this purpose. Other methods for the purification of the electrolyte also exist. To remove moisture, dry hydrogen hydrochloride is passed through the melt for a short period of time. Oxygen can be removed by passing tetrachloromethane through the melt. The cathode materials used in these processes are mainly tungsten, molybdenum, silver, steel or nickel. The best adhesion of the titanium deposits has been noted for silver cathodes; however, this metal is expensive. Liquid cathodes made of zinc or lead can hardly find wide application because they form intermetallic compounds with titanium, which are difficult to destroy.

During electrolysis of titanium chlorides, chlorine formed at the anode oxidises lower titanium chlorides present in the anode chamber to give $TiCl_4$, which is distilled off together with chlorine. In addition, electrolytic oxidation of $TiCl_2$ and $TiCl_3$ at the anode, leading to the same consequences, is possible. Meanwhile, titanium tetrachloride entering the cathode chamber would react with titanium metal, which would result in the loss of the pure metal. Therefore, the cathode and anode chambers should be separated by a diaphragm. The problem of selection of the diaphragm materials has not been solved yet, due to the high chemical reactivity of lower titanium chlorides; research along this line is now in progress. For instance, it has been proposed to manufacture the diaphragm from alumina (these diaphragms are not virtually metallised under certain conditions) or graphite (in this case, half-sintered metal is formed at the cathode at 1305 °C).^{4,5} It should also be noted that working with titanium chloride requires a high voltage at the electrolytic cell terminals (usually 9–12 V); therefore, power expenditure per unit product is high.

Whereas the expediency of one or another method for electrolytic production of titanium is still debated and electrolysis has not been adopted on an industrial scale, the efficiency of electrolytic refining of titanium is beyond doubt. The soluble anode can be manufactured from any material possessing electronic conduction, capable of reacting with the electrolyte and insoluble in it. Titanium forms lots of systems and compounds with such properties.

Powders with various chemical and grain-size compositions are currently produced from titanium by electrolysis with a soluble anode in the melts of alkali and/or alkaline earth metal chlorides. Electrolytic refinement of titanium is carried out using various electrolytes, namely, $NaCl$, $NaCl-KCl$, $NaCl-SrCl_2$, $NaCl-BaCl_2$, $KCl-LiCl$ and $KCl-NaCl-MgCl_2$. Electrolytes based on sodium chloride, an equimolar mixture of sodium and potassium chlorides and the $NaCl-KCl-MgCl_2$ ternary system are the most widespread. The electrolytic refinement of titanium consists in the anodic dissolution of the metal to be refined and cathodic deposition of the pure metal. Electrochemical investigations show that in the temperature range 750–850 °C, which is the best for the refinement, titanium passes from the anode to the melt as Ti^{2+} . An increase in the temperature or in the anode current density increases the yield of the Ti^{3+} ions. Upon anodic dissolution, titanium passes into the melt mostly in an ionic form, the average oxidation state being 2.02–2.13.

The total content of impurities, which are to be eliminated during titanium refinement (oxygen, nitrogen, hydrogen, carbon, iron) is normally relatively low, 1 mass %–2 mass %. In the studies dealing with the electrochemical refinement of titanium, special role belongs to the purification from oxygen. When the process is carried out under precisely pure conditions, the only way by which oxygen can pass from the anode to the cathode is the formation of the titanyl ion TiO^{2+} . Thermodynamic calculations indicate that the probability of formation of this ion is fairly low even at high concentrations of oxygen in the anode material. A significant role in the production of a high-quality powder at the cathode is played by the ratio of the titanium concentration in the electrolyte to the current density at the cathode. The best powders are obtained if this ratio ranges from 2 to 3. The anode current density during electric refinement should be 4–8 times lower than the cathode current density. In this case, divalent titanium disproportionates in the electrolyte (especially in the near-anode layer), resulting in the formation of highly dispersed metallic titanium in the bulk of the melt. The use of the refining tank for the synthesis of titanium borides is not expedient, due to the formation of an uncontrollable amount of dispersed titanium, which disrupts the stoichiometry of the product.

Various opinions concerning the role of fluoride ions have been expressed in studies dealing with the electrolytic refinement of titanium in mixed chloride–fluoride electrolytes (see, for example, Ref. 12). Some researchers believe that the addition of fluorides has a negative effect on the electrolysis characteristics (the anode material disintegrates, the current yield decreases). Conversely, some other investigators believe that fluoride additives are favourable for the performance characteristics of the process. It should be noted that anodic dissolution of titanium in a mixed chloride and fluoride electrolyte affords poorly soluble compounds of divalent titanium, which contaminate the cathodic product.

The foregoing demonstrates that halide melts are the most suitable systems for the high-temperature electrochemical synthesis of titanium compounds and production of the pure metal. However, when using chloride melts, one should create conditions for increasing the solubility of TiCl_4 and suppressing disproportionation, and when mixed chloride–fluoride electrolytes are used, the formation of poorly soluble divalent titanium fluoride should be prevented and the electroreduction of titanium complex ions should be performed in one stage.

2. State of titanium in halide melts

a. Thermodynamics of titanium-containing halide systems

Titanium halides react with titanium metal in molten alkali metal halides. The following heterogeneous equilibrium is established with time:



As a rule, one oxidation state of titanium predominates in the melt; the ratio of various oxidation states depends on the temperature and the nature of the salt acting as the solvent. Heterogeneous equilibrium (1) can be characterised by several parameters such as equilibrium constant, apparent standard potentials $E^*(\text{Ti}^{2+}/\text{Ti})$, $E^*(\text{Ti}^{3+}/\text{Ti})$ and the formal redox potential $E^*(\text{Ti}^{3+}/\text{Ti}^{2+})$.^{13,14} The equilibrium potential of the titanium electrode (E) would be simultaneously the potential of the Ti/TiCl_2 , Ti/TiCl_3 and $\text{TiCl}_2/\text{TiCl}_3$ systems. The apparent standard potentials and the formal redox potential are related (in accordance with the Luter rule) by the equation¹³

$$3E^*(\text{Ti}^{3+}/\text{Ti}) = E^*(\text{Ti}^{3+}/\text{Ti}^{2+}) + 2E^*(\text{Ti}^{2+}/\text{Ti}). \quad (2)$$

The task of finding these values reduces to the determination of the number of ionic forms of titanium in the potential measurement.

The equilibrium potentials of titanium in an equimolar mixture of potassium and sodium chlorides in the temperature

range 973–1148 K have been reported.¹⁴ The temperature variations of $E^*(\text{Ti}^{2+}/\text{Ti})$ and $E^*(\text{Ti}^{3+}/\text{Ti})$ are described by the following empirical equations:

$$E^*(\text{Ti}^{2+}/\text{Ti}) = -2.38 + 4.8 \times 10^{-4} T, \quad (3)$$

$$E^*(\text{Ti}^{3+}/\text{Ti}) = -2.16 + 3.2 \times 10^{-4} T. \quad (4)$$

The equilibrium potentials of titanium measured at 843 K vs. chlorine reference electrode amount to $E^*(\text{Ti}^{2+}/\text{Ti}) = -1.97$ V and $E^*(\text{Ti}^{3+}/\text{Ti}) = -1.90$ V.

In order to identify the full picture of equilibrium between metallic titanium and a chloride melt containing minor amounts of Ti^{4+} , in addition to Ti^{2+} and Ti^{3+} , the $E^*(\text{Ti}^{4+}/\text{Ti}^{3+})$ redox potential, and, hence, the standard $E^*(\text{Ti}^{4+}/\text{Ti})$ potential should be determined. The temperature variation of this potential in the $\text{KCl}-\text{NaCl}$ melt is described by the equation

$$E^*(\text{Ti}^{4+}/\text{Ti}) = -1.91 + 3.84 \times 10^{-4} T. \quad (5)$$

Various values for the arbitrary formal redox potential $E^*(\text{Ti}^{3+}/\text{Ti}^{2+})$ in a molten equimolar mixture of sodium and potassium chlorides, determined experimentally by potentiometric titration, have been reported in the literature: -1.807 ($T = 973$ K), -1.762 ($T = 943$ K), -1.726 V ($T = 984-1130$ K). The $E^*(\text{Ti}^{3+}/\text{Ti}^{2+})$ value calculated in accordance with the Luter rule from Eqn (2) using the known experimental $E^*(\text{Ti}^{3+}/\text{Ti})$ and $E^*(\text{Ti}^{2+}/\text{Ti})$ values is described by the equation

$$E^*(\text{Ti}^{3+}/\text{Ti}^{2+}) = -1.710 - 0.17 \times 10^{-4} T. \quad (6)$$

It can be seen that the theoretical value of the potential $E^*(\text{Ti}^{3+}/\text{Ti}^{2+})$ depends slightly on the temperature and at 1000 K it is equal to -1.727 V vs. chlorine reference electrode.

The known standard potentials for the Ti^{3+}/Ti and Ti^{4+}/Ti systems were used to calculate the $\text{Ti}^{4+}/\text{Ti}^{3+}$ redox potential and to elucidate its temperature dependence

$$E^*(\text{Ti}^{4+}/\text{Ti}^{3+}) = (-1.473 + 5.86 \times 10^{-4} T) \pm 0.007. \quad (7)$$

The variation of the equilibrium potential of titanium as a function of the concentration of titanium ions in the melt have shown that in alkali metal chloride melts, titanium is equilibrated with the Ti^{2+} and Ti^{3+} ions. Knowing the standard electrode potentials of the Ti^{2+}/Ti and Ti^{3+}/Ti systems, it can be written¹⁵

$$\log K = \log \frac{[\text{Ti}^{2+}]^3}{[\text{Ti}^{3+}]^2} = \frac{6 \times 10^4}{1.984T} [E^*(\text{Ti}^{3+}/\text{Ti}) - E^*(\text{Ti}^{2+}/\text{Ti})] \quad (8)$$

Thus the equilibrium constants for the reaction



can be calculated. For lithium chloride,

$$\log K = -4.234 + \frac{6351}{T}, \quad (10)$$

for potassium chloride,

$$\log K = -6.956 + \frac{8165}{T}, \quad (11)$$

for cesium chloride,

$$\log K = -6.956 + \frac{7440}{T}, \quad (12)$$

and for the $\text{KCl}-\text{NaCl}$ melt,

$$\log K = -5.038 + \frac{6774}{T}. \quad (13)$$

As the temperature increases, the equilibrium constant decreases, which points to disproportionation of Ti^{2+} . If the temperature remains constant, the equilibrium constant decreases with an increase in the radius (r) of the alkali metal cation of the molten salt, *i.e.* the equilibrium shifts towards disproportionation of Ti^{2+} . This dependence has the form

$$\log K = \frac{8468}{T} - \frac{1512}{Tr} - 9.073 - \frac{3.175}{r}. \quad (14)$$

A substantial number of studies have been devoted to the process of disproportionation (see, for example, Refs 16–18). The oxidation states of titanium can be described by four disproportionation reactions



These reactions occur simultaneously and are heterogeneous. The outcome depends on the experimental conditions, namely, temperature, composition of the atmosphere, surface area, and so on. It has also been noted that Ti^{3+} rapidly disproportionates in the lithium chloride melt. When lithium chloride is replaced by cesium chloride, the stability of Ti^{3+} increases. In halide melts, titanium metal reacts with the components of the melt. When the radius of the alkali metal cation in the melt is greater than the radius of potassium, Ti^{2+} ions appear; they disproportionate to give highly dispersed titanium metal; therefore, a high concentration of Ti^{2+} cannot be attained. In the case where the LiCl melt is used, the solution becomes rich in Ti^{2+} .

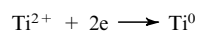
The main reaction which proceeds at a substantial rate in molten potassium chloride is



Thus, vast experimental data have been accumulated and a number of important practical conclusions have been drawn concerning the thermodynamics of titanium-containing chloride melts, namely, the equilibrium and standard potentials of titanium in various oxidation states were determined; the equilibrium constants for chemical reactions in the melts were calculated; and disproportionation of titanium ions in low oxidation states was detected. However, in some cases, the thermodynamic functions are rough. For example, the measurement of the equilibrium potentials of the Ti^{4+}/Ti , Ti^{3+}/Ti and Ti^{2+}/Ti systems does not appear quite correct because actually, the near-electrode layer would contain titanium ions in various oxidation states formed in chemical reactions. In addition, thermodynamic characteristics do not provide exhaustive information on the mechanism of electroreduction of titanium, which needs to be known for performing successful electrolysis of titanium-containing melts. Therefore, in addition to the thermodynamic characteristics, the mechanism of the electroreduction of titanium has also been studied.

b. Mechanism of the electroreduction of titanium

It is not always possible to interpret unambiguously experimental data characterising the mechanism and kinetics of electroreduction and electrooxidation of titanium complexes. The complexity of interpretation of these data is due to the fact that side processes, not related directly to electrode reactions, proceed in the melt. In some studies, it is suggested that titanium metal is evolved in the reaction of titanium-containing complex ions with an alkali metal, resulting from reduction at the cathode. In other studies, it is suggested that two processes of titanium deposition occur simultaneously; titanium is formed in the primary electrochemical process at the cathode



and in a secondary chemical process, thermal reduction by sodium in the bulk of the electrolyte. Some researchers believe that in the case of chloride melts, an alkali metal reduces Ti^{2+} ions (see, for example, Refs 19, 20) and in the chloride–fluoride melts, the species being reduced is Ti^{3+} . Titanium in higher oxidation states is preliminarily reduced to lower oxidation states by either electrochemical or chemical reactions. However, voltammograms characterising the cathodic evolution of titanium display a wave corresponding to the discharge of titanium complexes.¹⁸ In several studies (see, for example, Ref. 21), the mechanism of direct

reduction of TiCl_3 to the metal without the intermediate formation of Ti^{2+} has been assumed. A study of the electroreduction of TiCl_3 in the LiCl, CsCl and KCl–LiCl systems at 973 K by linear sweep voltammetry demonstrated that the reduction of Ti^{3+} in all three electrolytes involves the stage of recharge to Ti^{2+}



The stepwise character of the process was pointed out in several other publications.^{18, 22–26}

Electroreduction of titanium tetrachloride in the BaCl_2 – CaCl_2 – NaCl ,²² LiCl – KCl , KCl – LiCl – NaCl ²³ and BaCl_2 – KCl – LiCl ²⁴ melts occurs as three consecutive stages:



The voltammograms for the electroreduction of Ti^{2+} in the KCl – NaCl – TiCl_3 – NaF – $\text{Ti}(\text{solid})$ melt exhibit one clear-cut wave at potentials of $-(2.53–2.6)$ V vs. chlorine reference electrode, which corresponds to the electroreduction of titanium.²⁰

The diffusion coefficients for titanium in chloride melts have been calculated;^{21, 26, 27} in KCl – NaCl at 973 K, they are equal to 3.72×10^{-5} and $1.94 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ for Ti^{3+} and Ti^{4+} , respectively. The diffusion coefficient for divalent titanium in the LiCl – KCl melt at 773 K amounts to $(1.54 \pm 0.17) \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ (see Ref. 28).

Thus, certain progress in the study of chloride and chloride–fluoride titanium-containing melts has been achieved by now; however, the overall picture of the electrochemical and chemical behaviour of titanium in various oxidation states does not appear clear and unambiguous. There is no consensus of opinion on the mechanism of the cathodic process. Several aspects of the stability of systems containing titanium in various oxidation states are poorly documented, namely, which of the lower titanium chlorides is more stable and what is the limiting concentration up to which this stability is retained; what are the concentration limits for the stability of other titanium-containing species; what are the ratios of Ti^{2+} to Ti^{3+} in the melt at which the system remains stable, *i.e.* no disproportionation reactions occur, and what are the ways of suppressing these reactions. Answers to these questions present considerable interest from the practical viewpoint, because they would make it possible to create conditions for long continuous operation of an electrolysis cell and to estimate the influence of unstable titanium compounds on the technological parameters of the production of titanium and of the electrochemical synthesis of titanium compounds.

III. Electrochemical behaviour of boron

The electrochemical method permits preparation of high-purity boron in large quantities. In the first studies, carried out 70 years ago, elementary boron was produced by the electrolysis of borides. The product contained not more than 60%–70% of the target material, 20%–30% of oxygen and 5%–6% of the metal that served as the cathode material. When magnesium boride was used, elementary boron was formed at the cathode together with low-stability magnesium borides; the latter can be partially removed by treatment of the cathodic product with an acid.

Currently, oxygen-containing compounds of boron and boron halides are mainly used for the electrolytic production of boron. Numerous studies have been devoted to the electrolysis of oxygen compounds of boron. In all systems boron oxide serves as the source of boron.²⁹ When oxygen-containing melts are used, the process does not give high-purity boron because the product is contaminated by substantial amounts of oxygen. This is the major drawback of this method.

The use of purely fluoride electrolytes is limited because fluoride melts are corrosive and toxic.³⁰ The use of mixed chloride–fluoride electrolytes presents considerable interest; in this case, high-purity boron free from oxygen impurities can be obtained at relatively low temperatures, the corrosiveness of the melts being relatively low.^{30–36}

Several studies have been devoted to the mechanism of electroreduction of boron.^{37–46} The cathodic processes occurring during the electrodeposition of boron from a purely fluoride ($\text{LiF} - \text{KF} - \text{KBF}_4$) and fluoride–oxide ($\text{LiF} - \text{KF} - \text{B}_2\text{O}_3$) electrolytes have been studied.^{36,37} It was shown that in a purely fluoride melt, boron is reduced directly from the tetrafluoroborate complex anion in one step involving three electrons. In the $\text{LiF} - \text{KF} - \text{B}_2\text{O}_3$ system, boron oxide reacts with fluorine present in the electrolyte to give the $[\text{BF}_4]^-$ anion and oxyfluoride complexes, mainly those with a molar ratio of oxygen to boron equal to 1.66. The ratio of the concentrations of $[\text{BF}_4]^-$ and the oxyfluoride complexes is 0.1. The potentials of deposition of boron from these two electrochemically active species differ by 0.47 V, and the diffusion coefficient for $[\text{BF}_4]^-$ calculated from experimental data is $4.4 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ at 973 K.

In a study of the electrochemical properties of boron in chloride and chloride–fluoride melts, the solubility of BCl_3 in the CsCl melt was found to be $1.74 \times 10^{-1} \text{ mol.}\%$ at 973 K; thermodynamic functions of BCl_3 in CsCl were calculated, the equilibrium potentials of boron were determined and equations for them were reported.³² The equilibrium potentials of boron shift to the negative region in chloride–fluoride electrolytes, indicating that the reactivity of boron ions in fluoride complexes is lower than that in chloride complexes.^{31,32,34} The calculation of the average number of fluoride ions (three or four) in the complex ions by the procedure proposed by Ivanovsky *et al.*³¹ attests indirectly that in the temperature range studied, most of the boron ions in the chloride–fluoride melts occur in the $[\text{BF}_4]^-$ and $[\text{BF}_3\text{Cl}]^-$ groups. Based on the results of voltammetric studies, Chemezov³² arrived at the conclusion that electroreduction of boron in a chloride–fluoride electrolyte occurs by a one-stage mechanism; conversely, Tsiklauri *et al.*⁴¹ have discovered a recharge stage, $\text{B}^{3+} \rightarrow \text{B}^+$, followed by the discharge of B^+ at the cathode to give elementary boron.

For low current densities, charge transfer is the rate-determining step in the electrodeposition of boron, whereas for high current densities, the rate of the process is limited by the diffusion of boron from the bulk of the melt towards the surface. This is typical of both chloride and chloride–fluoride melts. A somewhat different opinion on the kinetics of electroreduction of boron is held by the authors of another study,³⁹ who claim that the rate of this process is limited by mass transfer over a broad range of polarisation rates and that the proper electrochemical stage is irreversible.

Examination of the switching-on curves (potential–time) for various polarisation current densities demonstrated³² that neither a homogeneous chemical reaction (*e.g.*, dissociation of the $[\text{BF}_4]^-$ or $[\text{BCl}_4]^-$ complexes), nor chemisorption of electrically active species on the electrode surface retards the reduction of boron in the melts studied. The $\log D - I/T$ plots (D is the diffusion coefficient of boron calculated from the Sand equation using the results of chronopotentiometric measurements, I is the current density and T is the temperature) in the temperature range 932–1123 K are straight lines; the calculation of the activation energy gives $35.5 \pm 2.3 \text{ kJ mol}^{-1}$ (see Refs. 31, 32). However, in another study,⁴¹ it has been stated that electrochemically active species (mainly molecular boron fluoride) are produced in a chloride–fluoride melt upon dissociation of boron complexes coupled with homogeneous exchange reactions between the initial complexes and the electrolyte.

Study of the solubility and the kinetics of electroreduction of BF_3 in the $\text{KCl} - \text{NaCl}$ melt at 973 K in the range of BF_3 pressures of $(1.01 - 5.05) \times 10^5 \text{ Pa}$ showed the presence of two sorts of electrochemically active species.⁴⁴ This accounts for the two

waves displayed on the voltammograms; the heights of the waves increase proportionally to the pressure. In the opinion of the researcher cited, the first wave corresponds to a two-electron transition involving BF_3 ; at the potential of the second wave, the product formed in the first stage is reduced, the mixed chloride–fluoride complex $[\text{BCl}_x\text{F}_3]^{x-}$ being involved in the cathodic process.

Thus, despite the large number of publications dealing with the electrochemical properties of boron, no clear views on the mechanism and kinetics of its electroreduction from halide electrolytes have been developed so far.

IV. Methods for the synthesis of titanium diboride. High-temperature electrochemical synthesis

The principal methods used to synthesise high-melting compounds have been classified²³ into the following groups: (1) direct synthesis from elements, (2) synthesis from solutions in melts, (3) thermal reduction of metal oxides by metals, (4) reduction of oxides and other compounds by nonmetals and their derivatives, (5) gas-phase synthesis, and (6) electrolysis of salt melts. This classification is also applicable to the methods used to prepare titanium diboride.

Direct synthesis from elements is based on the reaction of a metal (titanium) with a nonmetal (boron), which can be carried out (at various physical states of the elements) by fusing, sintering or hot pressing. In accordance with this, some researchers suggest conducting this synthesis by keeping samples of pure titanium for 5 h in amorphous boron at a temperature of 1273 K and a residual pressure of 0.133 Pa; according to other researchers, mixtures of titanium and boron powders should be heated by an electric discharge.⁴⁷ The advantages of this method include the possibility of preparing large amounts of the product, the possibility of hot moulding the product in order to manufacture the required articles, simplicity of the equipment and the relatively short time needed for the synthesis. The facts that it is difficult to prepare borides with a precise composition and that the temperature of the process is too high are drawbacks of the direct synthesis.

The synthesis from solutions in melts involves a chemical reaction between transition metal atoms and nonmetal atoms (or molecules of a nonmetal compound) occurring in molten salts or metals. An example is provided by the synthesis of titanium borides in an iron melt at temperatures of 1673–2273 K. This route can afford both pure, doped and complex (mixed) compounds. In addition, it ensures the recovery of metal serving as the solvent and is relatively simple. The drawbacks of this method include low yields and high cost of the product, caused by the large amounts of salts and metallic solvents consumed, the possible contamination of the product by the solvent, the necessity of vigorous stirring of solutions in melts in order to obtain homogeneous compounds and high temperatures of the process.

The thermal reduction of oxides consists in the reduction of titanium and boron oxides by a reducing metal (in the presence of oxygen-evolving compounds) to give borides at temperatures of 2273–3273 K over periods of 2–3 min. This is the simplest method among those listed above. However, it is not in general use because of the low quality and inhomogeneous composition of the products obtained in this way and also because it is difficult to isolate the product from the slag.

The fourth method is based on the reduction of oxides and other compounds by nonmetals and their compounds. For instance TiB_2 can be prepared by the reaction of BCl_3 with highly dispersed titanium at 873–1373 K. The advantages of this method include the possibility of preparing large quantities of the product and the fact that oxides and other readily available compounds of titanium and boron are suitable for the synthesis. The main drawback of this method is that the products of the synthesis are contaminated by metal and nonmetal oxides.

Gas-phase synthesis includes decomposition of chemical compounds followed by reactions of the fragments (both ions or

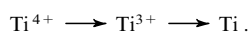
radicals and the atoms or molecules produced upon their reduction) occurring in the gas (vapour) phase to give high-melting compounds. A method for the synthesis of titanium diboride by the reduction of a vapour–gas mixture consisting of TiCl_3 and BCl_3 by hydrogen at temperatures of 1273–3773 K and pressures of 1–3 atm has been described.⁴⁷ The major advantage of this method is the possibility of preparing single crystals and coatings on various materials. The inhomogeneity of the phase composition and the relatively low yields of the products as well as complexity of the equipment and the processes involved are drawbacks of this technique.

High-temperature electrochemical synthesis from molten salts can be regarded as being one of the most promising methods for the preparation of high-melting compounds. The advantages of this method are relative simplicity of the equipment, the ready accessibility of the initial compounds, the possibility of preparing simple or complex composite coatings of high-melting compounds, the relatively low temperature of the process, and the possibility of controlling the morphology and the composition of the cathodic deposit by varying the electrolysis parameters. The theoretical grounds of this method have been described in detail,⁴⁸ and examples of its practical implementation can be found in reviews.^{49,50}

Depending on the nature of the electrolyte used, two variants of electrochemical synthesis of titanium diboride can be distinguished, namely, syntheses from oxygen-containing systems and from halide systems.⁵¹ The former variant commonly employs systems based on alkali and alkaline earth metal borates, which differ in the manner of saturation of the melt by the synthesis components. Boron can be introduced in the melt as B_2O_3 , and titanium can be added as TiO_2 ; the concentration of titanium in the electrolyte can be maintained by anodic dissolution of titanium metal.⁵¹ However, though seemingly advantageous, the synthesis based on oxygen-containing systems suffers from serious drawbacks. Specifically, the reaction temperatures are too high (> 1023 K), and a pure product (free from oxygen) cannot be prepared in this way.

The second variant can be implemented using either purely fluoride electrolytes, for example $\text{F/Li, Na, K, LiF-KF, Li, Rb, Cs/F}$ and cryolite and mixed chloride–fluoride electrolytes. The sources of titanium and boron in this case are either titanium and boron fluorides or soluble anodes made of boron, titanium and boron carbides or titanium diboride. The use of mixed chloride–fluoride electrolytes with the lowest possible content of fluorine is the most interesting. This decreases the corrosion activity and the cost of the melt; in the case where a soluble anode is used, the formation of fluorocarbons can be avoided and the stage of hydrotreating of the cathodic deposits can be simplified.

The mechanism of the cathodic process in the electrochemical synthesis of titanium diboride in the LiF-KF melt has been studied.^{52,53} Potassium hexafluorotitanate and tetrafluoroborate were used as the sources of titanium and boron. It was found that reduction of Ti^{4+} in the $\text{LiF-KF-K}_2\text{TiF}_6\text{-KBF}_4$ system occurs in two steps



This is followed by the reduction of boron complexes to elementary boron, which then reacts with the reduced titanium to yield titanium diboride. This is accompanied by electrode depolarisation, which is due, in the opinion of the researchers, to the great negative value of the Gibbs energy for the formation of TiB_2 .

Thus, analysis of the studies devoted to the methods of electrochemical synthesis of titanium diboride shows that mainly applied studies can be found in the literature. The information available from the literature is inadequate to interpret the mechanism of the synthesis; therefore, this process needs to be studied more comprehensively.

V. Electrochemical properties and stability of halide systems containing titanium in various oxidation states and boron

1. Study of electrochemical properties and stability of titanium-containing systems

Experiments on the stability of halide systems containing titanium in various oxidation states and boron and on the electrochemical synthesis of TiB_2 and titanium intermetallic compounds have been performed under an argon atmosphere, inert with respect to the melts under study.

The voltammograms characterising the electroreduction of Ti^{3+} at polarisation rates of $> 0.5 \text{ V s}^{-1}$ (Fig. 1) exhibit two persistent waves with clear-cut peak currents. The waves are due to the recharge and discharge of titanium ions

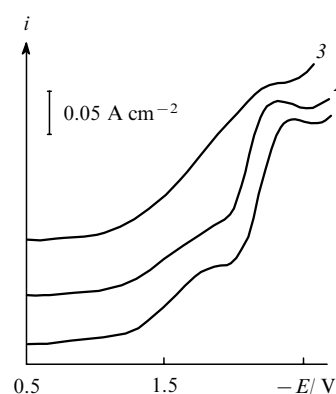
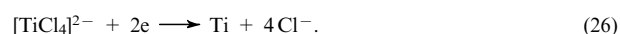
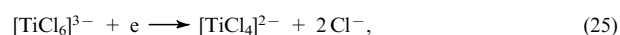


Figure 1. Voltammograms for the electroreduction of Ti^{3+} ions in the KCl-NaCl-TiCl_3 melt.

$T = 1000 \text{ K}$, $[\text{TiCl}_3] = 8.3 \times 10^{-5} \text{ mol cm}^{-3}$, chlorine reference electrode; polarisation rate $/\text{V s}^{-1}$: (1) 1.0; (2) 0.1; (3) 0.05.

To confirm the assumption that the potentials of the second wave correspond to the reduction of titanium complexes to the metal, potentiostatic electrolysis was carried out at these potentials. X-Ray diffraction identification of the electrolysis products showed the presence of titanium metal on the cathode.

When the potential sweep rate is $< 0.1 \text{ V s}^{-1}$, the peak current of process (25) becomes feebly defined and at polarisation rates of $< 0.05 \text{ V s}^{-1}$, the waves of processes (25) and (26) coalesce. As a consequence, the overall process appears as occurring in one stage (see Fig. 1, curve 3). In all probability, this is the reason for the disputes concerning the number of stages in the reduction of Ti^{3+} (see Refs 47, 51), because most of the studies have been carried out at polarisation rates close to the steady-state values (not higher than 10 mV s^{-1}).

Analysis of voltammograms of the type presented in Fig. 2 showed that at high polarisation rates, processes (25) and (26) are not complicated by any additional reactions and, in the range of TiCl_3 concentrations studied (up to 10 mass %), they completely obey the Faraday law. This is confirmed by the fact that the peak currents follow a linear dependence on the concentration of TiCl_3 .

The dependence of the peak potential on the polarisation rate and the magnitude of the transport coefficient αn , equal to 0.45, imply that at high polarisation rates, the charge transfer step in the recharge process (25) is retarded. The diffusion coefficient is equal to $(3.5 \pm 0.3) \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$.

The abnormal increase in the $i_p/V^{1/2}$ ratio at $V < 0.5 \text{ V s}^{-1}$ (see Fig. 2) is evidently due to the fact that the recharge is complicated by a catalytic reaction, *i.e.* electroreduction is accompanied by regeneration of electrochemically active species.

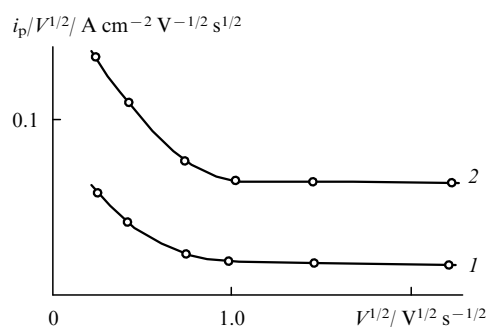


Figure 2. Variation of $i_p/V^{1/2}$ vs. $V^{1/2}$ (i_p is the peak current, V is the polarisation rate) for processes (25) (1) and (26) (2) in the KCl–NaCl–TiCl₃ melt.

$T = 1000$ K, $[\text{TiCl}_3] = 5.5 \times 10^{-5}$ mol cm⁻³.

This might be disproportionation of the divalent titanium formed. For a redox process not accompanied by catalytic reactions, the ratio of the peak currents of the waves obtained in the forward (cathodic) and reverse (anodic) recording of voltammograms should be equal to unity. If this ratio is greater than unity, the product of electroreduction enters into a subsequent chemical reaction; when this is disproportionation, it increases the current and changes correspondingly the $i_p/V^{1/2}$ value. Study of cyclic voltammograms for process (25) has confirmed⁵⁴ that disproportionation of divalent titanium occurs in the near-electrode layer

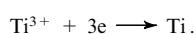


The minimum lifetime of the divalent titanium species is 0.08–0.8 s for the TiCl₃ concentration ranging from 5×10^{-4} to 5×10^{-5} mol cm⁻³; the rate constant for disproportionation is $(2.2 \pm 0.2) \times 10^4$ cm² mol s⁻¹.

Methods for controlling the course of electroreduction by varying the acid–base properties of the medium have been considered^{53–57} in relation to oxygen-containing complex ions. According to the idea of these studies, the electrochemical activity of oxygen-containing anions is due to the mechanism of formation of electrochemically active species peculiar to molten salts, namely, the acid–base interactions in the melt. The formation and interactions of electrochemically active species in the near-electrode layer occur at a limited rate because these processes require rearrangement of the structure of reacting species. Thus, by changing the acid–base properties of the medium, one can influence the mechanism and the rate of the process in a specified manner.

Elimination of disproportionation reactions by changing the mechanism of the process can be attained in two ways, namely, by addition of either cations possessing greater polarising ability than potassium and sodium or anions having stronger basic properties than the chloride anion. In the former case, the acidity of the melt diminishes, while in the latter case, the basic properties of the electrolyte are enhanced (for instance, when sodium fluoride is introduced).

The mechanism of the cathodic process in the electroreduction of titanium trichloride in chloride melts with different cationic compositions has been studied.⁵⁸ It was found that reduction of titanium in the cesium chloride melt occurs *via* recharge stage (25), whereas in an eutectic LiCl–KCl melt, when the temperature diminishes to 673 K, trivalent titanium is reduced to the metal in one stage



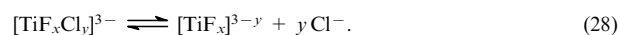
However, the LiCl–KCl system cannot be used for the synthesis of titanium diboride because the minimum temperature for the onset of the electrochemical synthesis markedly exceeds 673 K and amounts to 843 K.

It has been found⁵⁹ that fluoride ions added to the melt replace the chlorine in the titanium complex species and, as a consequence, the electroreduction process switches to a one-stage mechanism.

In order to elucidate the potential for the synthesis of titanium diboride from chloride and fluoride electrolytes, it is significant to study the influence of fluoride ions, in particular, the $[\text{Ti}^{3+}]:[\text{F}^-]$ molar ratio, on the mechanism of titanium electrodeposition and the type of titanium species in the melt. It is also necessary to determine the optimum electrolyte composition,⁶⁰ which would preclude both disproportionation reactions and the formation of lower titanium fluorides, insoluble in the melt.

As shown above, electroreduction of trivalent titanium in the chloride melt includes the recharge to the divalent state. Upon introduction into the chloride melt of fluoride ions in the ratio $[\text{Ti}^{3+}]:[\text{F}^-] > 1:2$, the peak current of the recharge wave decreases proportionally to the content of fluoride ions in the electrolyte. In addition, as the current of the recharge wave decreases, the peak current of the $\text{Ti}^{2+} \rightarrow \text{Ti}$ discharge wave proportionally increases. When the molar ratio $[\text{Ti}^{3+}]:[\text{F}^-] = 1:2$ is attained, the recharge wave is no longer displayed on the voltammogram and the discharge of the complex ions of titanium becomes a one-stage process (Fig. 3). The switching to a different mechanism is accompanied by the simultaneous shift of the wave potentials towards more negative values. Experimental results imply that the change in the anionic composition of the melt upon the introduction of fluoride ions results in the formation of mixed chloride- and fluoride-containing complexes. The replacement of chlorine in the $[\text{TiCl}_6]^{3-}$ complex (this is the species in which TiCl₃ occurs in the KCl–NaCl melt) by the smaller fluoride ion makes this complex stronger and changes the mechanism of its reduction. The fact that the mechanism changes at $[\text{Ti}^{3+}]:[\text{F}^-] = 1:2$ suggests that the composition of the resulting titanium complex is $[\text{TiF}_2\text{Cl}_4]^{3-}$.

Titanium chloride–fluoride complexes occur in equilibrium with components of the melt; generally, the equilibrium is described by the equation



Electroreduction involves dissociated species $[\text{TiF}_x]^{3-y}$, the concentration of which is lower than the total concentration of titanium in the electrolyte.

The dependence of the potential of the reduction wave peak on the polarisation rate in the broad range of potential sweep rates and also the value $\alpha n = 1.0 \pm 0.05$, found from the Matsuda–Ayabe equation, imply that the charge transfer step is slow.

The diffusion coefficient calculated from the Delahay equation using peak currents corresponding to the total concentration

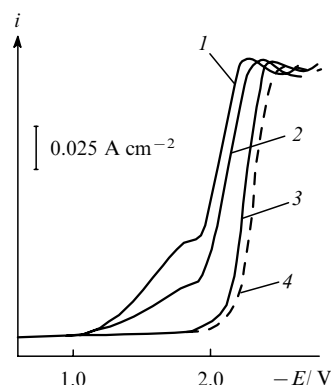


Figure 3. Voltammograms for the electroreduction of titanium ions in the KCl–NaCl–NaF–TiCl₃ melt at a $[\text{Ti}^{3+}]:[\text{F}^-]$ molar ratio, equal to 1:0 (1), 1:1 (2), 1:2 (3), <1:2 (4).

$T = 1000$ K, polarisation rate 1.0 V s⁻¹, $[\text{Ti}^{3+}] = 1.55 \times 10^{-4}$ mol cm⁻³, chlorine electrode as the reference electrode.

of titanium in the melt is equal to $(3.0 \pm 0.4) \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$. The underestimated value of the diffusion coefficient, $(0.7 \pm 0.4) \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$, found using the currents corresponding to high polarisation rates confirms the assumption that the concentration of electrochemically active species under these conditions does not coincide with the total titanium concentration in the melt.

The number of ligands attached to the initial $[\text{TiF}_2\text{Cl}_4]^{3-}$ species during titration of the melt by fluoride ions, determined on the basis of the slope of the straight line plotted in the 'shift in the wave peak – depolariser concentration' coordinates ($\Delta E - \ln c_{\text{F}^-}$) (Fig. 4) is equal to two. With allowance for the composition of the initial species, the composition of the titanium complex in the bulk of a melt containing an excess of fluoride ions should be $[\text{TiF}_4\text{Cl}_2]^{3-}$. Then the formation and discharge of electrochemically active titanium complexes can be described by the following scheme:

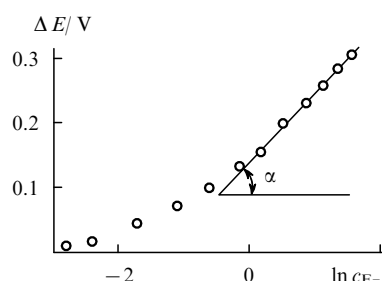
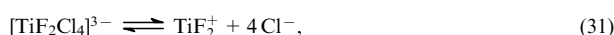
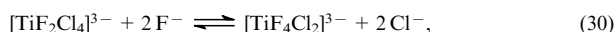
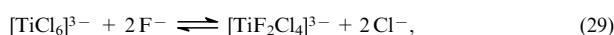


Figure 4. Calculation of the coordination number of titanium in the complexes occurring in the KCl–NaCl–NaF–TiCl₃ melt.

Thus, the electroreduction of trivalent titanium in the near-electrode layer of a chloride melt involves disproportionation of divalent titanium. In a chloride melt, the $\text{Ti}^{3+} \rightleftharpoons \text{Ti}^{2+}$ recharge is a catalysed process and the charge transfer step is retarded over a broad range of polarisation rates. Stabilisation of the KCl–NaCl–TiCl₃ system can be attained by changing the acid–base properties of the melt by introducing fluoride ions into the chloride electrolyte, which results in the formation of mixed chloride and fluoride complexes such as $[\text{TiF}_2\text{Cl}_4]^{3-}$. The reduction of these complexes at the molar ratio $[\text{Ti}^{3+}]:[\text{F}^-] < 1:2$ occurs in one stage involving the transfer of three electrons.

2. Study of electrochemical properties and stability of boron-containing systems

In order to arrange a high-temperature electrochemical synthesis of titanium diboride, it is necessary that the potentials of the evolution of products used in the synthesis be close. Therefore, investigations into the electrochemical properties and stability of boron-containing chloride–fluoride melts are topical. Analysis of the published data indicates that, despite the fact that numerous studies have been devoted to electroreduction of boron complexes, there are still no clear views on the electroreduction mechanism or the composition of the boron-containing species existing in chloride–fluoride melts.

The voltammograms of the electroreduction of boron exhibit one wave in the potential range from -2.35 to -2.7 V with a clear-cut peak current (Fig. 5). Further polarisation results in an increase in the current, caused by the discharge of alkali metal ions. The potentiostatic electrolysis at the potential corresponding to the reduction wave affords elementary boron. The dependence of the peak potential of the wave of electroreduction of boron

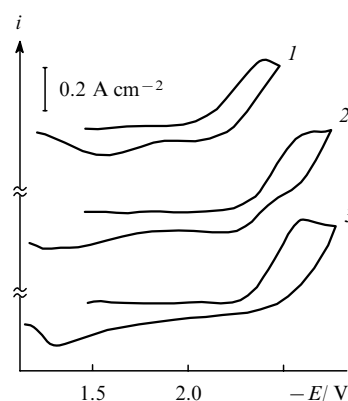
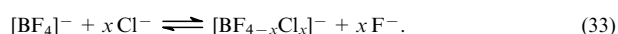


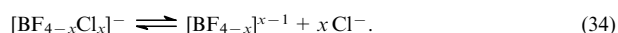
Figure 5. Cyclic voltammograms for the $\text{B}^{3+} \rightarrow \text{B}$ process occurring in the KCl–NaCl–NaF–NaBF₄ melt (vs. chlorine reference electrode). $[\text{B}^{3+}]:[\text{F}^-]$: (1) 1:0, (2) 1:7, (3) 1:14.

complexes on the polarisation rate, the substantial difference between the wave peak potentials found in the forward and reverse recording of voltammograms, and the values $\alpha n = 0.96$ – 1.08 for the three-electron process calculated from the Matsuda–Ayabe equation lead to the following conclusion. In the range of polarisation rates from 0.1 to 20.0 V s^{-1} , the discharge of boron complexes is irreversible, *i.e.* it is controlled by the rate of charge transfer.⁶¹

The $[\text{BF}_4]^-$ ions added to a chloride melt enter into an exchange reaction with chloride anions to give mixed chloride–fluoride complexes



The unstable boron complexes undergo thermal dissociation, which can be generally represented by the following scheme:



Electroreduction involves species resulting from dissociation of the initial complexes; the concentration of these species in the melt bulk is small compared to the total concentration of boron ions in the electrolyte. Thus, the melt contains simultaneously two sorts of species, namely, the initial $[\text{BF}_{4-x}\text{Cl}_x]^-$ complexes and electrochemically active species $[\text{BF}_{4-x}]^{x-1}$. Upon the discharge of boron complexes, the near-electrode layer becomes depleted in the $[\text{BF}_{4-x}\text{Cl}_x]^-$ complexes, which displaces the equilibrium towards the formation of electrochemically active species. Analysis of the $i_p/V^{1/2} - V^{1/2}$ dependence shows⁶² that a decrease in the potential sweep rate diminishes the influence of dissociation on the electroreduction of boron complexes. The influence of $i_p/V^{1/2}$ on $V^{1/2}$ can be extrapolated to the $i_p/V^{1/2}$ axis if the peak current of the wave corresponds to the total concentration of boron in the melt. The linear type of dependence of the peak currents on the boron concentration in the melt implies that the preceding chemical reaction exerts no retarding influence under these conditions. The diffusion coefficient calculated from the Delahay equation using the peak current values corresponding to the total concentration of boron in the melt is equal to $(3.3 \pm 0.4) \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$.

Thermal dissociation of alkali metal fluoroborates added to a chloride melt yields volatile boron fluorides, poorly soluble in the melt and passing into the gas phase. This results in a lower concentration of electrochemically active species and, hence, in a lower rate of boron electroreduction.⁶³ The non-controllable change in the concentration of one component hampers the selection of operating conditions suitable for the electrochemical synthesis of titanium diboride. Therefore, it is necessary to find a method for stabilisation of the chloride melt containing an alkali metal fluoroborate. It has been shown^{61,62} that the introduction of NaF into the KCl–NaCl–NaBF₄ melt induces a shift of the

peak potential of the wave corresponding to the discharge of mixed chloride–fluoride boron complexes, due to the replacement of chloride ions by fluoride ions. When $[B^{3+}]:[F^-] \geq 1:2$, the melt is stabilised upon the formation of mixed chloride–fluoride complexes of boron and the rate of the reduction of boron no longer varies with time. It is of interest to determine the composition of boron-containing complexes in the initial chloride melt and the complexes formed upon titration of the melt by fluoride ions.

The coordination number of boron in the chloride–fluoride complex was calculated using a procedure taking account of the dependence of the shift of the wave peak potential for the reduction of boron complexes on the concentration of the free ligand in the melt. The concentration of the free ligand was assumed, as the first approximation, to be equal to the total concentration of fluorine added to the melt. The coordination number determined from the slope of the straight line plotted in the $\Delta E - \ln c_{F^-}$ coordinates (Fig. 6) is equal to unity, i.e. during titration of the KCl–NaCl–NaBF₄ melt by fluoride ions, one fluoride ion adds to the initial species. Hence, the mixed chloride–fluoride complex of boron in the NaCl–KCl melt has the composition $[BF_3Cl]^-$ and the species occurring in the melt with excess fluoride ions is BF_4^- . The application of a correction for the concentration of the bound ligand, determined by the molar ratio $[B^{3+}]:[F^-] = 1:1$, did not alter the results.

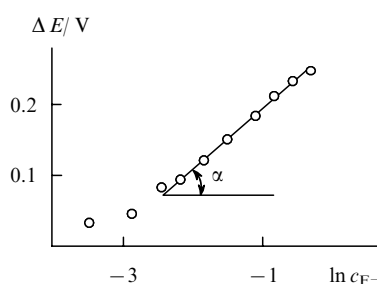
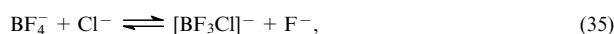


Figure 6. Calculation of the coordination number of boron in the complexes occurring in the KCl–NaCl–NaF–NaBF₄ melt.

Based on the foregoing, it can be concluded that the formation of mixed chloride–fluoride complexes of boron can be described by the following equations.

In the absence of excess fluoride ions in the melt



and in the presence of excess fluoride ions in the melt



VI. Electrochemical synthesis of titanium diboride and titanium intermetallic compounds in a chloride–fluoride melt

1. Joint electroreduction of titanium and boron in the chloride–fluoride melt and electrodeposition of titanium diboride powders

It has been shown⁶⁴ that the addition to the KCl–NaCl–NaF–KBF₄ melt of titanium trichloride in a concentration close to half that of potassium tetrafluoroborate results in a sharp increase in the current at potentials 0.25 V more positive than the potential of reduction of titanium complexes. This brings about a wave characterised by a steeper slope than the waves for the discharge of the titanium and boron complex ions. This wave is displayed on voltammograms over broad ranges of polarisation rates and TiCl₃ and MBF₄ concentrations (Fig. 7). If the ratio $[Ti^{3+}]:[B^{3+}] = 1:2$ does not hold, then electroreduction

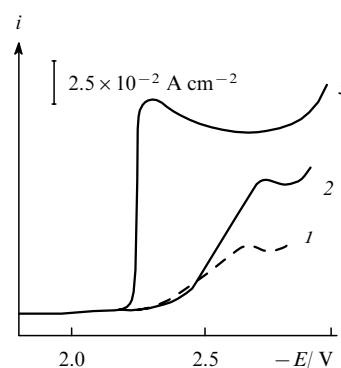
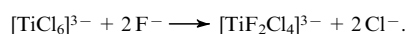


Figure 7. Voltammograms for various processes ($T = 1000$ K, polarisation rate 1.0 V s^{-1} , chlorine reference electrode); (1) electroreduction of titanium from the NaCl–KCl–NaF melt containing $4.5 \times 10^{-5} \text{ mol cm}^{-3}$ of TiCl₃; (2) electroreduction of boron from the NaCl–KCl–NaF melt containing $8 \times 10^{-5} \text{ mol cm}^{-3}$ of NaBF₄; (3) electrochemical synthesis of titanium diboride from the NaCl–KCl–NaF–TiCl₃–NaBF₄ melt ($[Ti] + [B] = 1.2 \times 10^{-4} \text{ mol cm}^{-3}$).

of TiB₂ is followed (before the discharge of the alkali metal) by the discharge of the excess (with respect to this ratio) of a component (titanium or boron). When this ratio is lower than 1:2, this wave is exhibited at less negative potentials than in the case where the ratio is greater than 1:2. The cyclic voltammograms (reverse recording) for $[Ti^{3+}]:[B^{3+}] = 1:2$ were found to contain one peak, while those for $[Ti^{3+}]:[B^{3+}] \neq 1:2$ exhibit at least two peaks. Identification of the products of potentiostatic electrolysis demonstrated that the electrolysis product obtained at the potential of the first cathodic wave is titanium diboride, while that deposited at the second cathodic wave potential is titanium diboride together with the component (either titanium or boron) in excess with respect to the ratio $[Ti^{3+}]:[B^{3+}] = 1:2$.

The formation of titanium diboride is accompanied by evolution of a substantial amount of energy; therefore, its synthesis proceeds at more positive potentials than the separate reduction of either component of the synthesis. Depolarisation is equal to 0.15–0.3 V (with respect to the initial components), depending on the electrolyte composition. Comparison of the dependences of $i_p/V^{1/2}$ on $V^{1/2}$ for the joint and individual electroreduction of titanium and boron shows that at high polarisation rates, the peak current of the synthesis wave is much lower than the sum of the partial currents corresponding to the discharge of the titanium and boron complexes. This fact implies that the process is retarded due to the preceding chemical reaction; the higher the polarisation rate, the more pronounced the retardation (Fig. 8). This is due to the fact that the titanium and boron complex ions present in the melt form mixed complexes such as $[B_2TiF_xCl_y]$.⁶⁵ The absence of a horizontal section on the $i_p/V^{1/2}$ vs. $V^{1/2}$ plot (as well as on the plots for the partial currents for titanium or boron), which would be due to the flow of electrochemically active species moving from the bulk melt, provides grounds for considering, according to the diagnostic electrochemical criteria, that the lifetime of the arising species is short with respect to the lifetime of species formed by titanium and boron in the corresponding systems. A decrease in the polarisation rate results in a lower contribution of the formation of joint complexes. Extrapolation of this dependence for the limiting current to the rate axis gives the current corresponding to the total concentration of titanium and boron in the melt.

The introduction of boron as BF_4^- into the chloride melt containing $[TiCl_6]^{3-}$ ions gives rise to exchange reaction (35). The fluoride ion thus liberated adds to the titanium complex



When there is no excess fluoride ions in the melt, the composition of the joint complex is $[B_2TiF_8Cl_4]^{3-}$. The wave of

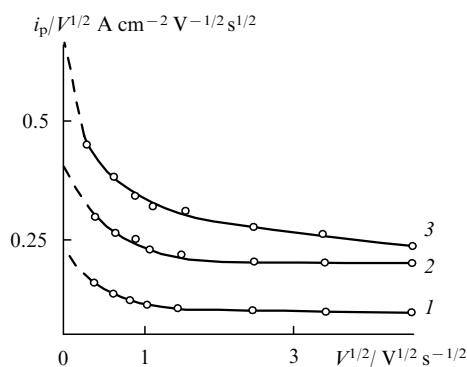


Figure 8. Variation of $i_p/V^{1/2}$ vs. $V^{1/2}$ for a number of processes; (1) electroreduction of titanium complexes, $[Ti] = 6 \times 10^{-5} \text{ mol cm}^{-3}$; (2) electroreduction of boron complexes, $[B] = 1.2 \times 10^{-4} \text{ mol cm}^{-3}$; (3) electrochemical synthesis of titanium diboride, $[Ti] + [B] = 1.8 \times 10^{-4} \text{ mol cm}^{-3}$, $[Ti^{3+}]:[B^{3+}] = 1:2$.

the joint electroreduction (synthesis) is extended along the potential axis; the peak width reaches 0.5 V and the potential difference between the peaks of the waves displayed during the forward and reverse recording of voltammograms is 1.0 V. The introduction of fluoride ions into the melt decreases the width of the wave and shifts the wave to the negative region; the difference between the potentials of the peaks of the cathodic and anodic waves decreases simultaneously. For the molar ratio $([Ti^{3+}] + [B^{3+}]):[F^-] \geq 1:15$, the wave width and the difference between the peak potentials barely change.

The shift of the peak potentials of the synthesis wave towards negative values is due to the formation of stronger complexes upon the attachment of the fluoride ions in the melt to the initial complex species



The fact that the peak and half-peak potentials of the synthesis waves do not depend on the polarisation rate as well as the S-shape of the voltammograms imply a reversible step of charge transfer at polarisation rates of $< 2.0 \text{ Vs}^{-1}$. The number of electrons involved in the elementary electrochemical step, calculated using the Matsuda–Ayabe equation, is equal to 9. This means that the discharge of the arising joint complexes at a polarisation rate of $< 2.0 \text{ Vs}^{-1}$ involves simultaneous transfer of nine electrons without kinetic limitations. Study of the electrochemical behaviour of a titanium diboride electrode in a chloride–fluoride melt showed that there is no equilibrium between the electrode and the melt and that the electrochemical step proper is reversible. During dissolution of titanium diboride, limitations appear associated with the chemical interaction at the electrode–melt interface.

As noted above, the charge transfer steps in the separate discharge of titanium and boron complexes are retarded and the electrochemical stage of the synthesis of titanium diboride is reversible. This confirms the assumption that the complexes react chemically in the bulk of the melt to give electrochemically active species, the discharge of which is reversible.

The calculation of the coordination number for a mixed titanium and boron complexes shows that during titration of the melt with fluoride ions, four fluoride ions are attached to the initial species, $[TiB_2F_8Cl_4]^{3-}$, to give $[TiB_2F_{12}]^{3-}$.

It has been established relying on chronovoltammetric measurements^{72,73} that, for the discharge of joint titanium and boron complexes to persist, the molar ratio $([Ti^{3+}] + [B^{3+}]):[F^-] = 1:4$ (for $[Ti^{3+}]:[B^{3+}] = 1:2$) should be maintained in the melt.

The results obtained were taken as the basis for practical implementation of the high-temperature electrochemical synthesis of titanium diboride. The influence of temperature, current density, and the concentrations of the synthesis components on the composition and properties of the product were studied. A

crucial condition for this process is that the molar ratio $[Ti^{3+}]:[B^{3+}] = 1:2$ is maintained in the melt. In this case, a homogeneous phase of titanium diboride is deposited at the cathode over a broad range of current densities. If this condition is not fulfilled, titanium diboride is deposited at the cathode at relatively low current densities (up to 0.5 A cm^{-2}), while at higher current densities, it is deposited together with the component present in excess with respect to this ratio. The total concentration of titanium and boron in the electrolyte in the 0.6 mol.%–30 mol.% range does not influence significantly the product composition or economical characteristics of the process. A decrease in the total concentration to $< 0.6 \text{ mol.}\%$ is not expedient for technological reasons (frequent correction of the cell, low current density and low output), whereas an increase in the concentration to $> 30 \text{ mol.}\%$ brings about a greater loss of boron due to the thermal dissociation of potassium tetrafluoroborate, enhanced corrosiveness of the melt, and difficulty in washing out the cathodic deposit.

The temperature threshold for the onset of the electrochemical synthesis of titanium diboride in the system studied is 873–893 K.⁶⁶ The optimum temperature range is 963–1123 K. An increase in the temperature above 1123 K is not expedient as it diminishes the thermal stability of the cell and deteriorates the conditions of the formation of the metal salt precipitate. In the temperature range of 963–1123 K, highly dispersed titanium diboride powders with a specific surface area of up to $10 \text{ m}^2 \text{ g}^{-1}$ are produced.

Dispersed powders of titanium diboride were obtained using the $KCl-NaCl-NaF$ (30 mol.%)- $TiCl_3$ (5 mol.%)- KBF_4 (10 mol.%) system as the electrolyte, current densities of 0.5 to 1.6 A cm^{-2} , and a temperature of 1023 K. The degree of dispersion of the powders increased with an increase in the current density; when the current density was $< 0.5 \text{ A cm}^{-2}$, dendrites were formed, while at a current density of $> 1.6 \text{ A cm}^{-2}$, titanium diboride was deposited at the cathode together with an alkali metal.

2. Joint electroreduction of titanium, nickel, cobalt and iron and electrodeposition of titanium intermetallic compounds

In the electrolysis of melts containing simultaneously titanium and iron (nickel, cobalt) chloride, powdered intermetallic compounds (IMC) of titanium, $TiFe$, $TiFe_2$, Ti_2Ni , $TiNi_3$ and $TiCo$, are formed at the cathode.^{67–69} The ways of controlling the processes of formation of IMC have been studied allowing for the mechanisms proposed for high-temperature electrochemical synthesis.

Electrochemical behaviour of titanium and iron chlorides occurring in the melt has been studied by linear chronovoltammetry with cyclic potential sweep according to the three-electrode scheme.⁶⁷ The dependence of the limiting current on the concentration was non-linear (unlike this dependence for simple reversible or irreversible processes). The fact that the height of the wave remains constant when the potential sweep rate increases above 0.5 Vs^{-1} implies a retarding influence of the preceding chemical reaction. The illegibility of the peak wave also confirms that the chemical and electrochemical stages are coupled.⁷⁰ It was noted⁶⁷ that potential of the cathode current shifts to the negative region and that the difference between the peak and half-peak potentials of the cathode current increases with an increase in the potential sweep rate. In view of the foregoing, with the assumption of first-order chemical reactions, two stages of high-temperature electrochemical synthesis can be distinguished.

1. Chemical reaction to give the equilibrium



where $z = 3x + 2y$, which shifts towards the formation of the heteronuclear complex $[Ti_xFe_y]^{z+}$; the heat of formation of the corresponding intermetallic compound increases.

2. Electrochemical reduction of the heteronuclear complex cation after the discharge potential has been attained



Analysis of the diffusion coefficients shows that charge numbers of 3 and 4 are preferred for complex IMC (the particular number depends on the particular compound). Therefore, the intermetallic chloride complexes discharged at the cathode are $[\text{TiFe}_2]\text{Cl}_3$ and $[\text{TiFe}]\text{Cl}_3$.

A series of experiments dealing with the influence of the concentration of titanium on the peak potential of nickel discharge has been carried out.⁶⁸ Titanium is formally considered as a 'quasi-ligand', although, in accordance with the views of the coordination chemistry of melts,⁷¹ it is incorporated in the nucleus of the heteronuclear complex $[\text{Ti}_x\text{Ni}_y]^{n+}$. The variation of the difference between the potentials of nickel reduction ΔE_{pNi} in the presence and in the absence of TiCl_3 as a function of the Napierian logarithm of the ratio of TiCl_3 and NiCl_2 concentrations has three linear sections characterised by different slopes and a horizontal section for a large excess of titanium (Fig. 9). The formal coordination numbers of nickel with respect to titanium (the number of titanium atoms per nickel atom in the complex), determined from the slopes of the linear sections, are 0.4, 0.95 and 1.78. They are close to theoretical values of 0.33, 1.0 and 2.0 respectively, which correspond to the heteronuclear complexes $[\text{TiNi}_3]^{n+}$, $[\text{TiNi}]^{n+}$, $[\text{Ti}_2\text{Ni}]^{n+}$. The assumed formation of these complexes has been confirmed⁶⁸ by X-ray diffraction analysis of the products of electrolysis at the potential of the intermediate wave of the synthesis; in addition to nickel, the powder contained intermetallic compounds TiNi_3 , TiNi and Ti_2Ni .

The reaction of NiCl_2 and TiCl_3 can be represented in the following way. According to spectroscopic measurements,⁷² Ni^{2+} and Ti^{3+} cations form octahedral complexes $[\text{NiCl}_6]^{4-}$ and $[\text{TiCl}_6]^{3-}$ with chloride anions. Evidently, when the titanium concentrations are low ($5 \times 10^{-5} \text{ mol cm}^{-3}$) and the ratio $[\text{Ti}]:[\text{Ni}] = 1:1$, only these nickel and titanium complexes exist. The fact that upon an increase in the titanium concentration, a wave for the discharge of the intermetallic compound $[\text{Ti}_x\text{Ni}_y]^{n+}$ appears between the discharge waves for titanium and nickel implies⁶⁸ a reaction between the two species to give heteronuclear complexes according to the following equations



When titanium is present in a 25-fold (or higher) excess with respect to nickel, the potential of nickel discharge does not shift to negative values. Apparently, this situation corresponds to that in systems with excess complex-forming ions. In these systems, the structures of complexes are distorted; they are destroyed or turn into chain structures or into structures of individual molten salts.⁷¹

A study of the electrochemical behaviour of titanium and cobalt present simultaneously in chloride melts⁶⁹ has been the

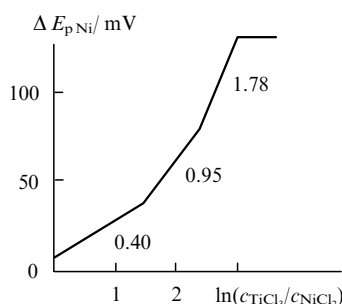


Figure 9. ΔE_{pNi} vs. $\ln(c_{\text{TiCl}_3}/c_{\text{NiCl}_2})$ plot for the $\text{KCl}-\text{NaCl}-\text{NiCl}_2-\text{TiCl}_3$ melt; $T = 973 \text{ K}$.

The numbers on the curve are explained in the text.

generalising stage in the investigations into the possibility of producing intermetallic compounds of titanium with iron group elements by high-temperature electrochemical synthesis. The appearance of the synthesis wave and the character of its variation for $\text{Ti}-\text{Co}$ and $\text{Ti}-\text{Ni}$ systems are similar.⁶⁸ The negative slope ratios for the variation of the product of the limiting cathode current by the polarisation rate vs. the limiting cathode current of the synthesis wave makes it possible to propose a process of electrochemical reduction of the heteronuclear complex $[\text{TiCo}]^{n+}$. The electrolysis yields a black finely dispersed metallic powder, TiCo . The powder is based on aggregates of dendrites with an average size of $20 \mu\text{m}$. The specific surface area of the powder is $30 \text{ m}^2 \text{ g}^{-1}$.

The works that are worth mentioning among the most recent studies devoted to the electrochemistry of titanium and its alloys include investigation of the influence of the cationic and anionic compositions of the melts on the corrosion of titanium in alkali and alkaline earth metal halides,⁷³ deposition of silicon,⁷⁴ silver^{75,76} and copper^{77,78} protective coatings onto titanium articles and preparation of titanium and its alloys for deposition.⁷⁹ Electrochemical behaviour of titanium and boron and electrodeposition of titanium intermetallic compounds have been studied in detail.^{80,81}

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Reactivity of lignin and problems of its oxidative destruction with peroxy reagents

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Abstract. Published data on reactivity and oxidation of lignin and model compounds with hydrogen peroxide, ozone and chlorine dioxide as well as on oxidative destruction of the sulfate pulp lignin with various reagents during bleaching are systematised and generalised. Concepts of lignin activation towards its selective oxidation and kinetic features of sulfate pulp oxidative delignification are considered. The bibliography includes 157 references.

I. Introduction

Wood represents a complex polymeric composition in which lignin and cellulose are the main components.^{1–7} During its processing, lignin and cellulose undergo a variety of parallel redox transformations and behave as a single complex (technical pulp).

Selective oxidative destruction of lignin in pulp, especially in sulfate pulp where lignin has been modified during the sulfate pulping process of the native polymer, is a difficult problem, mostly due to the complexity of lignin, which is built up of a multitude of non-uniform structural elements, and the extremely high variability of properties of this polyfunctional polymer.

The problem of oxidative destruction of residual lignin[†] with peroxy reagents [O_3 , $RC(O)OOH$, H_2O_2] is of considerable practical importance since current manufacture of pulps (predominantly of sulfate pulps) consumes a million tons of chlorine for bleaching and results in toxic chlorine-containing pollutants, including dioxins.

The known multi-step schemes for complete oxidative destruction of the residual lignin with various sets of reagents

have been developed empirically. Such schemes usually have no solid physicochemical background and, as a result, do not always take into account the impact of the preceding technological operations on the physicochemical properties of the residual lignin and the effect of acid-base catalysis. Consideration of these factors takes on especial significance on replacement of the chlorine and chlorine-containing compounds (used so far in the pulp industry) by hydrogen peroxide, oxygen and ozone, which are ecologically friendly but possess relatively low reactivities towards lignin.

The reactivities of the native and residual lignins in pulps and the mechanisms of lignin reactions with various reagents during pulp preparation from a wood raw material have been considered in a series of reviews.^{4,8–10} The last two of them,^{9,10} present a survey of the mechanisms of elementary reactions and characteristics of the majority of reagents used in wood chemistry and depict reaction schemes for the low-molecular-weight compounds that model lignin fragments. However, all these data allowed one only to explain rather than to predict the results of the action of any particular oxidant on the residual lignin. This is associated with the fact that the oxidative destruction of the residual lignin during pulp delignification is usually performed in several stages, because lignin cannot be selectively and completely oxidised in one step with any particular reagent.

It should be noted that lignin (more correctly, lignins) represent chemically labile polyfunctional polymers, which cannot be isolated as individual compounds in native states. Consecutive stages of oxidative destruction on each occasion deal with a 'different' lignin of a lignino-cellulose composition (technical pulp). Any chemical action on lignin not only alters its functional and polymeric composition but it also changes the number, ratio and strength of electrophilic and nucleophilic centres and the contents of 'weak' bonds in a lignin macromolecule.

The necessity to account for, and systematise, all the above-mentioned factors has led to the development of a new approach, in which the multi-step process of oxidative destruction of the residual lignin is considered as a united combination of redox transformations, wherein each particular stage 'prepares' and activates lignin for the subsequent technological stage through creation in lignin of new centres reactive towards nucleophilic or electrophilic reagents.

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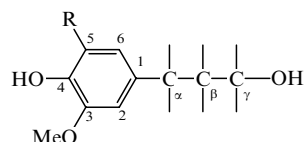
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[†] Lignin that remained in the sulfate pulp after cooking.

This review includes a brief description of the lignin structure, a consideration of the reactions of some model compounds which are hard to oxidise with oxygen, hydroperoxide anions, ozone and chlorine dioxide as well as delignification of the sulfate pulp with hydrogen peroxide and ozone and activation of lignin towards its oxidative destruction with various reagents. It also introduces a concept of selective lignin oxidation by consecutive action of peroxy reagents, which has led to the development of the most efficient schemes for pulp bleaching. In addition, the kinetic features of oxidative lignin destruction in the processes of the sulfate pulp delignification are discussed.

II. Lignin structure

Lignins represent macromolecular polyfunctional aromatic compounds; a structural model of softwood lignin according to Freudenberg is described in Scheme 1. Being the components of wood tissues, lignins are responsible for vital mechanical, chemical and biological functions,^{1–4} viz., they impart durability and protection against oxidation and microbial action. Lignin is biosynthesised in close proximity to macromolecules of cellulose and non-cellulosic polysaccharides, which results in a lignin–carbohydrate polymeric matrix. Chemical, physicochemical and mechanical interactions of lignin with cellulose ensure the formation of a complex polymeric composition, viz., the wood tissue, and predetermine the reactivities of its main components in chemotechnological processes. Wood lignins are built up of substituted phenol–propane units. Guaiacyl- and syringylpropanol units are the most common structural elements.^{11–17}

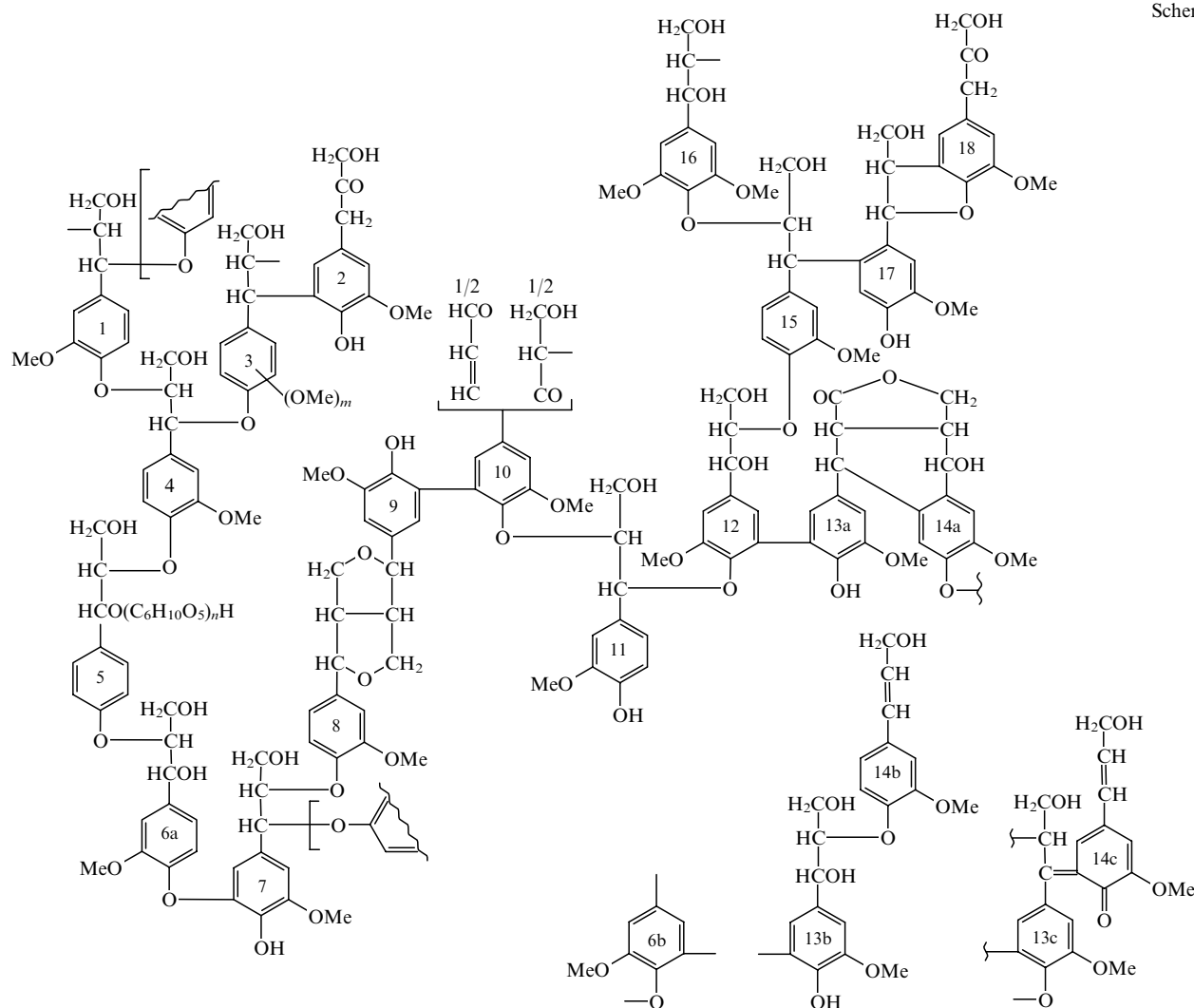


R = H, OMe.

The structural units are linked to each other with various ether and carbon–carbon bonds.^{18–21}

Because of structural irregularity and great variety of the chemical bonds in lignin, the description of its macromolecule as a simple combination of a few (or a multitude of) monomers (substituted phenol–propane units) seems to be impossible.^{22–26} The structure of lignin is still the subject of model studies.^{27–30}

Several lignin structures, *e.g.*, that shown in Scheme 1,²⁸ have been proposed based on the results of studies of lignin ethanolysis, thioacetolysis, oxidation^{31–33} and hydrogenolysis³⁴ products, data of elemental analysis, functional group determinations, comparative analysis of properties of native lignin and synthetic dehydropolymers (DHP) built of substituted phenol–propane units, spectroscopic data (¹H and ¹³C NMR, IR, UV),^{20, 22, 35, 36} the results of gel and gas chromatography and mass spectrometry. A segment of lignin macromolecule represented in the Freudenberg scheme contains 18 phenol–propane units and reflects the ratio of the main types of structural units, bonds and functional groups. This scheme can be supplemented by alternative structural elements, *e.g.*, 6b, 13b, 14b, 13c and 14c. Later, Adler³⁷ suggested a structural scheme for a segment of the fir-wood lignin



Scheme 1

Table 1. Types and number of linkages between the structural elements in different lignin models.¹⁸

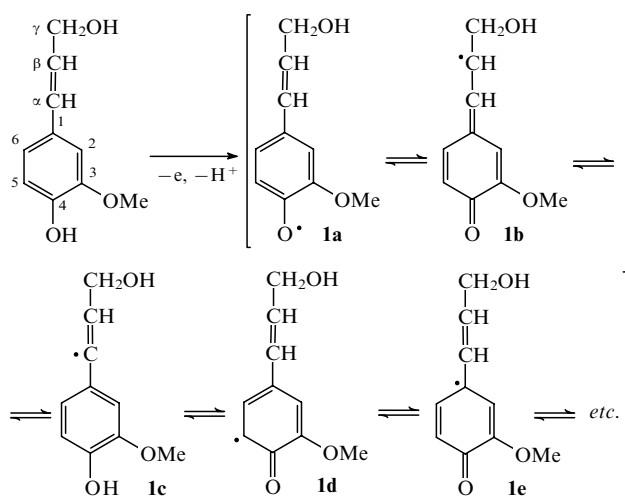
Linkage type	Number of linkages per 100 phenol–propane units ^a		
	I	II	III
C(β)–O–C(4)	55	65	49–51
C(α)–O–C(4)	—	—	6–8
C(β)–O–C(5)	16	6	9–15
C(β)–C(1)	9	15	2
C(5)–C(5)	9	2.3	9.5
C(4)–O–C(5)	3	1.5	3.5
C(β)–C(β)	2	5.5	2
C(α)–O–C(γ)	10	—	—
C(α)–C(β)	11	2.5	—
C(β)–C(6), C(6)–C(5)	2	—	4.5–5.0 ^b

^a I, the Glasser model,³⁹ II, the Nimz model,⁴¹ III, the Erickson model.⁴⁰^b Including the C(1)–O–C(4) and C(1)–C(5) bonds.

macromolecule comprising 16 phenol–propane units. It is obvious that in such small segments it is rather difficult to take precisely into consideration the ratio of certain lignin structural elements and bonds. A recently proposed³⁸ model of fir-wood lignin contained 28 phenol–propane units and included some alternative structural elements that were previously absent in the Adler scheme. In addition to the models with a relatively small number of phenol–propane units built up by random combination of functional groups, bonds and structural elements, several more complete computer structural models for fir-wood lignin have been suggested. Thus the Glasser model³⁹ for lignin with molecular weight > 17 000 contains 94 phenol–propane units and takes into account most of the known analytical data. The results of simulations of the lignin structure (models suggested by Glasser,³⁹ Erickson⁴⁰ and Nimz⁴¹) are presented in Table 1.

The structural heterogeneity of lignins is associated with specific features of lignin biogenesis in wood tissues. The first stage of lignin biosynthesis is the enzymic oxidative deprotonation of *p*-hydroxycinnamyl alcohols (coumaryl, coniferyl and sinapyl alcohols) leading to the formation of a system containing the radicals **1a–e** (Scheme 2).³⁸

Scheme 2



Recombination of two radicals affords one of 36 possible dimers. Upon the action of peroxidases, the latter undergo further oxidation producing dimeric radicals which, in turn, can form several hundred combinations of tetramers. The random character of the electron localisation predetermines the sporadic character and irregularity of the lignin structure.^{3,5}

However, not all combinations in the coupling of monomers are of the equal probability. It has been shown by quantum-chemical calculations that the electron density distribution favours the formation of the ether C(β)–O–C(4) linkage resulting from the coupling of radicals **1a** and **1b**. Indeed, this linkage type predominates in lignins (Table 1). The functional group distribution with regards to the linkage types for the C(α), C(β) and C(γ) atoms in the side chain is described by the Ridholm diagram³⁸ (Table 2). Thus, the literature data available to date do not provide an unambiguous definition of lignin as an individual chemical compound and this substantially prevents assessment of its reactivity by the methods of classical organic chemistry, *i.e.*, by studying reactions of simple monomers and dimers mimicking different substituted phenol–propane structural units of lignin. Such studies may only provide helpful information regarding the elementary reactions of the lignin functional groups with oxidants rather than predict unambiguously their reactions with lignin itself.

The residual lignin in sulfate pulp from *Pinus radiata* has been studied by means of mass spectrometry and ¹³C NMR spectroscopy.³⁶ Residual lignin was isolated by treating the sulfate pulp with cellulase. As the duration of sulfate cooking is increased, the number of the C–C bonds increases and the portion of the β-aryl-ether bonds in the residual lignin is decreased, thus indicating the higher degree of lignin condensation. Despite the reduction of a

Table 2. Functional group distribution in lignin according to bond types based on ¹³C NMR spectroscopic data (the Ridholm diagram).

Group	Structural unit ^a	Pro-portion
C(γ)–OH	coniferyl alcohol type	0.04
C(γ)–OH	dihydroconiferyl alcohol type	0.03
C(γ)–OH	guaiacylglycerol type	0.02
C(γ)–OH	other primary alcohols	0.60
C(γ)=O	coniferyl aldehyde type	0.03
C(γ)–O–C(α)	pinosresinol, phenylisochroman, open-type units	0.18
C(γ)–O–C(4)	ether group	0.02
C(γ)H ₃	methyl group	0.04
C(γ)H ₂	γ-lactone (ring 14a)	0.02
C(γ)=O	the same (ring 13a)	0.02
		total 1.00
C(β)–O–C(4)	general type	0.44
C(β)–C(5)	the same	0.14
C(β)–C(6)	"	0.04
C(β)–C(β)	"	0.14
C(β)–C(1)	"	0.10
C(β)–C(α)	coniferyl alcohol and coniferyl aldehyde type	0.07
C(β)H ₂	coniferyl alcohol type	0.03
C(β)–OH	guaiacylglycerol type	0.04
		total 1.00
C(α)–OH	coupling of rings 12–15; C(β)–C(1) bonds; guaiacylglycerol type	0.25
C(α)=O	keto group	0.06
C(α)=O	aldehyde group	0.11
C(α)–O–C(γ)	pinosresinol, phenylisochroman, open-type units	0.20
C(α)–O–C(4)	coupling of rings 17–18	0.11
C(α)–C(β)	coniferyl alcohol and coniferyl aldehyde type	0.07
C(α)H ₂	dihydroconiferyl alcohol type and others	0.06
C(α)–O–C(4)	general type, <i>e.g.</i> , in coupling of rings 3–4	0.10
C(α)–O–	bonds with carbohydrates and others	0.04
		total 1.00

^a For structural units and ring numbers, see Scheme 1.

Table 3. Functional group content in LMP and sulfate lignin.¹⁸

Functional groups	Number of groups per 100 phenol–propane units		Method of analysis
	fir-wood LMP ^a	pine-wood sulfate lignin ^b	
OH (total amount)	120	120	acetylation
guaiacol type	30	60	oxidation with KIO ₄
catechol type	—	12	reaction with Fe ²⁺ , calorimetry
aliphatic	90	48	see footnote ^c
COOH	5	16	methylation
CO (total)	20	15	treatment with (NH ₂ OH)·HCl, volumetry, KBH ₄
coniferyl aldehyde type	3	—	reduction, Δε _i -method ^d
α-CO	7	5	the same
β-CO and others	10	10	see footnote ^c

^a Molecular formula for a structural unit of fir-wood LMP is C₉H_{8.8}O_{2.4}(OCH₃)_{0.96}. ^b Molecular formula for a structural unit of pine-wood sulfate lignin is C₉H_{7.9}O_{2.1}S_{0.1}(OCH₃)_{0.82}. ^c Calculated by difference. ^d Method of differential UV spectroscopy based on the measurement of a difference in absorption of compounds with ionised and non-ionised phenolic and hydroxy groups in solutions of different pH.¹²

percentage of the β-aryl-ether bonds in lignin from 70% to 50%, the portion of these bonds in the residual lignin remained to be considerable even in the cases of low lignin content in pulp upon profound delignification. The sulfate lignin differs from slightly modified lignin of mechanical pulps (LMP) in the content of functional groups (Table 3).

The sulfate pine-wood lignin contains fewer carbonyl and aliphatic hydroxy groups and more carboxy and phenolic OH groups.^{1–3} It is free from the coniferyl–aldehyde groups, which are lost during the sulfate cooking,⁴² and virtually free from the benzyl alcohol OH or ether groups. During the sulfate cooking partial loss of the γ-hydroxymethyl and methoxy groups is also observed. In addition, contrarily to LMP, sulfate lignins contain the thiol group and elementary sulfur.^{8, 42}

Softwood lignins are mostly built up of guaiacol derivatives, while guaiacol and syringol derivatives are the main constituents of hardwood lignins. Thus non-fractionated sulfate birch-wood lignin contains approximately equal amounts of both types of derivatives.³⁶ The fractionation of lignin has shown that the ratio of syringol and guaiacol derivatives is increased from 0.8 to 1.5 with diminishing of the lignin molecular weight from 3500 to 650.²⁹

Examination of DHP has shown that these compounds have different structures and properties depending on the manner of addition of initial monomers (substituted phenol–propane units) to the reaction mixture. When the monomer is added in one portion, the couplings of dimeric radicals with a monomer occur more rarely than in the gradual addition, whereas the couplings of a ‘monomer–monomer’ type become more abundant. In this case, the C(β)–C(5) bonds predominate.¹⁵ The probability of the radical coupling of a ‘polymer–polymer’ type is higher on gradual addition of the monomer due to the low concentration of the latter. In this case, the C(β)–O–C(4) bonds predominate. It should be noted that recent hydrodynamic investigations of DHP and slightly modified softwood lignins do not quite agree with this hypothesis of the existence of two types of lignins.²

The native lignin is synthesised in plants from monomeric molecules that usually have from two to four functional groups.^{15, 28} The formation of both branched chains and network structures (at gel-point) is theoretically possible.²⁴ As has already

been pointed out, the interaction of the growing lignin polymeric chains with surrounding macromolecules of non-cellulosic polysaccharides in plant tissues results in the formation of an amorphous lignocellulosic matrix. According to the Erin’sh hypothesis,^{7, 26} the three-dimensional structure of this matrix represents a superposition of three networks, *viz.*, a network of hydrogen bonds between lignin and carbohydrates (H-network), a network of the lignin–carbohydrate bonds (LC-network) and a network of lignin itself. The most important arguments in favour of this hypothesis are insolubility of native lignin in all neutral solvents without preliminary chemical or mechanical treatment and high polydispersity of lignins isolated from wood tissues. Based on the theory for branching processes, the average molecular masses for sol fractions of model lignin compounds have been calculated³⁰ to be 1300–13 800. According to these values, the lignin extracted with ethanol in the absence of catalysts can be considered as a sol fraction of the native lignin. A new promising direction in the study of biosynthesis and the structure of lignin is a computer-assisted simulation of the growth of fractal clusters with fractional dimensionalities.²⁴

Thus the currently available results of direct and indirect chemical, physicochemical and physical investigations taken altogether do not allow one to define unambiguously the formula and all levels of structural organisation for lignin. The properties and reactivities of industrial lignins depend to a considerable extent on the preparation methods.^{1, 17} The residual lignin is the most condensed and high-molecular-weight part of the lignin matrix involved into a lignin–cellulose composition, and its selective removal from cellulose fibres can only be achieved with the use of oxidants.⁴³ The presence of different types of functional groups and bonds in sulfate lignin and in the residual one predetermines a wide range of reagents used for lignin oxidative destruction in the preparation of cellulose from raw wood materials.

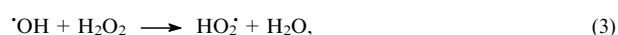
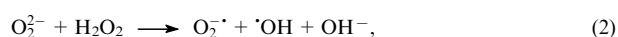
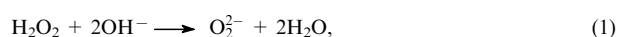
The main method for the study of lignin transformations is based on the analysis of reaction products resulting from the reaction of model compounds with oxidants. The most efficient reagent used for oxidative destruction and solubilisation of residual lignin in the pulp bleaching are molecular chlorine,^{44–46} sodium hypochlorite,^{47–49} hypochlorous acid,^{48, 50} sodium chlorite,⁵⁰ chlorine dioxide,^{51, 52} organic^{9, 10, 53} and mineral⁵⁴ peroxy acids, hydrogen peroxide,^{55–57} oxygen^{58, 59} and ozone.^{60–62} One of promising approaches to oxidative destruction of residual lignin in industrial pulps during bleaching is the biotechnological method.^{63, 64}

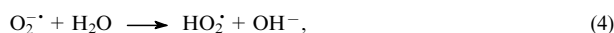
Molecular chlorine is widely employed in the pulp industry for oxidation of lignin during the pulp bleaching, however, its application is accompanied by concomitant formation of a number of toxic aromatic chlorine-containing products,^{65, 66} including dioxins.⁶⁷ The use of sodium hypochlorite for the pulp bleaching is accompanied by the formation of chloroform.⁶⁸ Chlorinated hydrocarbons are dangerous for both living organisms and the Earth ozone layer. Therefore, the oxidation processes based on the use of environmentally safer reagents, such as hydrogen peroxide, chlorine dioxide and ozone, are of great importance. The reactions of model lignin compounds with these reagents are discussed below.

III. Oxidation of model compounds

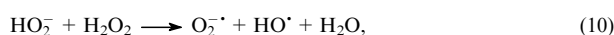
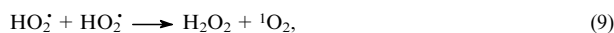
1. Oxidation with hydrogen peroxide and oxygen

In an alkaline medium, hydrogen peroxide can undergo various transformations. When the concentration of a base is high, the decomposition of H₂O₂ follows predominantly a radical mechanism with the formation of molecular oxygen:^{69, 70}



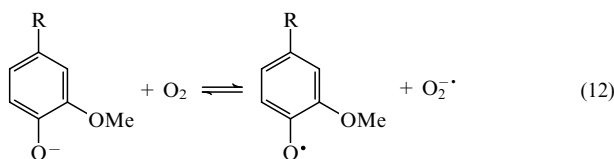


The oxidation of lignin with oxygen in an alkaline medium is accompanied by generation of the radical anions $\text{O}_2^{\cdot-}$, hydroxyl radicals and singlet oxygen ($^1\text{O}_2$). The schemes of generation of the reactive oxygen forms and their mutual transformations are described by the following equations



Comparison of these equations with the equations (1)–(5) shows that both systems contain all the above-mentioned species independently of the oxidant used (O_2 or H_2O_2).^{70, 71} The equations (8), (9) and (11) account for the chemiluminescence observed in the oxidation of lignin with oxygen.^{71–73} The decomposition of H_2O_2 is catalysed by transition metal ions (Fe, Mn, Cu, Zn, *etc.*) that are present in plant tissues and lignin.^{59, 74, 75}

The rate and the depth of the lignin oxidation with H_2O_2 and O_2 depends on the reaction conditions. The reaction (6) leads to the single-electron oxidation of a phenolic fragment in lignin.

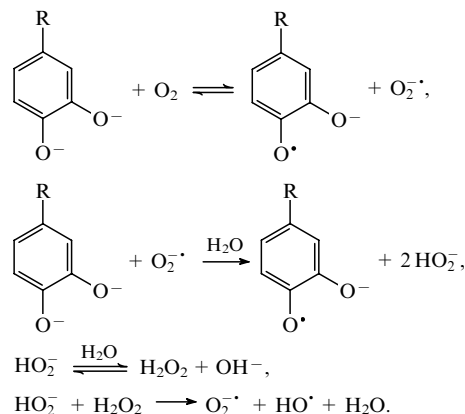


The superoxide radical anion $\text{O}_2^{\cdot-}$ takes part in the single-electron transfer as a reducing agent and in nucleophilic deprotonation [equation (7)] and substitution reactions. In aqueous and non-aqueous media, this radical anion can oxidise hydroquinones⁵³ and aromatic dianions.^{69, 70} Vanillin, acetovanillone and guaiacol are resistant to the action of the radical anion in aprotic (pyridine, DMSO) solvents, while α -methylvanillyl alcohol is rapidly oxidised by this oxidant to acetovanillone and hydroquinone is oxidised to acids.⁷⁶ Despite the oxidation of some model compounds, the sulfate lignin itself does not undergo any noticeable changes except the partial loss of the phenolic hydroxy groups (according to the data of liquid chromatography, ^1H NMR, IR and UV spectroscopy).^{77–79}

The hydroxyl radical $\text{HO}^{\cdot}$ acts as an electrophile to form σ -complexes with aromatic structural units of lignin. The latter undergo subsequent transformations involving cleavage of the side-chain C–C bonds of lignin, cleavage of the aryl–aryl bonds and demethylation.^{80, 81} The radicals $\text{HO}^{\cdot}$ also induce lignin hydroxylation, cleavage of biphenyl bonds and degradation of aromatic rings.⁴³ In this respect, these radicals are more reactive than $\text{O}_2^{\cdot-}$. On the contrary, in reactions with carbohydrates,^{71–73} the radical $\text{HO}^{\cdot}$ is less reactive: its addition to the aromatic fragments of lignin occurs fivefold faster than hydrogen abstraction from carbohydrates. Unlike $\text{HO}^{\cdot}$, the superoxide radical anions react with lignin with difficulty but easily destroy cellulose.⁷⁰ This apparently is a result of a different ratio of the nucleophilic and electrophilic reactive centres in lignin and carbohydrates.

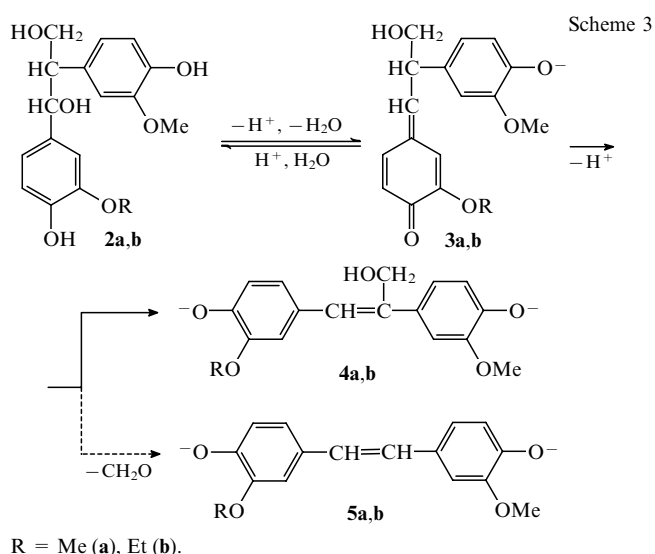
It was found⁷⁰ that lignin and catechol are readily oxidised at pH 14 with hydrogen peroxide even at room temperature producing the radical anions $\text{O}_2^{\cdot-}$. The latter are detected by the appearance of an intense violet colour in the presence of Tetrazolium Violet 1–2 min after the beginning of the reaction. Such model compounds as guaiacol, isoeugenol, vanillic and

ferulic acids, β -guaiacyl ether of α -guaiacylethanone and β -guaiacyl ether of α -guaiacylethanol did not react with H_2O_2 even at 60 °C for 4 h. An important practical outcome of this study was the finding that catechol and the Pepper lignin do not virtually undergo oxidation at $\text{pH} \leq 11.0$. On increasing pH to 12.25, the rate of the catechol oxidation is sharply increased, which is rationalised⁷⁰ as the result of the second-step dissociation of catechol ($\text{p}K_a \sim 12.5$, for the first step $\text{p}K_a = 9.45$). Kinetic studies provide evidence on an induction period prior to the appearance of H_2O_2 in the system, which catalyses the process described by the following equations



Thus, at high concentration of a base (NaOH), low content of oxygen and moderate temperatures the most probable reaction centres in lignin are the catechol structural units, and hydrogen peroxide acts on lignin in the same manner as does oxygen.

The oxidation of dimeric model lignin compounds of the 1,2-diarylpropane-1,3-diol type with hydrogen peroxide and oxygen has been studied⁷⁹ in the example of 1-(4-hydroxy-3-methoxyphenyl)-2-(4-hydroxy-3-methoxyphenyl)propane-1,3-diol (**2a**) and 1-(3-ethoxy-4-hydroxyphenyl)-2-(4-hydroxy-3-methoxyphenyl)propane-1,3-diol (**2b**). It was preliminarily shown that compound **2b** forms 3-(3-ethoxy-4-hydroxyphenyl)-2-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-ol (**4b**) and 3-ethoxy-4,4'-dihydroxy-3'-methoxystilbene (**5b**) (side reaction) dianions at pH 11–13 in the absence of oxygen (in vacuum), the equilibrium mixture containing *ca.* 95% of the initial dimer (Scheme 3).



Analogous stilbene derivatives were earlier^{80, 81} obtained from diols of the type **2a,b**. However, the α,β -elimination products are formed in higher yields only in the case of structures containing hydroxymethylphenyl fragments.⁸²

Vanillin and ethylvanillin instead of stilbene dianions **4b** and **5b** were obtained in experiments with preliminary passage of air or

nitrogen through the system, thus indicating the oxidative character of the process. This result can be explained by rapid autooxidation of the initially formed stilbenes with a trace amount of oxygen dissolved in the alkaline solution.

The oxidation of diol **2b** with a solution of H_2O_2 stabilised at pH 10.5 results in the formation of ethanol, methanol ethylvanillin and small amounts of other compounds (the conversion of the initial diol is 30%) (Table 4). After 4 h of the treatment, 85% of hydrogen peroxide still remained unconsumed. Some amount of H_2O_2 is lost due to decomposing, and about 1%–2% of the oxygen thus generated is consumed in the oxidation of diols as follows from the analysis of stilbene and the initial diol autooxidation products.

Diols of the type **2** are less reactive towards H_2O_2 than the products of their initial oxidation.⁷⁹ According to the composition of the oxidation products, the main direction of the oxidation of these diols with the stabilised hydrogen peroxide (*i.e.*, in an oxygen-free system) involves the nucleophilic attack of the HO_2^- anions on quinonemethide anion **3** and the oxidation of stilbene dianion **4**. The hydroperoxide thus formed undergoes consecutive rearrangement and fragmentation yielding the hydroquinone dianion (**6**) and α -(4-hydroxy-3-methoxyphenyl)- β -hydroxypropanol anion (**11**). The latter is converted into the guaiacylglycol anion (**8**) (Scheme 4).

The oxidation of phenylpropan-2-one with hydrogen peroxide follows the same mechanism, this reaction may be regarded as an alkaline analogue of the Baeyer–Villiger reaction.⁸² It should be noted that dihydroxyphenyl derivatives, like guaiacylglycol, have also been obtained by the action of basidiomycetes *Phanerochaete chrysosporium* on diols of the type **2**.⁸³ The same mechanism for conversion of α -hydroperoxide into guaiacylglycol and ethylvanillin has been proposed in another study.⁸⁴

The mechanism of oxidation of stilbenes **4b** and **5b** with hydrogen peroxide in alkaline media in the absence (or virtual

Scheme 4

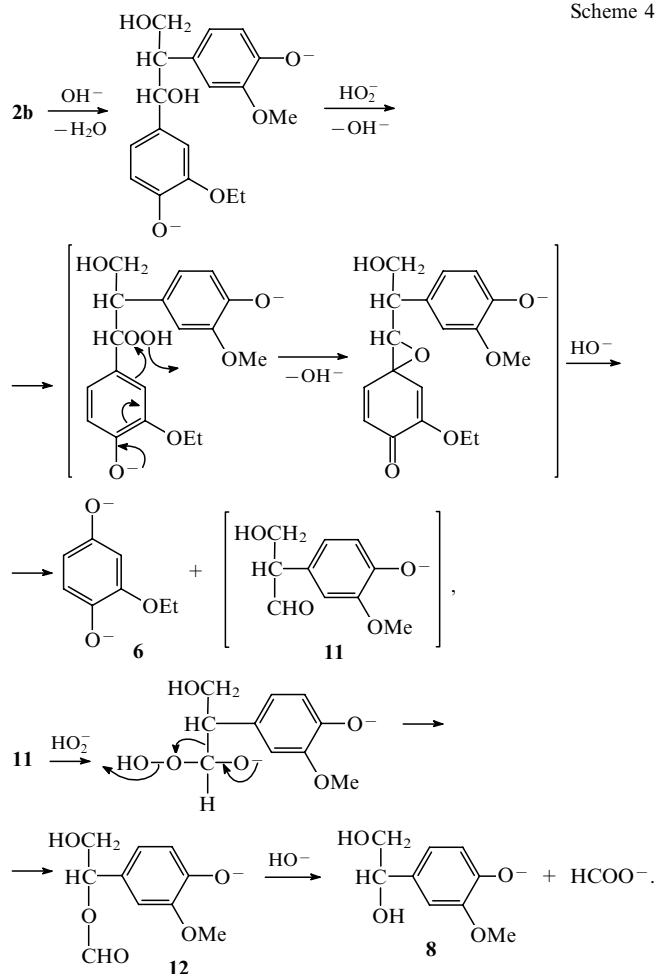


Table 4. Oxidation products of the diol **2b** in a stabilised solution of hydrogen peroxide (*A*), with hydrogen peroxide in the absence of a stabiliser (*B*) and with atmospheric oxygen (*C*).⁷⁰

Component of the reaction mixture	Yield (with respect to the theoretical one) (mol. %)		
	<i>A</i> ^a	<i>B</i> ^b	<i>C</i> ^c
1-(3-Ethoxy-4-hydroxyphenyl)-2-(4-hydroxy-3-methoxyphenyl)propane-1,3-diol (2b)	70	31	14–18
Ethoxyhydroquinone (6)	traces	~1	0
Ethylvanillic acid ^d	"	4	0
Ethylvanillin (7)	6–7	~14	60
Guaiacylglycol (8)	2	4	7.5
ω -Hydroxyacetoguaiacone (9)	0	2	traces
Methoxyhydroquinone	—	—	"
1,2,4-Trihydroxybenzene (10)	—	3.5	0
Methoxy- and ethoxybenzoquinones	—	traces	1–2
3-(3-Ethoxy-4-hydroxyphenyl)-2-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-ol dianion (4b)	0	—	—
3-Ethoxy-4,4'-dihydroxy-3'-methoxy stilbene dianion (5b)	1	—	—
Methanol	15	29	36
Ethanol	7	17	4–5
Residual H_2O_2	85	5	—

^a Reaction conditions: 45 °C, 4 h, pH 10.5, [dimer] = 0.07×10^{-3} , [DTPA] = 0.4×10^{-3} , $[\text{MgSO}_4]$ = 0.16×10^{-3} mol litre⁻¹, $[\text{H}_2\text{O}_2]/[\text{dimer}]$ = 3. ^b Same reaction conditions but without addition of DTPA and MgSO_4 . ^c Reaction conditions: 45 °C, 4 h, pH 10.5. ^d Hydroxyethylvanillin in the case of the method *B*.

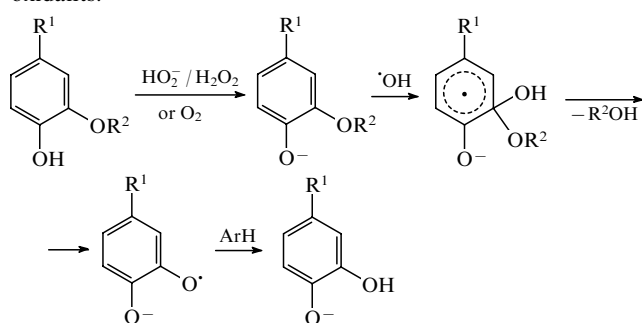
absence) of oxygen is rather difficult to describe in detail since the hydroperoxide anion, as a strong nucleophilic reagent, cannot directly attack the electrophilic alkene structures. The oxidation occurs as the result of preliminary rearrangement of the stilbene dianion **4b** into quinonemethide and subsequent attack by the hydroperoxide anion. ω -Hydroxyacetoguaiacone, ethoxyhydroquinone and acetoguaiacone were expected to be the products of these reactions. However, only a trace amount of ethoxyhydroquinone has been detected (Table 4). Thus, the reaction of non-dissociated hydrogen peroxide with the stilbene **4b** seems to be more probable.⁷⁹

Comparison of the results of oxidation of the diol **2** with a non-stabilised alkaline solution of hydrogen peroxide at constant pH 10.5 with those obtained in its oxidation with stabilised H_2O_2 in the absence of oxygen (Table 4) allows one to reveal a number of differences, *viz.*, the decomposition of non-stabilised hydrogen peroxide is almost complete, the degree of conversion for the initial diol is increased from 30% to 69%, the yields of the oxidation products (especially of ethanol, methanol, ethylvanillin and alkoxyhydroquinone) are higher, and the products contain the following organic acids:⁷⁰

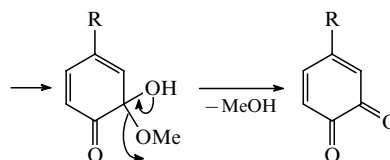
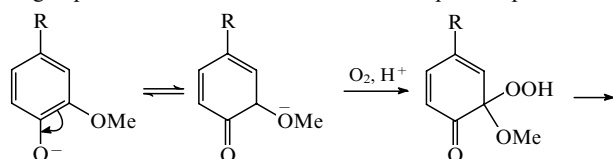
Acid	Yield (%)
Succinic	≤ 1
Oxalic	≤ 1
Hydroxymaleic	1–2
Malonic	5
Glycolic	1–2

These differences are explained by the presence in the reaction mixtures of some additional oxidants: oxygen, hydroxyl radicals and superoxide radical anions along with non-stabilised hydrogen peroxide, which are formed in the reactions (1)–(4). In the other

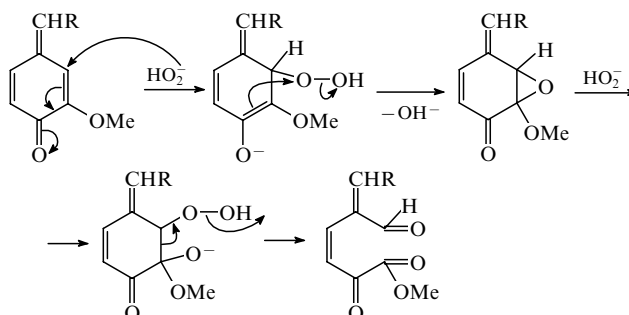
words, the oxidation process induces the generation of new oxidants.


$$R^1 = \text{OH, OAc}; R^2 = \text{Me, Et.}$$

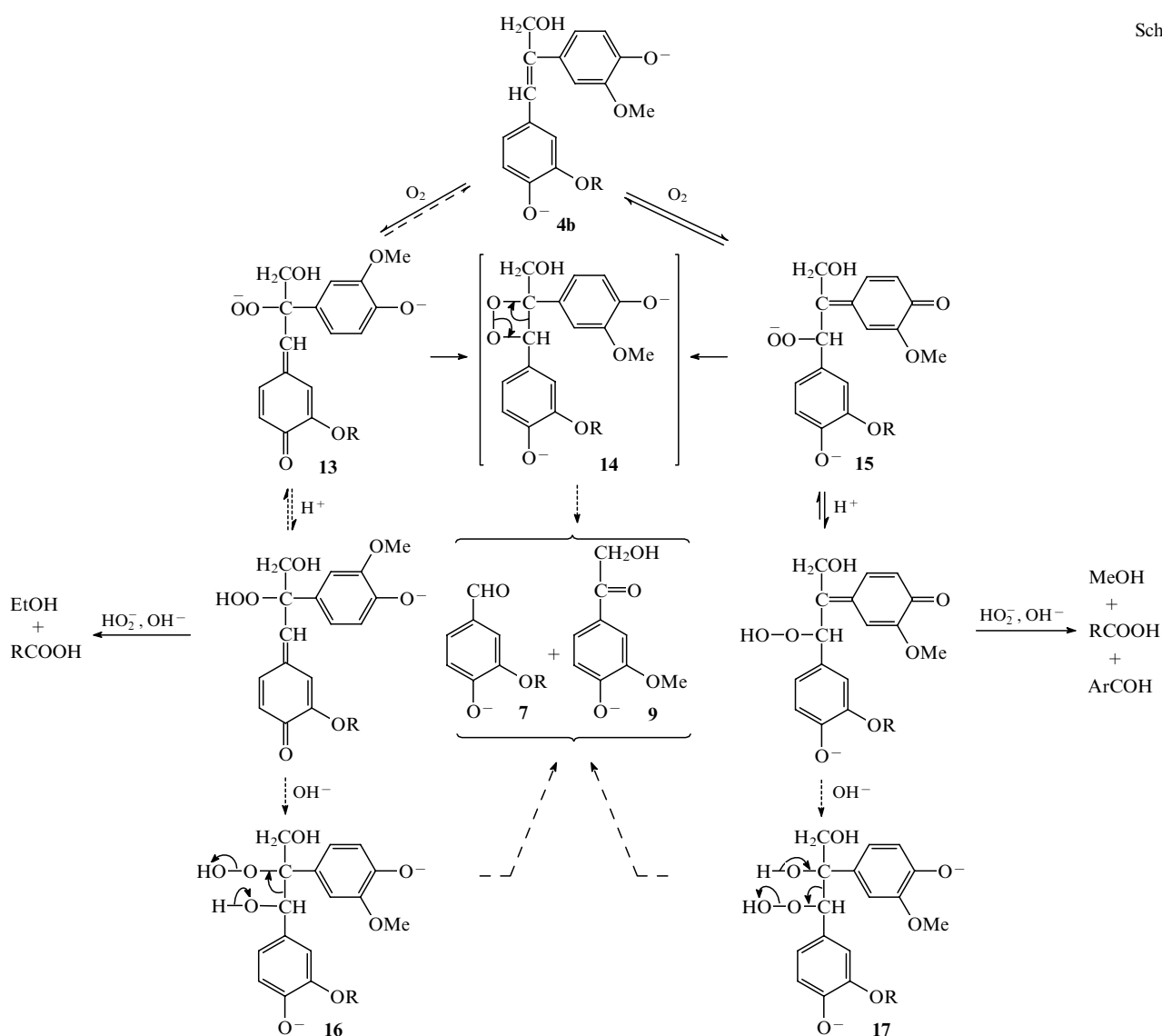
The action of oxygen generated upon decomposition of hydrogen peroxide results in the formation of quinoid products.



Quinonemethides of the type **3** and *o*-quinones which appear in the reaction mixture are oxidised by hydroxyperoxide anions to carboxylic acids.



When the diol **2b** is allowed to react with H₂O₂ in the absence of a stabiliser and without maintenance of pH at 12.5, the pH value is decreased to 10 due to the accumulation in the reaction



Scheme 5

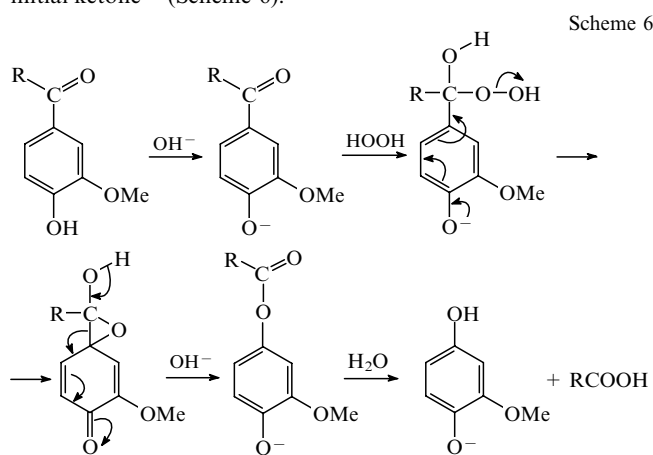
mixture of carboxylic acids. Simultaneously, there is observed an increase in the portion of nonconsumed diol and an increase in the total yield of ethylvanillin and ethoxyhydroquinone (from 15% to 29%) as a consequence of the increased concentrations of hydroperoxide anion and non-dissociated hydrogen peroxide in the solution.

The particular contribution of oxygen generated *in situ* in the total oxidation process was estimated in the oxidation of the diol **2b** with molecular oxygen, which allowed the authors⁷⁹ to propose a more detailed mechanism for this reaction (Scheme 5), which takes into account the published data.^{80,81} As has already been shown, the diols **2a,b** are partially converted in alkaline media into the stilbene dianions **4** and **5**, which undergo intense oxidative destruction with oxygen. According to the much higher yield of methanol compared with that for ethanol, the reaction predominantly proceeds by a pathway involving the intermediate formation of hydroperoxide **15**.

The data considered above show that model structures like **2a,b** have low reactivity towards hydroperoxide anion but can be relatively easily oxidised with oxygen to low-molecular-weight products. In the presence of hydrogen peroxide, stabilisers, and at $\text{pH} \leq 10.5$, the main oxidising reagent is the hydroperoxide anion, whereas molecular oxygen and its other reactive forms, *i.e.*, O_2^- , O_2 and $\cdot\text{OH}$, become the major oxidants upon increase in pH to 12.

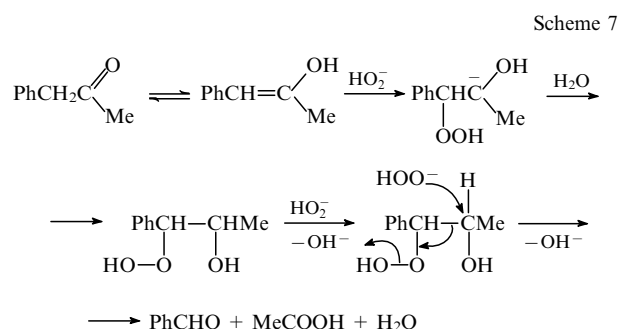
Alkaline hydrogen peroxide readily oxidises α,β -unsaturated ketones of the coniferyl aldehyde type and α,β -diketones but not α -ketones with an etherified phenolic hydroxy group, nor (virtually) propioveratrone and α -hydroxypropioveratrone.⁷⁹

α -Ketones are oxidised through addition of the hydroperoxide anion to the electrophilic carbon atom of the carbonyl group with the intermediate formation of a quinoid compounds. Following recovery of the aromatic system, an ester is formed, which is then hydrolysed. The products of such reactions are vanillyl alcohol and a carboxylic acid with the same aliphatic radical as in the initial ketone⁸² (Scheme 6).

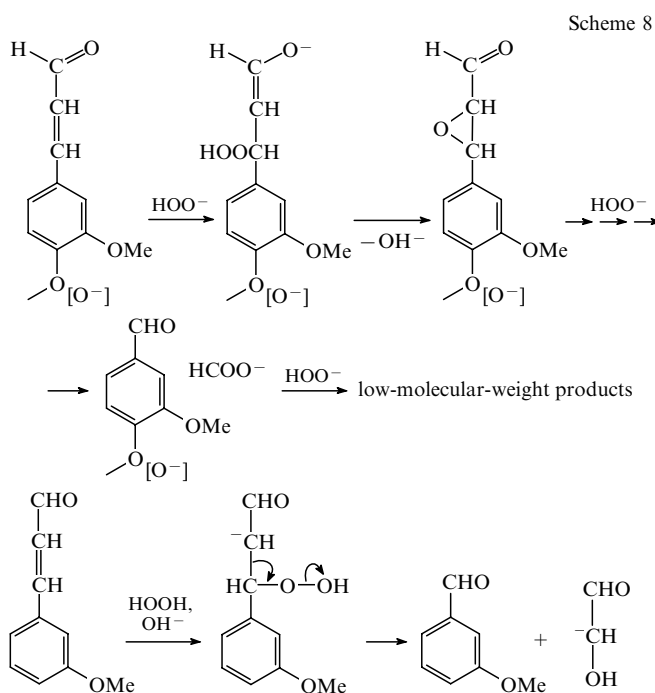


In the case of model compounds of the general formula $\text{ArCH}_2\text{C}(\text{O})\text{Me}$, the intermediate formation of enolic tautomers is observed.¹⁰ An investigation of the oxidation of a series of ketones bearing different substituents in the positions 3 and 4 of the benzene ring has shown⁸² that these reactions mainly result in the rapid cleavage of the initial phenylpropan-2-one into benzaldehyde and acetic acid (Scheme 7).

The mechanism of these reactions apparently involves an attack by the hydroperoxide anion of an enolic tautomer on its $\text{C}(\alpha)$ atom and an intermediate formation of β -hydroxyhydroperoxide anion, fast protonation of this anion by water and subsequent attack by the hydroperoxide anion on the $\text{C}(\beta)$ atom of the initial carbonyl group, leading eventually to synchronous cleavage of the $\text{O}-\text{O}$ bond in the intermediate organic peroxide



and the $\text{C}(\alpha)-\text{C}(\beta)$ bond. The oxidation of α,β -unsaturated ketones of the coniferyl aldehyde type to benzaldehyde occurs *via* the corresponding hydroperoxides and epoxides (Scheme 8).



The reactions of the hydroperoxide anions with quinoid structures result either in the ring opening or in the splitting off of the side chains (Scheme 9).^{8,85} In the oxidation of methoxy-substituted quinones, the demethoxylation and formation of methanol were also observed.

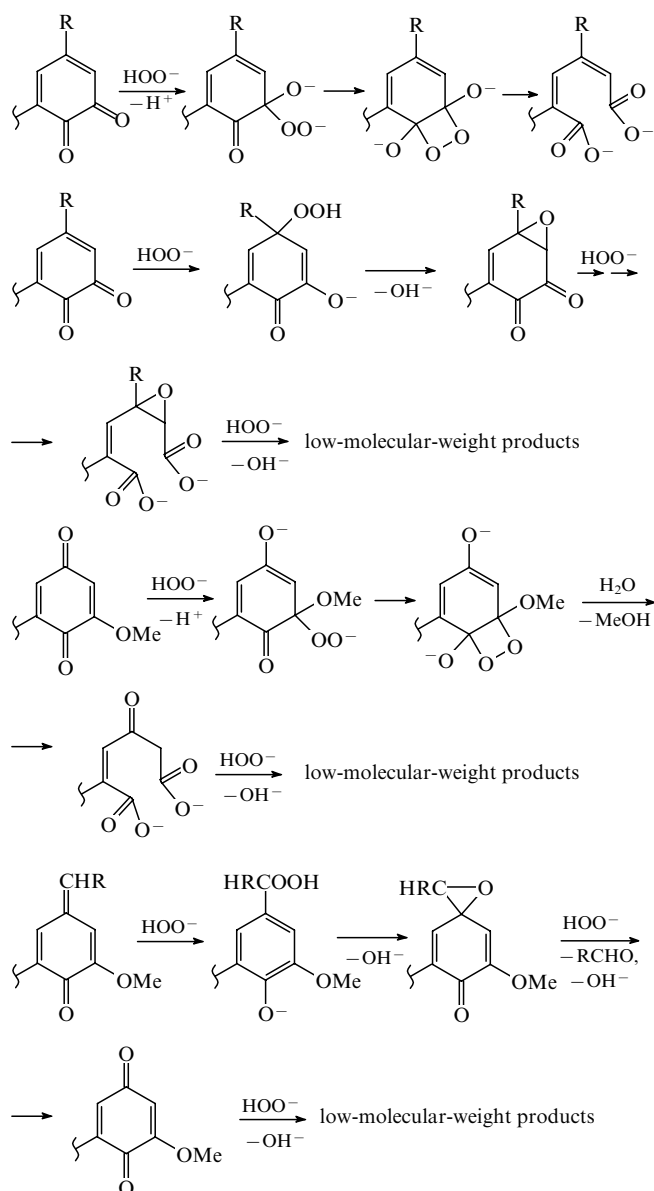
The oxidation of the quinone rings represents apparently a longer reaction pathway in lignin oxidative destruction, even if decomposition of non-terminal units is considered. This requires a larger amount of an oxidising reagent for the scission of the carbon chains than for the side-chain oxidation.

An important feature of the reactions shown in Schemes 6–9 consists in participation of the hydroperoxide anion as a reactive nucleophilic species, which reacts with electron-withdrawing (electrophilic) sites of lignin.

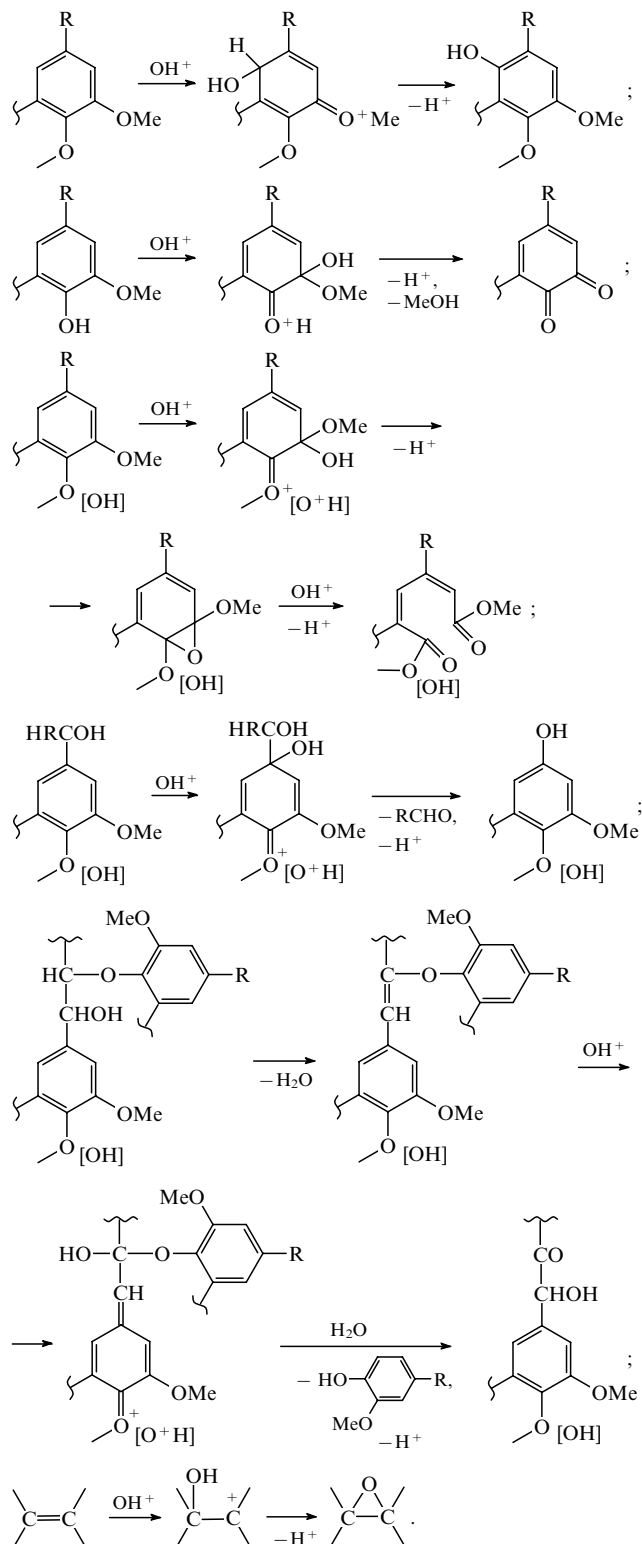
In an acidic medium, the mechanism of reaction of hydrogen peroxide with organic compounds is analogous to that of peroxy acids. In this case, either a protonated hydrogen peroxide H_3O_2^+ or a hydroxonium ion are those reactive electrophilic species which attack the aromatic structures.¹⁰

The oxidation of model lignin compounds with hydrogen peroxide and peroxy acids mainly results in the hydroxylation of the aromatic nuclei, oxidative demethoxylation, oxidative benzene ring opening, splitting off of the side-chains, cleavage of the $\text{C}(\beta)-\text{O}$ ether bonds and formation of epoxides (Scheme 10).

Scheme 9



Scheme 10



Salts of peracetic, performic and mono- and diperoxysulfuric acids in alkaline media are employed as the oxidants for oxidative delignification of wood tissues and mechanical pulps.^{8–10, 86–88} Under conditions favouring stabilisation of the peroxy anion, this acts as a nucleophilic reagent.

The oxidation of structures of the benzyl alcohol type with hydrogen peroxide and peroxy acids to ketones and aldehydes may follow the radical mechanism involving hydroxyl radicals.^{8–10, 85}

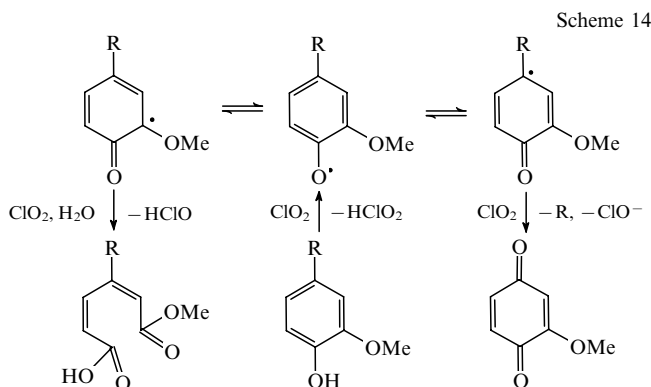
It should be noted that studies on the oxidation of compounds that mimic the lignin structural fragments are only useful in drawing a probable scheme (and in some cases, in elucidation of the mechanism) of reactions of the residual pulp lignin. In fact, the processes of oxidative destruction of the residual lignin under the action of a majority of peroxides do not go to completion (except for ozonolysis) and kinetic parameters determined for the oxidation of model compounds substantially differ from those observed during the lignin destruction in a polymeric lignocellulosic matrix.

2. Ozonolysis of model compounds

Reactions of ozone with organic compounds are widely used in organic synthesis, qualitative and quantitative analyses and chemical technology. The mechanisms of these reactions have been considered in detail.^{89, 90} In application to lignin, ozonolysis has been employed to prove its aromatic nature, to determine the nature of substituents in the aromatic rings⁹¹ and to study the three-dimensional structure of side chains in the phenol–propane structural units.⁹²

3. Oxidation of lignin with chlorine dioxide

Chlorine dioxide oxidises lignin in lignin–cellulose matrices without affecting cellulose. Lignin phenolic structural units are oxidised with ClO_2 upon abstraction of the hydrogen atoms from the phenolic hydroxy groups. Muconic acids and quinoid compounds are the final products of such reactions, which are formed without loss of the methoxy groups^{99–101} (Scheme 14).

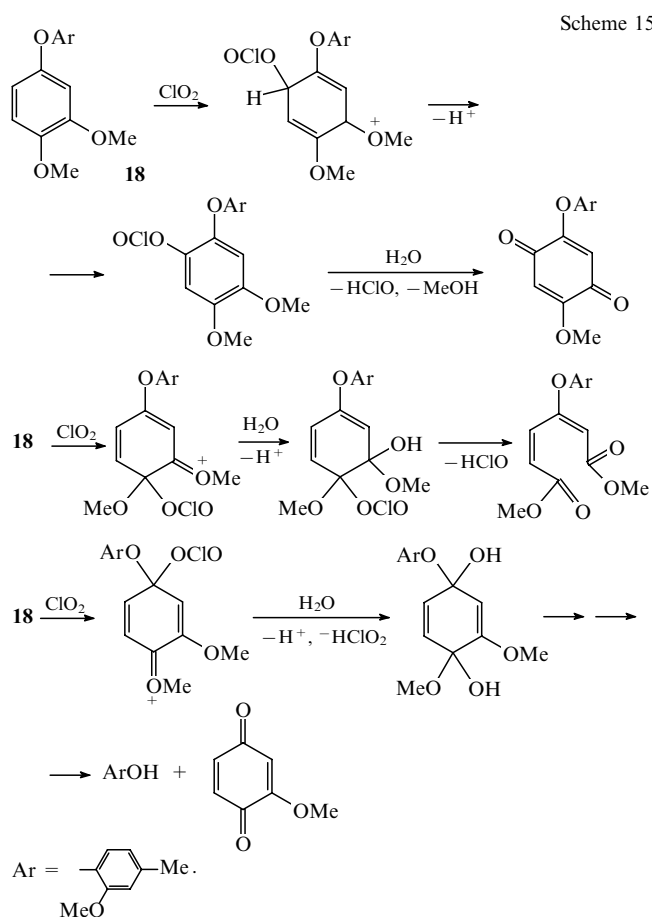


In the case of aromatic ethers, *e.g.*, 4-methyl-2,3',4'-trimethoxydiphenyl ether (**18**), three different directions for the reaction with chlorine dioxide are possible.^{99,100} These involve the formation of quinoid structures, opening of one of the aromatic rings and cleavage of the diaryl ether bond leading to the formation of hydroquinone and phenol derivatives (Scheme 15).

Veratryl β -guaiacyl ether (**19**) undergoes homolytic fragmentation under the action of chlorine dioxide, one of the reaction products being veratraldehyde. In parallel, the oxidative dehydrogenation of the α -hydroxy group occurs (Scheme 16).

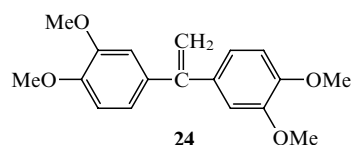
The oxidation of 4,4'-dihydroxy-3,3'-dimethylstilbene (**20**), 4-hydroxy-3,3',4'-trimethoxystilbene (**21**) and 3,4,3',4'-tetramethoxystilbene (**22**) (the most common model compounds of native and residual lignins) with chlorine dioxide has been studied.^{99–101} The main transformations of stilbenes **20–22** are shown in Scheme 17.

Yet another model compound of the residual lignin is 3,4-dimethoxy- β -(2-methoxyphenoxy)styrene (**23**). It reacts with chlorine dioxide by a similar mechanism (Scheme 18). The oxidation involves the formation of a complex of the oxidant with the π -electronic system of the alkene fragment.¹⁰¹ In an acidic medium, this complex is protonated to form a resonance-stabilised radical cation and HClO_2 . The addition of ClO_2 to the β -radical generated leads first to the chlorous ester (**A**), which is

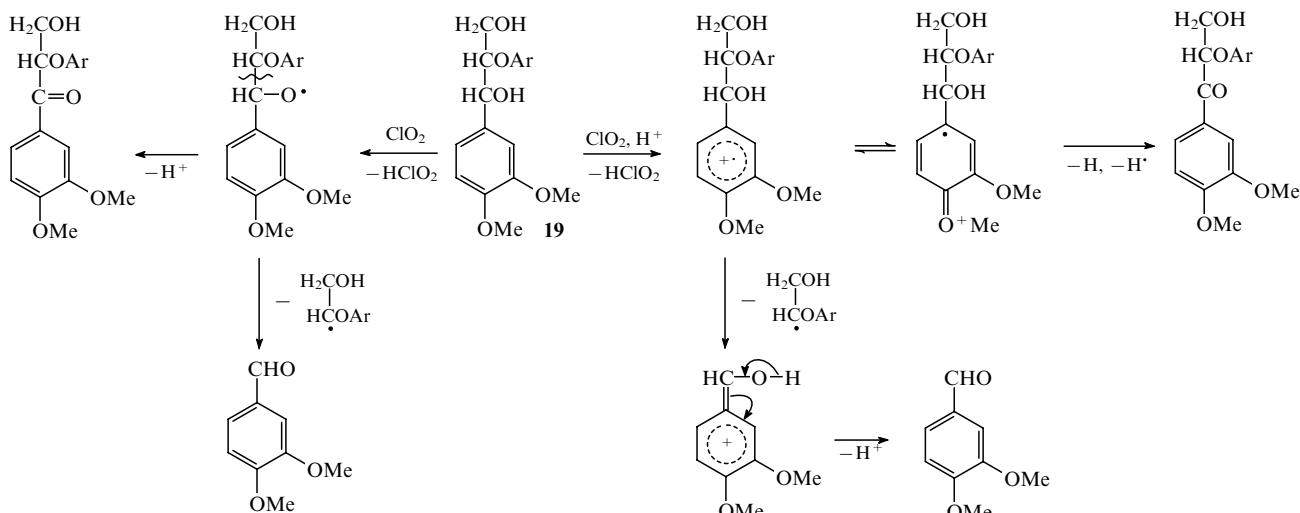


further converted into the ester **B**, from which aldehydes, ketones and esters are formed as the final products.

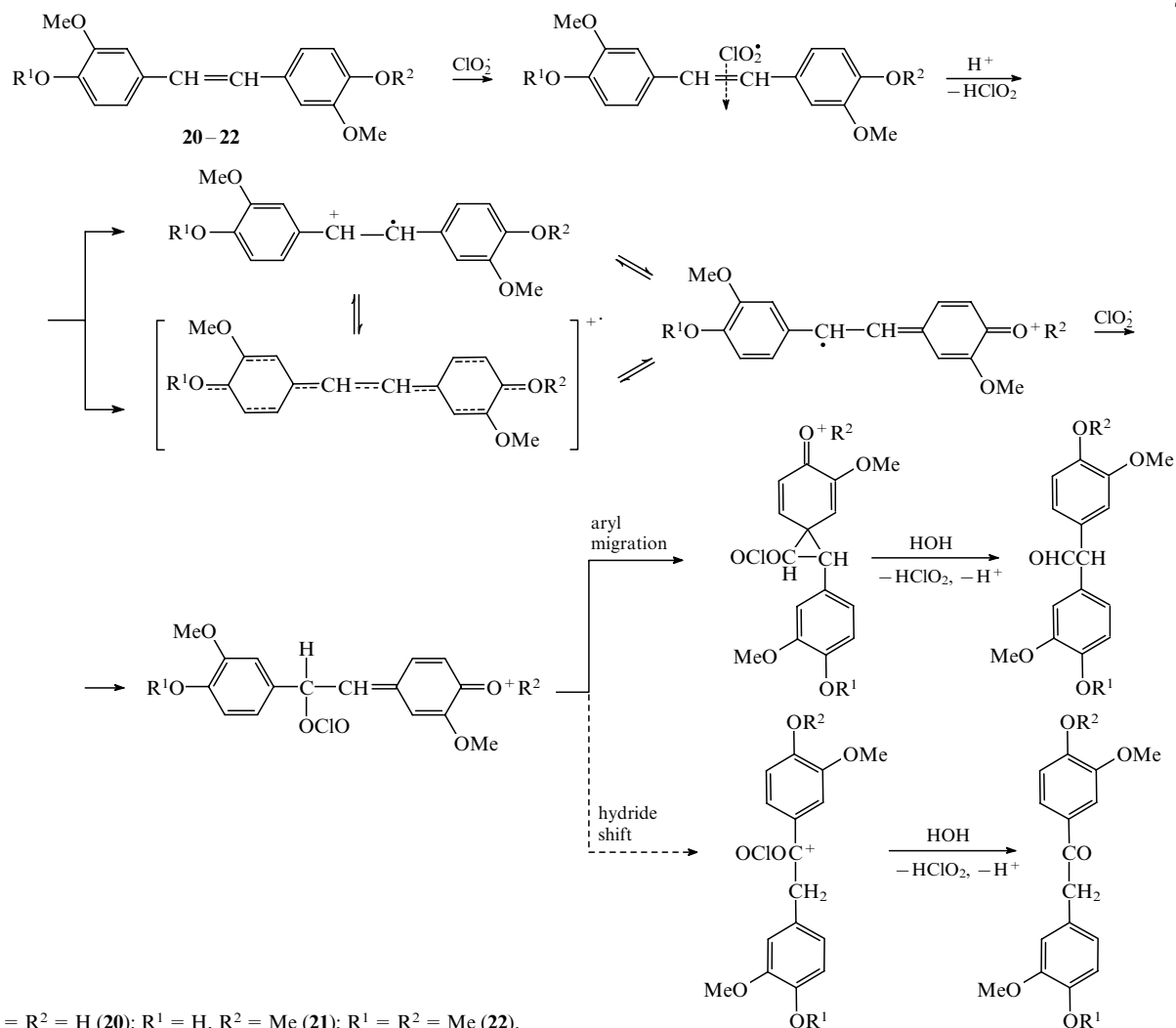
A possibility of the formation of 1,1-bis(3,4-dimethoxyphenyl)ethylene (**24**) from the corresponding stilbene as a result of aryl radical migration has been shown.¹⁰²



Scheme 16

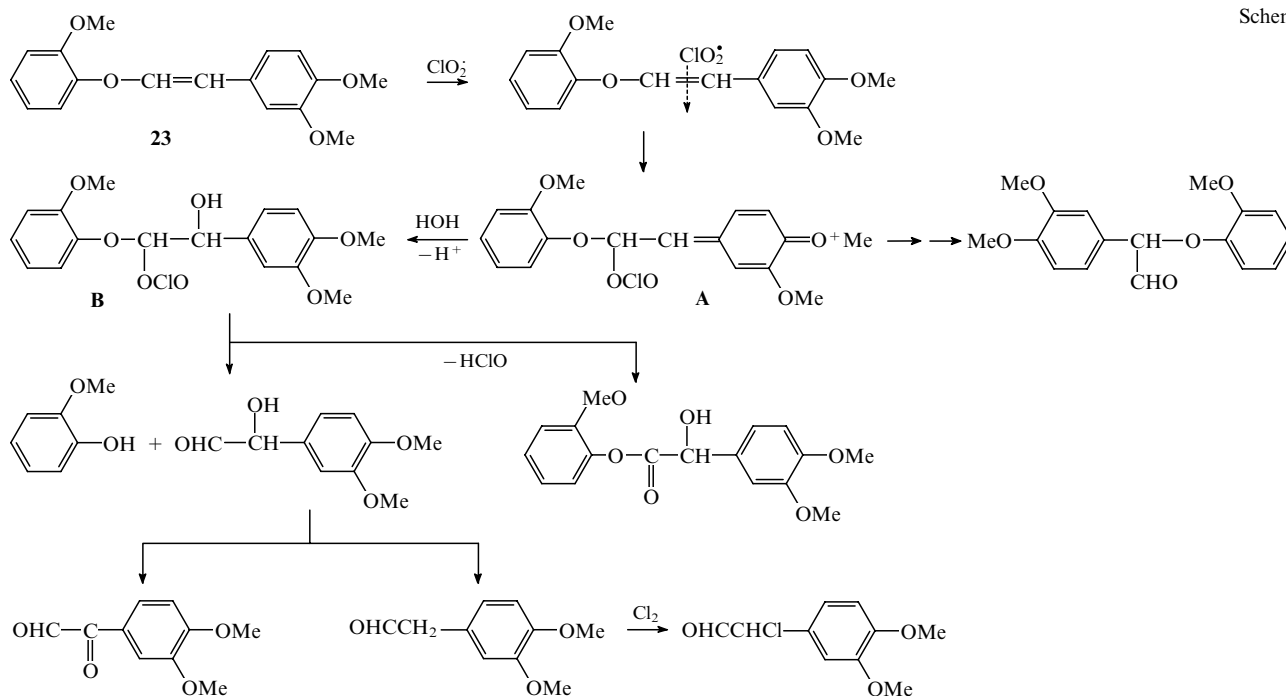


Scheme 17



$\text{R}^1 = \text{R}^2 = \text{H}$ (**20**); $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$ (**21**); $\text{R}^1 = \text{R}^2 = \text{Me}$ (**22**).

Scheme 18



Unlike stilbenes **20–23**, compound **24** does not undergo fragmentation under the action of chlorine dioxide. Among the

reaction products, only mono- and dichlorinated derivatives have been found. Oxidative demethoxylation also takes place.

In general, the early stages of the reactions of model lignin compounds with chlorine dioxide result in the formation of conjugated carbonyl groups, *i.e.*, in new chromophoric groups and systems which, as has been shown earlier, are readily oxidised with hydrogen peroxide according to the ionic mechanism involving the nucleophilic addition of the hydroperoxide anion.

IV. Combined action of oxidants on the sulfate pulp lignin

As has already been mentioned, lignin remaining in the sulfate pulp after cooking represents the most condensed, and strongly bound to polysaccharides, part of modified natural lignin (residual lignin). Despite the fact that the composition (various combinations of bonds, functional groups and structural units) and three-dimensional (network^{5,7,26} and fractal^{22,24,25}) polymeric structure of lignin do not allow prediction of the degree and the rate of its oxidative destruction, analysis of the results of the studies on an oxidation of model lignin compounds with hydrogen peroxide, oxygen, ozone, chlorine dioxide and other reagents (*vide supra*) makes it possible to elucidate general features of this process.^{8–10}

The reactivity of lignin towards oxidants depends on the nature of the reactant and the presence of nucleophilic and electrophilic sites in the lignin macromolecule. Under conditions of acid and base catalysis, each particular reagent can produce differently reacting species depending on the medium acidity. A classification of reagents¹⁰ used for lignin oxidation according to their electron-donor and electron-acceptor properties (or nucleophilicity and electrophilicity, respectively) is given in Table 5. The mechanisms of their interaction with lignin and the reactivity of residual lignin itself substantially affect the rate and the depth of the sulfate pulp delignification and a number of the operation steps in pulp bleaching.

The oxidation of nucleophilic alkene fragments in lignin occurs as the initial addition of an electrophile followed by the attack of a nucleophile (Scheme 19).¹⁰ The addition of electrophiles to lignin results in the appearance of new electrophilic sites in the lignin macromolecule and their activation towards the action of nucleophiles.

If one form of the reagent predominates and no cooperation exists between nucleophilic and electrophilic species, the rate of dissolution of the electrophilic reaction products of residual lignin is substantially decreased, which apparently leads to deceleration of the sulfate pulp delignification and to non-rational consumption of bleaching reagents in the chemotechnological processes. The efficiency of the sulfate pulp delignification is especially low when such environmentally safe reagents as hydrogen peroxide and ozone are used compared to chlorine-containing reagents (Table 6).¹⁰³

Normally, complete dissolution of the reaction products of lignin with electrophilic oxidants requires treatment with alkali, *i.e.*, the second stage in the pulp bleaching process is the treatment of pulps with a nucleophilic reagent (alkali). As a rule,

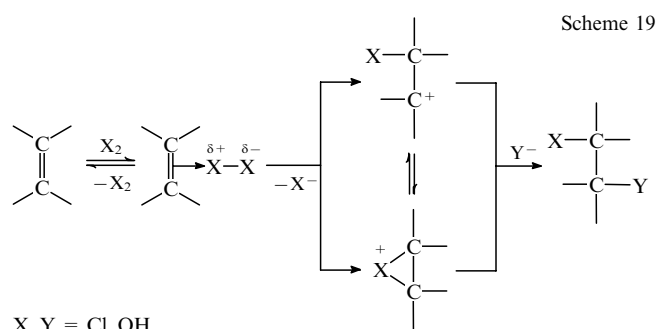
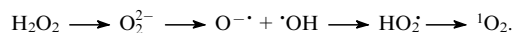


Table 6. The depth of oxidative destruction of lignin in sulfate softwood pulps with equivalent amounts of different reagents.⁹⁵

Reagent (conditions)	Oxidant consumption (% of the pulp mass) ^a	Depth of residual lignin oxidation ^b
Ozone	0.59	0.19
Hydrogen peroxide	1.26	0.30
Ozone + extraction with a NaOH solution	0.59	0.42
Sodium hypochlorite (pH 10)	2.63 ^c	0.53
Sodium hypochlorite + hypochlorous acid (pH 7.5)	2.63 ^c	0.64
Chlorine dioxide	1.00	0.67

^a With respect to the reagent mass. ^b Corresponds to the degree of lignin conversion; the initial lignin content in sulfate softwood pulp is expressed as 76 permanganate units (1 p. u. is referred to the content of lignin in pulps according to Björkman, State standard 6845-54). ^c Per active chlorine unit (active chlorine is defined as an overall amount of chlorine-containing oxidants determined by iodometry).

Cl₂ + NaOH and O₃ + NaOH pairs are used for this purpose. In the second stage, some part of chlorine in chlorolignin is replaced by hydroxy groups, thus enhancing the hydrophilicity of the chlorinated lignin. Delignification of the sulfate pulp can be enhanced by applying 'oxidative alkalification', whereon oxidants such as sodium hypochlorite or hydrogen peroxide are added to an alkaline pulp solution.¹⁰⁴ The hypochlorite anion (ClO⁻) acts on lignin as a nucleophilic reagent, while H₂O₂ in the absence of stabilisers and at high alkalinity of the medium generates various forms of oxidants:



The electrophilic mechanism predominates in the oxidation of lignin;^{10,15,18,105} this has earlier been shown for some lignin model compounds.^{75–80}

Table 5. Reactive forms of the reagents, involved in pulp bleaching processes.

Process (medium)	Substrate	Reagent type	Reactive form	Reacting species	Number of electrons involved in the reaction
Oxidation (acidic)	aromatic and unsaturated structures	electrophile	cation	H ⁺ , OH ⁺ , O ₃ , Cl ⁺ , NO ⁺ , NO ₂ ⁺	2
			radical	H [·] , HO [·] , HO ₂ [·] , O ₂ [·] , Cl [·] , ClO [·] , ClO ₂ [·] , NO [·] , NO ₂ [·]	1
Reduction (alkaline)	non-conjugated and conjugated carbonyl compounds	nucleophile	anion	H ⁻ , HO ⁻ , HO ₂ ⁻ , ClO ⁻ , ClO ₂ ⁻ , S ₂ O ₄ ²⁻	2
			radical	H [·] , e _{aq} ⁻ , SO ₂ ^{·-}	1

Note. The list of reacting species includes both commercial bleaching reagents and the species that are not commercial bleaching reagents but can take part in various pulp bleaching processes.⁹

The most important characteristic of a delignifying reagent is the minimum content of lignin in pulp rather than the portion of lignin removed by this reagent from the pulp (bearing in mind that the initial content of lignin in pulps may vary) at which delignification with this reagent, taken in small excess, is terminated. According to this criterion, the reagents used for delignification of the sulfate pulp (after cooking) can be arranged in the following order: oxygen < hydrogen peroxide < chlorine (with subsequent extraction with a NaOH solution) < sodium hypochlorite < chlorine dioxide.¹⁰³

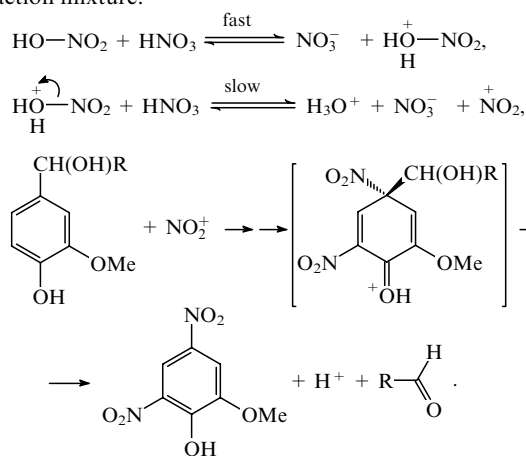
Lignin in industrial pulps (including sulfate pulp) cannot be selectively destroyed to give water-soluble products and completely removed from pulps by either of the oxidants. To achieve complete delignification (and concomitant bleaching) of sulfate pulp, it is necessary to combine oxidative treatment with different reagents in several (from two¹⁰⁶ to five–seven¹⁰⁷) stages.

Since the 1950s, a large number of publications has appeared that are devoted to the problem of more efficient lignin oxidation with oxygen and hydrogen peroxide aimed at the development of environmentally safe technologies. It should be noted that hydrogen peroxide was used first only for the 'oxygen-induced' type of lignin transformations (quite often together with molecular oxygen¹⁰⁷) because most of researchers referred to the hydroperoxide anion exclusively as the class of 'lignin-preserving reagents',^{10, 75} probably judging from the results of industrial application of these reagents in pulp bleaching.

V. Lignin activation towards oxidative action of oxygen and hydrogen peroxide

Not only chlorine but also nitrogen oxides NO and NO₂ can be used in the bleaching of sulfate pulps.¹⁰⁸ The pulp treated with these oxides is then better bleached with sodium hypochlorite or hydrogen peroxide rather than undergo alkaline extraction as a version of processing.

The use of nitrogen oxides or a system HNO₃–NaNO₂ to increase the efficiency of subsequent sulfate pulp delignification with oxygen has been described.^{109–112} The treatment with nitrogen oxides was applied as an 'activating stage'. According to the published data,¹¹¹ the effect of activation is based on lignin fragmentation as the result of electrophilic substitution and elimination of side chains in phenol–propane structural units, together with partial destruction of the residual lignin. The electrophilic reagent in this process is NO₂⁺ generated in the reaction mixture.¹¹³



Preliminary activation with nitrogen oxides makes it possible to reduce twofold the content of lignin in pulps (hardness) following treatment with oxygen (or H₂O₂ under conditions of the 'oxygen'^{109–112} mechanism): from 10 to 5 Kappa units[§] for

different sorts of pulps. The minimum value of pulp hardness given in some studies^{109–112} equals 3.5 Kappa units, while that in another study was¹¹⁴ ~ 7.0–7.5 Kappa units. In the latter work, the pulp pretreatment with other oxidants (chlorine, chlorine dioxide, ozone, *etc.*) was proved to be efficient. It has also been found¹¹¹ that the selectivity of the sulfate pulp delignification with oxygen and hydrogen peroxide is higher in the case of preliminary pulp treatment with chlorine and ozone than with nitrogen oxides. The minimum hardness of pulps was 6–9 Kappa units after treatment with chlorine (chlorine usage rate was 1%–3% with respect to the mass of absolutely dry pulp) and 6.1 Kappa units after ozonolysis (O₃ usage rate — 1%) at the degree of polymerisation in the range of 1300–1400. This degree of polymerisation without pulp pretreatment was observed only for pulps with hardness of about 15 Kappa units (after pulp delignification with oxygen under pressure of 0.5 MPa in the presence of 0.5% MgSO₄ at 110 and 120 °C or with hydrogen peroxide under the same conditions in the presence of 4% NaOH).

It should be noted that a mixture of nitrogen oxides and oxygen was initially proposed to be used in the pulp pretreatment step for lignin activation.¹¹² However, oxygen only caused stronger destruction of cellulose. Methods involving lignin activation with nitric acid permit removal of up to 75% of residual lignin from pulps.[¶]

One of extremely toxic side products of the lignin nitration is hydrogen cyanide, which is formed at high concentrations of nitrogen oxides. Sodium nitrite, nitrous acid, peroxyntitric acid as well as a redox-composition NaNO₂–H₂SO₄ and some others have been proposed as safer reagents.^{116, 117} After oxidation in these systems and delignification with oxygen, the content of lignin in pulps is reduced to 8–9 Kappa units.

The common principle of the methods of lignin oxidation considered above (oxidation during bleaching of the sulfate pulp) based on lignin activation by the action of nitrogen oxides, chlorine and chlorine dioxide is as follows: (E⁺ + H₃O⁺)–(E⁺ + OH[–]), *i.e.*, an electrophile in an acidic medium—an electrophile in an alkaline medium (see also Refs 118–121).

It has been shown^{122–126} that hydroperoxide anions also delignify pulps even somewhat better than oxygen and concomitant radicals generated upon hydrogen peroxide decomposition (or directly upon the action of O₂). In the absence of a hydrogen peroxide stabiliser and at pH ≥ 12, the realisation of the mechanism H₂O₂ → O₂ leads to 45% delignification of the sulfate softwood pulp, while in the presence of a stabiliser (sodium silicate, *etc.*) and at pH about 10 solubilisation of the residual lignin reaches 50% at the initial content of lignin of 76 permanganate units (p. u.).¹²⁷ However, even this depth of lignin conversion is achieved only in the case of pretreatment of unbleached pulp with a weakly acidic solution for removal of cations of transition metals. Preliminary washing of sulfate pulps with acids or solutions of chelating reagents reduces the loss of hydrogen peroxide due to its decomposition and to some extent decreases pulp destruction with superoxide radical anions.

Methods of acid-catalysed and acid-electrophilic activation of the residual lignin based on acid treatment of the residual lignin in sulfate pulps and aimed at partial hydrolysis of the C(β)–O–C(4) ether bonds at temperatures above 70 °C have been proposed.^{123–126, 128–131} Such pretreatment not only changes the structure of the residual lignin, but also activates it to the action of the hydroperoxide anions owing to formation of the carbonyl groups near the site of the ether bond cleavage. Following acid-catalysed activation, the degree of lignin conversion in sulfate hardwood pulps is increased from 0.5 to 0.8 upon the oxidative destruction with hydroperoxide anions. The addition of an oxidant (hydrogen peroxide, monoperoxysulfuric acid)

§The Kappa unit characterises the lignin content in industrial pulps accepted as a standard unit in Russian State Standard 1 007 074 and in a number of foreign standards.

¶Quantification of lignin in pulps expressed in Kappa units gives overestimated values for the depth of delignification compared to that determined by photometry.¹¹⁵

at the stage of activation leads to additional fragmentation of lignin and its more rapid solubilisation in the next technological step including oxidation with the hydroperoxide anions.

The acid-catalysed activation makes somewhat more efficient the lignin destruction under the action of oxygen in highly basic media. However, this effect is nearly the same as that achieved on treatment of lignin with acids at room temperature (removal of cations and destruction of sulfides¹³⁰) or with chelating reagents^{132, 133} where the maximum degree of lignin conversion is about 0.5 and cellulose undergoes higher hydrolytic destruction.

In general, all schemes of oxidative delignification of the type 'reagent + catalysis' can be arranged according to the degree of lignin conversion in sulfate pulps in the following order:¹³¹ oxygen in alkaline media ($O_2 + OH^-$); hydroperoxide anions in alkaline media ($HOO^- + OH^-$); acid-catalysed activation + oxygen in alkaline media [$(H_3O^+) - (O_2 + OH^-)$]; acid-electrophilic activation + oxygen in alkaline media [$(NO_2^+ + H_3O^+) - (O_2 + OH^-)$]; acid-catalysed activation + hydroperoxide anions in alkaline media [$(H_3O^+) - (HOO^- + OH^-)$]; acid-electrophilic activation + hydroperoxide anions in alkaline media [$(OH^+ + H_3O^+) - (HOO^- + OH^-)$].

The selectivity of action of hydroperoxide anions on the residual lignin in sulfate pulps is described by a plot of the degree of cellulose polymerisation as a function of the degree of lignin conversion (Fig. 1).

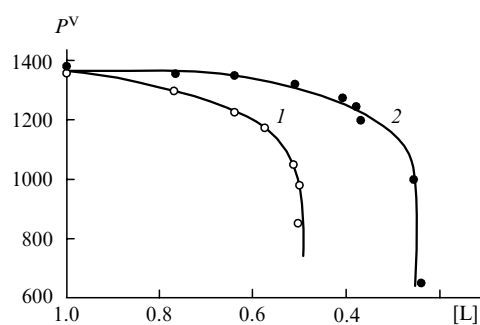


Figure 1. Dependence of the degree of polymerisation (P^V , measured by viscosimetry) on the relative lignin content $[L]$ of sulfate softwood cellulose upon delignification under the action of HOO^- : (1) without preliminary activation; (2) after preliminary acid-catalysed activation.

In the studies on the mechanism of the acid-catalysed activation it was found that the reduction of activated lignin in sulfate pulps with sodium borohydride at pH 10 leads to partial deactivation of lignin^{129, 130} towards the hydroperoxide anions. In this particular case, successive treatment of lignin with two different nucleophilic reagents did not give the expected result, although the former ($NaBH_4$) acts as a reducing agent, and the latter (HOO^-) acts as an oxidant.

VI. Ozonolysis of sulfate pulps

Ozonolysis is one of the methods of delignification of sulfate pulps in the course of bleaching. The selectivity of lignin oxidation in the ozonolysis depends on the conditions and, first of all, on the pH of a medium. In neutral media (pure water), destruction of cellulose predominates.⁹⁷ To perform the sulfate pulp delignification, ozonolysis is carried out in acid media (pH 2–3) in which, as well as in alkaline media, the destruction of cellulose is substantially lower.⁹⁷ The selectivity of delignification is also influenced by the character of the preozonolysis treatment and by the lignin content in pulps subject to ozonolysis.¹³¹

The products of lignin ozonolysis formed upon treatment of unbleached sulfate softwood pulps with ozone are not dissolved instantly (Figs 2 and 3, curves 1). Using photometric assay of the lignin content, it was found that the changes in selectivity of the

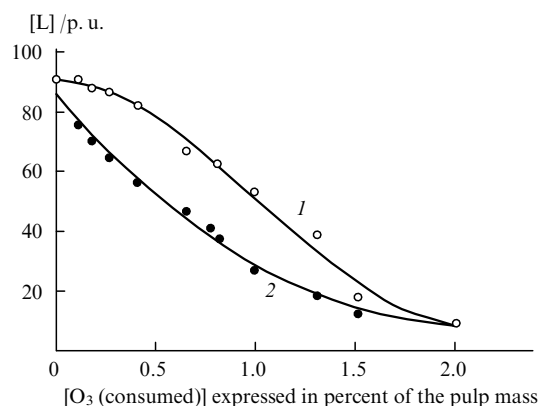


Figure 2. Dynamics of changes in lignin content $[L]$ in sulfate softwood pulp during its delignification with ozone: (1) ozonolysis; (2) ozonolysis and subsequent extraction with a solution of NaOH; p. u. are permanganate units.

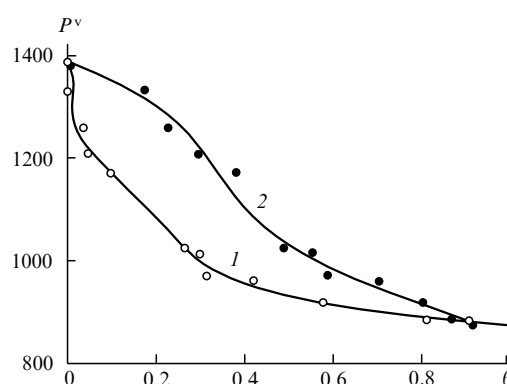


Figure 3. Selectivity of delignification of sulfate softwood pulp with ozone (θ is the degree of lignin conversion equal to the portion of solubilised lignin): (1) after ozonolysis; (2) after ozonolysis and extraction with a solution of NaOH.

oxidative processes during the ozonolysis of sulfate softwood pulps have a rather unusual character. At high lignin contents in pulps, the destruction of cellulose is predominant. Then, in parallel with a decrease of the lignin content, the direction of the process is gradually changing and, after dissolution of a half of the initial lignin, the selective pulp delignification becomes the major process.[†] A part of ozonolysed lignin is dissolved in an alkaline medium (Figs 2 and 3, curves 2). Special tests have shown that destruction of cellulose upon ozonolysis in the presence of lignin is higher indeed. The ozonolysis of pulps partially delignified by other reagents (*i.e.*, semibleached) is also accompanied by destruction of cellulose. However, this destruction is always less than in the ozonolysis of unbleached pulps with high initial lignin content.

The highest degree of the residual lignin oxidation and complete solubilisation of the ozonolysis products in acid media are observed in the case of lignin pretreatment with hydroperoxide anions.¹³⁶ A similar effect is achieved on treating lignin with sodium borohydride. Obviously, a decrease in the number of carbonyl and aldehyde groups in the side chains of the lignin phenol–propane units due to their oxidation or reduction (upon the action of HOO^- or BH_4^- , respectively) favours more selective oxidation of lignin aromatic rings with ozone.

The best results are achieved by successive treatment of lignin, at first, with hydrogen peroxide in an acid medium (with

[†] Assay of lignin content $[L]$ by permanganate method¹²⁷ (especially in Kappa units^{107, 127, 134, 135}) in pulps with a low lignin content typical of semibleached pulps can be incorrect because of deviation of the relationship 'Kappa number – lignin rate' from linearity at $[L] \leq 1\% - 2\%$.

Table 7. Effect of sulfate softwood pulp pretreatment on solubilisation of the residual lignin in the ozonolysis (reagent usage rate constituted 0.225% from the mass of absolutely dry pulp).¹³¹

Pretreatment scheme	Lignin content prior to ozonolysis ^a	Lignin content after ozonolysis ^a		Degree of delignification in one and two stages (%)		Portion of solubilised lignin (%) ^b
		O ₃	O ₃ –NaOH	O ₃	O ₃ –NaOH	
Without pretreatment	91	87	68	4	25	16
OH ⁺ –HOO [–]	33	11	11	67	67	100
OH ⁺ –(H ₂ O ₂ → O ₂)/NaOH	39	30	23	23	41	56
OH ⁺ –NaOH	51	38	33	25	35	71
H ₃ O ⁺	58	46	41	21	29	72

^a Expressed in permanganate units. ^b At pH ≈ 2.

peroxyacids), then with a solution of hydrogen peroxide stabilised at pH 10 and finally with ozone in an acid medium (OH⁺ → HOO[–] → O₃, Table 7).¹³¹

Thus, according to both absolute and relative parameters, the maximum solubilisation of the residual lignin in the ozonolysis of semibleached sulfate pulps is achieved after pretreatment with hydroperoxide anions. On the whole, with consideration of sulfate pulp cooking and preliminary acid-catalysed electrophilic activation, the optimum sequence of the operations is as follows: sulfate cooking (SH[–] + OH[–]) → acid-catalysed electrophilic activation (OH⁺ + H₃O⁺) → delignification with hydroperoxide anions (HOO[–] + OH[–]) → ozonolysis (O₃ + H₃O⁺), *i.e.*, an alternation of treatments in acid and alkaline media.

VII. A schematic approach to the selective destruction of residual lignin with peroxy reagents

The oxidative destruction of lignin as a heterochain polymer containing ether bonds predominantly of the C(β)–O–C(4) type occurs under conditions of acid or base catalysis.^{12,13,137} The alternation of the action of acids (H₃O⁺) and bases (OH[–]) allows one to achieve partial sulfate pulp delignification.¹²⁴ It should be noted, however, that the treatment of pulps according to the HCl–NaOH scheme requires rather drastic conditions and the selectivity of delignification is low: along with twofold reduction of the lignin content, the degree of polymerisation of cellulose is also diminished almost twice.¹²² The analysis of the published data on delignification of industrial pulps with chlorine-containing reagents and oxygen in alkaline media as well as the experimental studies of various compositions of oxidising reagents and media have shown that the oxidation schemes without alternation of treatments in acid and alkaline media are less efficient (Table 8).¹³¹

The properties and reactivities of lignins depend on the methods of their preparation. Therefore, the schemes in Table 8 include the stage of sulfate cooking.

In order to achieve selective oxidative lignin destruction under the action of peroxy reagents with minimal changes in cellulose, it is necessary to apply a complex of different chemical operations which combine a pulp delignification stage and a stage of activation of the residual lignin towards the action of other reagents.

The residual lignin is more labile than cellulose, and its reactivity depends on the method of its preparation or pretreatments. Therefore, enhancement of reactivity of lignin as a result of activation is also a method for an increase in the selectivity of the sulfate pulp delignification.

An electrophilic attack of lignin by peroxy reagents (hydrogen peroxide, peroxy acids, ozone) is realised in acid media, whereas the presence of stabilisers and weakly alkaline media are necessary for treatment of lignin with nucleophiles.^{8–10}

On the basis of the aforesaid, the most important factors affecting the selectivity and depth of the sulfate pulp (and other pulps) delignification can be deduced. These are:

- (1) the reactive form of a reagent;
- (2) the nature and the number of reactive sites in the residual lignin;
- (3) acid–base catalysis;
- (4) cooking method and type of pulp pretreatment.

As the result of an analysis of the selectivity and depth of oxidative destruction of lignin with different chlorine- and oxygen-containing reagents, a general statement concerning the selectivity of oxidative lignin destruction with peroxy reagents has been formulated:¹³¹ the oxidative destruction of the residual lignin is a maximum provided the stages based on the action of electrophilic and nucleophilic reagents alternate, and that the

Table 8. Schematic presentation and operational schemes for oxidative destruction of residual sulfate lignin.

Schematic presentation	Operational scheme	Catalysis	Degree of lignin conversion (%)	Ref.
(N [–])–E ⁺ –N [–]	(Na ₂ S)–H ₂ SO ₅ –H ₂ O ₂	–	80–83	104, 116
	(Na ₂ S)–HCl–H ₂ O ₂	(OH)–H ₃ O ⁺ –OH [–]	70–80	112, 114
	(Na ₂ S)–H ₂ SO ₄ –H ₂ O ₂	(OH)–H ₃ O ⁺ –OH [–]	70–80	116
	(Na ₂ S)–Cl ₂ –NaOH	–	70–80	39, 124, 125
(N [–])–E ⁺ –E ⁺	(Na ₂ S)–NO ₂ –O ₂ /NaOH	(OH [–])–H ₃ O ⁺ –OH [–]	50–70	98–102, 105, 107–111
	(Na ₂ S)–NO ₂ –H ₂ O ₂ /NaOH	(OH [–])–H ₃ O ⁺ –OH [–]	50–70	98–102, 105, 107–111
(N [–])–E ⁺	(Na ₂ S)–O ₂ /NaOH	(OH [–])–OH [–]	≤ 50	37, 96, 98, 105
	(Na ₂ S)–H ₂ O ₂ /NaOH	(OH [–])–OH [–]	≤ 50	37, 96, 98, 105
(N [–])–N [–]	(Na ₂ S)–H ₂ O ₂	(OH [–])–OH [–]	< 50	104, 112, 114

Note. Here and in Table 9, the reagents and species participating in the process of sulfate cooking are presented in parentheses; E⁺, electrophile, N[–], nucleophile.

most complete destruction of the chromophore-containing structures is achieved by the action of electrophilic reagents in acid media and of nucleophilic reagents in alkaline media as described by the general formula $[(E^+ + H_3O^+) - (N^- + OH^-)]_n$.

At first glance (from the position of organic chemistry), this statement seems to be obvious. However, its formulation became possible only after development of the methods of pulp delignification with hydroperoxide anions, acid-catalysed and acid-electrophilic activation of the residual lignin as well as after studies on ozonolysis of unbleached and semibleached sulfate pulps^{114, 124–126, 128–130} and generalisation of studies on activated pulp delignification with oxygen in alkaline media.^{109–112, 118–121} All this made it possible to establish a close relationship between the general concepts of organic chemistry and new experimental results obtained in studies on the sulfate pulp delignification with peroxy reagents.

Deviations from the order of operations described above (including the cooking stage) lead to substantial decrease in the lignin reactivity towards oxidants (even to such a reactive one as chlorine dioxide) and, as a consequence, to a decrease in the depth of oxidative delignification and to loss of the pulp brightness (Table 9).

Table 9. The effect of the sequence of oxidative treatments on the depth of delignification of sulfate softwood pulps.

Run	Schematic presentation	Reagents	Degree of lignin conversion (%)	Pulp brightness (%)
1	$(N^-) - E^+ - N^-$	$ClO_2 - H_2O_2$	91	79
2	$(N^-) - N^- - E^+$	$H_2O_2 - ClO_2$	85	62
3	$(N^-) - E^+ - N^-$	$ClO_2 - H_2O_2$	82	80
4	$(N^-) - N^- - E^+$	$H_2O_2 - ClO_2$	87	65
5	$(N^-) - E^+ - N^-$	$H_2O_2 - H_2O_2$	52	64
6	$(N^-) - N^- - E^+$	$H_2O_2 - H_2O_2$	40	57

Note. Usage rates for reagent are the same in pairs of runs: (1) and (2), (3) and (4), (5) and (6). Usage rate: ClO_2 in runs (1), (2), 0.8%, in runs (3), (4), 1.3% from the pulp mass; H_2O_2 in runs (1)–(4), 2.0%, in runs (5), (6), 1.0% [run (5) at pH 2 and 10, run (6) at pH 10 and 2 in the first and second stages, respectively].

On the basis of the statement mentioned above, a number of methods for sulfate pulp bleaching and ways of activation of the residual lignin with hydrogen peroxide and ozone have been proposed^{124, 125, 129, 130} which are not inferior in the selectivity of delignification to the bleaching processes based on the use of chlorine-containing compounds.

VIII. Kinetic methods for assessment of residual lignin reactivity

Depending on the mechanism of lignin destruction, different kinetic models for assessment of its reactivity are employed. Most often, these are correlations for homogeneous reactions with an assumption that these reactions are homogeneous and heterophase¹³⁸ and that the volume of the phase where the reaction takes place is constant.^{139, 140}

In addition to the kinetic methods for examination of homogeneous reactions,¹⁴¹ kinetic models of topochemical reactions are widely applied for description of chemical transformations of lignin, first of all, the Avraami–Kolmogorov–Erofeev equation.¹⁴² The validity of this equation is substantiated only formally, while no physical correlation between topochemical models and the processes of delignification has been found. It was shown¹⁴³ that a diffusion kinetics model is more appropriate to the description of the kinetics of softwood pulp delignification in organic solvents in which the rate-determining step is diffusion

of lignin and hemicellulose destruction products into the cooking solution.

Since lignin is a polymer which is chemically and physically bound in pulp to polysaccharides the processes of the lignin chemical transformations should be considered as reactions in a polymeric matrix. The kinetics of chemical reactions in polymers is featured by the influence of various levels of the local matrix organisation and temperature-dependent matrix reorganisations on the conformity to the Arrhenius law, what is manifested in the so-called polychronous kinetics.^{144–147}

A model of polychronous kinetics has been used for the first time by Bel'kova *et al.*^{148, 149} in the study of pulp delignification with nitric acid. Later, this model was applied to the study of softwood lignin destruction in alkaline media^{150–153} and to oxidative lignin destruction in pulp bleaching processes.^{130, 154–156} The application of the polychronous kinetics theory to the description of processes of chemical destruction and solubilisation of lignin (*i.e.*, wood delignification) under the action of various reagents is based on three postulates. The first one is that reactions occur either in a solid phase or in an interface and are characterised by kinetic non-equivalence of chemically homogeneous species. The second one is that under isothermic conditions the processes do not proceed to completion, and at a certain depth of the conversion, the sharp deceleration of the reactions (the so-called kinetic stop) takes place. The third postulate says that the depth of the conversion depends on the temperature.

Thus the major features of chemical processes that follow the polychronous kinetics are their kinetic stop and non-observance of the principle of the temperature–time superposition. Although at higher temperature the reactions proceed deeper, they also stop at a certain point. According to the 'classical' approach,¹⁴⁴

$$n(\tau, T) = n_0 \int_{\ln k_{\min}}^{\ln k_{\max}} f(\ln k) G(k, \tau) d \ln k = n_0 \int_{\ln k_{\min}}^{\ln k^*} f(\ln k) d \ln k,$$

where $n(\tau, T)$ is the number of species which has entered into the reaction after time τ at temperature T ; $f(\ln k)$ is a distribution function; $G(k, \tau)$ is a function describing the kinetics of the process in an elementary group with fixed values of the activation energy (E); $k(E) = k_0 \exp(-E/RT)$ is the reaction rate constant; $k_{\min}$ and $k_{\max}$ are the minimum and maximum rate constants, respectively; G for the simplest case is expressed as $G_1 = \exp(-k_1 \tau)$.

The kinetic curves are straightened in the coordinates $C/C_0 - \ln \tau$ (straight lines of the type $y = ax + b$). From these equations the values for $k_{\min}$, $k_{\max}$ and the parameter of the kinetic non-equivalence [$S = \ln(k_{\max}/k_{\min})$] are found using the relationships¹⁴⁴

$$1 - \theta = a - b \ln \tau,$$

where $a = 1 - \ln 1.76 k_{\max} / \ln(k_{\max}/k_{\min})$, $b = (\ln k_{\max} - \ln k_{\min})^{-1}$. In general case, $\ln \tau = \ln k$.

Recent publications^{146, 147} consider the kinetic peculiarities of reactions in a polymeric matrix not as a violation of the classical Arrhenius law but, in contrast, as a particular case of a general model for polychronous kinetics (the so-called integral Arrhenius law).

As a rule, in studies of the delignification processes (including those for oxidative destruction of the residual lignin), the necessity of imposing limitations in the framework of the formal kinetic analysis often arises. Such a lignocellulosic composite as unbleached sulfate pulp is so complex in structure and functional composition that the formulation of a direct kinetic model for the description of its oxidative destruction under the action of radicals and ions generated from peroxy reagents seems to be impossible.

By comparison with other kinetic approaches, the model of polychronous kinetics allows one to characterise more completely the processes of oxidative destruction of the residual lignin by the effects observed in delignification of a lignocellulosic material (see Refs 154–157 on polychronous kinetics for the oxidative deligni-

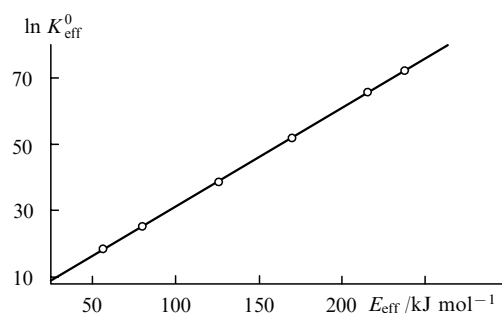


Figure 4. Kinetic compensative effect.

fication of sulfate pulps with hydroperoxide anions and oxygen). The main kinetic peculiarities of oxidative lignin destruction (on bleaching of sulfate softwood pulps) with peroxy reagents include the existence of the kinetic stop and kinetic compensative effect (KCE, a linear relationship between preexponential factors K_{eff}^0 for separate ensembles of macromolecules and effective activation energy E_{eff} , Fig. 4), the dependence of the highest degree of lignin conversion (from 0.07 to 0.55¹⁵⁷) on the parameter of kinetic non-equivalence S and temperature (Fig. 5) and the non-linear character of the relationship between $\ln \tau$ and $1/T$ in the temperature range from 293 to 373 K (Fig. 6).

The values of the rate constants (k) for oxidative delignification in the temperature interval from 80 to 100 °C range approximately from $10^{17} \exp(-143 \text{ kJ mol}^{-1}/RT) \text{ s}^{-1}$ to $16 \exp(-19 \text{ kJ mol}^{-1}/RT) \text{ s}^{-1}$. The larger values correspond to low-temperature processes with a degree of lignin conversion $\theta = 0.35$, while the smaller values of the rate constant correspond to high-temperature processes with a degree of lignin conversion $\theta = 0.10$.

At a low degree of lignin conversion ($\theta \leq 0.1$) under the action of hydroperoxide anions, the rate of delignification is apparently determined by diffusion of the soluble products of lignin destruction (their molecular weight can reach 15 000–25 000) from the lignocellulosic matrix.¹⁴⁸ Preliminary treatment of the residual lignin does not virtually affect the rate of the pulp delignification, since this treatment does not change the structure of cellulose fibres. With an increase in the degree of lignin conversion, the rate of the process sharply (exponentially) falls down, while the effective energy of activation rises. These effects are probably caused by slow molecular relaxation in a polymeric matrix so that the time for realisation of the most energetically favourable activated complex during an elementary reaction act (a kinetic constituent) is insufficient.¹⁴⁴

On the one hand, the acid-catalysed and acid-electrophilic activations of the residual lignin lead to its destruction and better solubilisation (due to the smaller size) in alkaline media. On the other hand, they activate the lignin electrophilic sites. In the range of moderate temperatures (313–333 K), the preactivation results

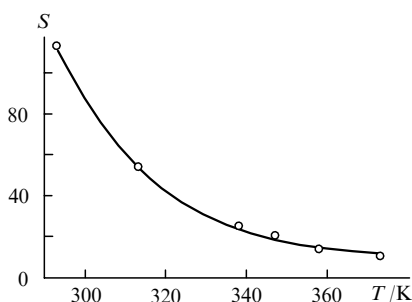


Figure 5. Effect of temperature on the parameter of lignin kinetic non-equivalence (S) in the oxidative pulp delignification with hydrogen peroxide.

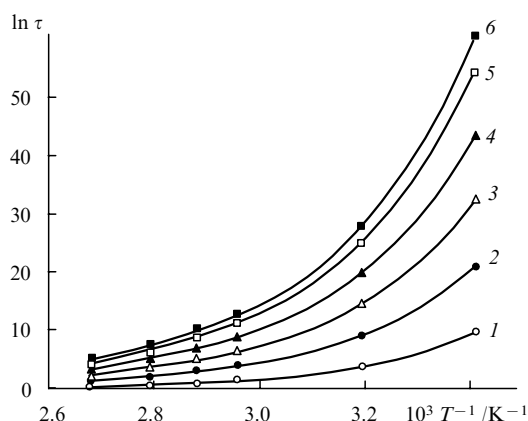


Figure 6. Plot of $\ln \tau$ as a function of $1/T$ for various ensembles of lignin macromolecules in the sulfate pulp delignification in a stabilised solution of hydrogen peroxide at $\theta = 0.1$ (1); 0.2 (2); 0.3 (3); 0.4 (4); 0.5 (5); 0.55 (6).

in diminishing of the kinetic non-equivalence for lignin reactive sites (at 333 K the activated lignin has $S = 21$ –23, while non-activated one has $S \sim 30$). Despite the fact that the values of the minimum rate constant differ for different methods of lignin preactivation and that this constant bears an obvious physical meaning [$-\ln k_{\text{min}} = \ln \tau (\theta = 1.00)$, where $\ln \tau (\theta = 1.00)$ is a logarithm of the time of complete lignin conversion], unambiguous interpretations based on analysis of this constant are hardly possible due to the very low values of this constant. The main manifestation of the lignin activation is an increase in the maximum degree of lignin conversion in its oxidative destruction with hydroperoxide anions and certain decrease in the parameter of kinetic non-equivalence associated probably with destruction-induced changes in the morphological structure of cellulose fibres.

IX. Conclusion

Lignin substantially differs in its behaviour in chemical reactions from low-molecular-weight model compounds, first of all, in a diversity of transformations and their depths. The reactivity of the residual lignin and the depth of its oxidative destruction with peroxy reagents depend to a considerable extent on the character of chemical pretreatments, which functionalise lignin and affect various structural changes in the polymeric lignocellulosic matrix. The depth of lignin destruction in the processes of pulp bleaching with peroxy reagents can be enhanced owing to alternation of the action of electrophilic and nucleophilic reagents under conditions of acid and base catalysis, respectively.

However, the quantitative assessment of the lignin reactivity is rather difficult to perform because of the chemical and structural (topological and supramolecular) heterogeneity of industrial lignin, structural heterogeneity of the polymeric lignocellulosic matrix and some kinetic peculiarities of reactions in polymers. Aforementioned features of lignin, its polyfunctionality as well as diversity of oxidants, generated in reactions of oxygen, hydrogen peroxide and ozone, and the differences in mechanisms of the reactions of these reagents with lignin in acid and alkaline media provide a reason to consider the oxidative destruction of the residual lignin as a complex fundamental problem that demands further investigations.

Despite some achievements in the studies of lignin reactions, an increase in the reactivity of the residual lignin remains a very important practical problem due to the permanently rising requirements for the environmental safety of technological processes in the pulp industry. Examination of the behaviour of lignin in chemical reactions and technological processes involving hydrogen peroxide, oxygen and ozone is not unambiguous, and further investigations and data systematisation are necessary in this field. Exploration of selective oxidative lignin destruction is a

very important direction in wood chemistry, organic chemistry, chemistry of high-molecular-weight compounds and related fields of the sciences.

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^b — *Russ. J. Appl. Chem. (Engl. Transl.)*

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Alginic acids and alginates: analytical methods used for their estimation and characterisation of composition and primary structure

A I Usov

Contents

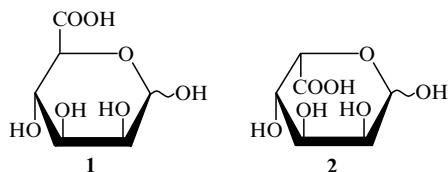
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Abstract. The history and state-of-the-art in the detection, quantitative determination and characterisation of the primary structure of alginic acids and their salts (alginates) are reviewed. A brief survey of the structure and properties of these polysaccharides is given. Numerous analytical methods including chemical, physicochemical and enzymic procedures for the structural analysis of alginates which can also be used for the investigation of other uronic acid-containing polysaccharides are discussed. The bibliography includes 211 references.

I. Introduction

Alginic acids were first isolated from several brown algae by Stanford more than 100 years ago.¹ Later, these polysaccharides were detected in all brown algal species without exception as cell wall and intercellular matrix components. Their content in the biomass may amount to 40% of the dry weight; this strongly depends on the species and growth conditions.^{2–4} Some bacteria (mostly, the representatives of the genera *Azotobacter*⁵ and *Pseudomonas*⁶) also produce alginic acids. In 1982, alginates were unexpectedly detected in one of the species of calcareous red algae belonging to the family Corallinaceae.⁷ Our recent studies^{8,9} have shown that the presence of alginates is virtually a characteristic feature of the representatives of this family. In other plants, these polysaccharides have not been found.

Alginic acids are polyuronides, *i.e.*, polysaccharides the molecules of which are built up of uronic acid residues. At first, D-mannuronic (**1**)^{10,11} and then L-guluronic (**2**)¹² acids were identified as the components of alginic acids.



Partial hydrolysis and isolation of the corresponding disaccharide revealed that the residues of both uronic acids are the components

of the same polymeric molecule.¹³ According to present-day concepts based on numerous studies including methylation,^{14,15} periodate oxidation^{16,17} and several physicochemical methods of structural analysis (mostly, NMR spectroscopy^{18–21}), molecules of alginic acids are linear and made up of β -D-mannuronic and α -L-guluronic acid residues (in the pyranose form) linked by 1 $\rightarrow$ 4 bonds.

Bacterial alginic acids differ from the algal ones in that some of their hydroxy groups are usually acetylated.^{22,23} Acetyl groups occupy positions 2 or 3 (sometimes, both simultaneously) in D-mannuronic acid residues.²⁴ The degree of polymerisation of native polymers is rather high and the number of monosaccharide residues may amount to 1000–10 000.

Alginic acids isolated from various sources can differ in the ratios of mannuronic and guluronic acids (M/G)²⁵ and in the distribution of the monomers along the polymeric chain. Fractionation of oligomeric products formed upon partial hydrolysis has shown that some regions in the molecules of alginic acids are built of only one uronic acid species (M-blocks and G-blocks). These blocks are separated by fragments which contain approximately equal amounts of both monosaccharides arranged into more or less strictly alternating sequences (MG-blocks).^{26,27} Such a peculiar structure is a result of stepwise biosynthesis of polysaccharide molecules where the formation of linear mannuronan precursors is followed by epimerisation of some β -D-mannuronic acid residues at the C(5) atom under the action of a specific enzyme, mannuronan-C(5)-epimerase, resulting in the appearance of α -L-guluronic acid residues within the polymer structure.²⁸

The size and mutual distribution of individual blocks strongly affect the properties of alginic acids and their salts (alginates). As a matter of fact, β -D-mannuronic and α -L-guluronic acid residues, being structurally very close [they differ only in the configuration at one of the asymmetric centres, *viz.*, at the C(5) atom], have opposite conformations of the pyranose rings ($^4C_1$ and $^1C_4$, respectively), which results in completely different shapes of the polymeric molecules in the poly-M and poly-G regions (Fig. 1). This creates spatial conditions for the tight binding of bivalent metal cations with G-blocks. Moreover, the coordination with such cations favours the cooperative binding of different molecules of the polymer with one another,²⁹ eventually resulting in the formation of ionotropic gels (Fig. 2). Therefore, the total content of α -L-guluronic acids (in the first approximation) or, more precisely, the relative length of G-blocks are important criteria of the most valuable property of alginates, *viz.*, their ability to form gels.^{30–32} The block structure is responsible for many other characteristics of alginates including their biological activity.^{33–35}

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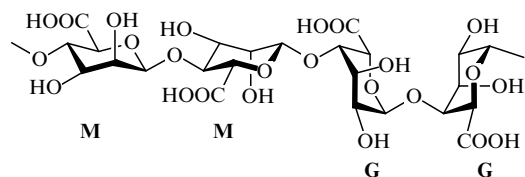


Figure 1. The conformations of monosaccharide units in the molecule of alginic acid.

By virtue of their unique physicochemical properties, alginic acids and their salts have found wide application in the production of foods and in some other branches of industry^{36,37} including biotechnology and medicine.³⁸ This explains the fact that the majority of reviews devoted to alginic acids provide information about their structure, biosynthetic mechanisms and practical application, but pay insufficient attention to problems concerned with the analytical chemistry of alginates. Thus a special issue of the journal *Carbohydrates in Europe*, which is all devoted to alginates and consists of four reviews describing the chemistry and physical properties,³⁹ genetics and biosynthesis of alginates,⁴⁰ as well as biotechnological and clinical applications of alginate gels⁴¹ and commercial applications of alginates,⁴² is laid out on this principle.

Because of considerable practical utility of alginates, their isolation from brown sea weeds has become the main goal of their processing. It is obvious that estimation of alginic acid content in the algal biomass and standardisation of alginic acid preparations and alginate-containing products demand elaboration of convenient analytical procedures, while structural characterisation of these polysaccharides is necessary for determining the most rational approaches to the utilisation of particular preparations containing alginic acids. Proper allowance must be made for the fact that the analytical chemistry of alginates has specific features as compared with that of other polysaccharides.

Alginic acids form water-soluble salts with monovalent cations but are precipitated upon acidification. Alginates of many bivalent cations, particularly, of Ca^{2+} , Sr^{2+} and Ba^{2+} , are insoluble in water. This property is utilised in the isolation of alginic acids from algae.⁴³ At first, bivalent cations and concomitant water-soluble polysaccharides are extracted from the bio-

mass with a dilute mineral acid; then alginic acids are extracted with an alkaline solution with subsequent precipitation from the extract by treatment with ethanol,⁴⁴ acidification or conversion into Ca^{2+} salt.⁴⁵ Preparative yields of alginic acids may be used for determination of their content in the algal biomass; it should be remembered, however, that the results obtained with the use of different isolation procedures can give substantially different results for the same algal specimen. This depends on a number of factors, such as reagents used, the number of precipitations and the degree of achieved purity. Thus special experiments aimed at comparing the efficiency of three most popular laboratory procedures^{46–48} revealed that the relative scatter in the values of preparative yields of alginates may amount to 20%–40%.⁴⁹ Additional problems may arise when this approach is used for the analysis of food compositions where the behaviour of pectin components is similar to that of alginates as regards their extraction and precipitation.

Some procedures for the estimation of alginic acids are based on specific reactions of uronic acids. These reactions include decarboxylation and degradation under the action of concentrated sulfuric acid with subsequent formation of coloured products in the presence of carbazole, indole, 3-hydroxybiphenyl, *etc.* These methods have found wide application, although it is evident that the presence of other polysaccharides containing uronic acids in the specimen under study will inevitably give erroneous results of alginate assays.

The use of acid hydrolysis of alginates for the preparation of monomeric uronic acids is a rather complex problem. Glycosidic bonds of uronic acid residues are highly resistant to acid hydrolysis. Low solubility of alginic acids in acid media creates an additional problem. Total acid hydrolysis of alginic acids is accompanied by the destruction of some monomers. It is of note that L-guluronic acid residues are destroyed faster than D-mannuronic acid residues and specific losses of each monomer depend on the pattern of their block distribution within the polymeric molecule. Therefore, it is very difficult to select versatile conditions for hydrolysis and to find correction factors for the destruction of monomers that would be equally suitable for the determination of the composition of alginates differing considerably in the ratios and the distribution of uronic acid residues in their molecules.

Nondestructive physicochemical methods, in the first place, ^1H and ^{13}C NMR spectroscopy, have assumed great importance in structural characterisation of alginic acids. These methods can be used both for the determination of the monomer ratio in alginic acid molecules and their characterisation in terms of their arrangement into individual blocks. In the subsequent sections, the above-mentioned analytical approaches will be considered in more detail and illustrated, mostly by the studies of sea weeds, although these methods are equally suitable for the characterisation of bacterial alginates. Additional information can be retrieved from several reviews devoted mostly to alginates of bacterial origin.^{50–55}

II. Chemical methods

1. Assays based on cation exchange

If a starting material is used in sufficiently large amounts (*i.e.*, the alginic acid content in a sample under study is no less than 100 mg), alginic acids can be determined by the gravimetric method. Polymeric alginic acids are precipitated upon acidification of weakly alkaline solutions, while calcium alginate is precipitated from neutral sodium alginate solutions upon addition of calcium chloride. Drying of the precipitates is problematic, since these compounds tightly retain water and are readily decomposed on heating. Volumetric analysis is more preferable in experiments with smaller amounts of the material. In this case, the polysaccharide is also precipitated as calcium salt, this is washed with a dilute acid to remove metal cations, and the insoluble alginic acid is washed with water and titrated with

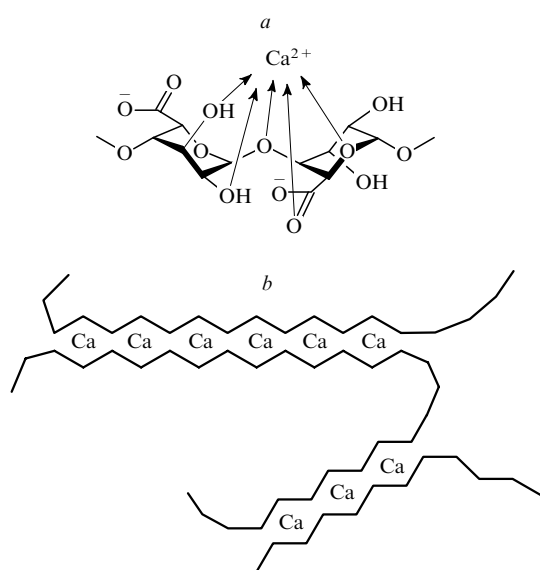


Figure 2. The coordination of calcium ions by α -L-guluronic acid residues in the molecule of an alginate (*a*) and the role of these ions in intermolecular interactions during gel formation (*b*) (the 'egg-box' model).²⁹

sodium hydroxide in the presence of phenolphthalein or using conductometric⁵⁶ or potentiometric⁵⁷ control. The formation of viscous sodium alginate solutions in the course of titration can be avoided if an excess of calcium acetate is added to alginic acid, and the liberated acetic acid is titrated.⁵⁸ A procedure is described which combines titration with colorimetry and is designed for the determination of the content of alginic acid in algae.⁵⁹

An alternative, rather lengthy procedure for quantitative analysis of alginates is based on the ability of alginic acid-containing algal biomass to bind calcium ions.⁶⁰ To this end, samples of a ground plant material are dialysed against dilute hydrochloric acid to remove metal cations; the mineral acid is removed by dialysis against water. Then, alginic acid is converted into calcium salt by dialysis against a calcium acetate solution; the excess of the reagent is removed by repeated dialysis against water. Upon this treatment, all the residues of uronic acids in the alginate are converted into calcium salts where one cation corresponds to two uronic acid residues. Bound calcium ions are then quantitatively extracted by dialysis against dilute hydrochloric acid. The calcium concentration in the diffusate is determined by atomic adsorption spectrophotometry, and the alginate content in the original biomass is calculated. The main drawback of this method is that the presence of other polyanions (e.g., sulfated polysaccharides) in the biomass can overestimate the experimental results.

As polyanions, alginic acid molecules form salts with coloured inorganic (bivalent copper cations⁶¹ or ruthenium red⁶²) and organic cations (cationic dyes of the Methylene Blue type^{63–65}). In this case, quantitative assays are based on the measurement of the decrease in the optical density of the original coloured solution upon formation of poorly soluble salts or on the changes in the spectral characteristics of the dye (metachromasia) due to its binding to the polymer. This method, which is characterised by high sensitivity and precision, has been recently proposed for quantitative determination of alginates in microcapsules used in cell transplantation.⁶⁶ The experimental procedure is based on the analysis of metachromatic changes in the spectrum of 1,9-dimethyl-Methylene Blue as a result of its interaction with the alginate. This type of reactions also includes precipitation of polyanions (as salts) with cationic detergents (Cetavlon precipitation).⁶⁷ Polyhexamethylenebiguanidinium chloride used for the precipitation of alginic acids is the most studied reagent of this class.⁶⁸ Precipitation of alginic acids with this reagent is virtually independent of the presence of salts (< 2.5%), pH (5.5–7.6), temperature (10–60 °C) and the M/G ratio. The analytical procedure is based on the measurement of the decrease in the reagent absorption at 235 nm. Although this method was recommended for the analysis of industrial extracts of brown algae,^{69, 70} other acid polysaccharides can be precipitated by cationic detergents together with alginic acids. It was proposed⁷¹ to use coloured hydrazides formed by the reaction of 2-nitrophenylhydrazine in the presence of water-soluble carbodiimide in colorimetric assays of alginates and their fragments instead of coloured salts;⁷¹ however, this method has not found wide application.

2. Assays based on degradation of uronic acids

Heating of alginates results in decarboxylation and evolution of CO₂.⁷² The samples under study are usually heated with 19% HCl, and the CO₂ evolved is absorbed and weighed as in the micro-analytical determination of carbon in organic compounds by combustion.^{73, 74} Although this method was described in a popular practical guide to biochemical assays of algae,⁷⁵ it requires special skill and equipment (cf. Refs 76–78). This is also true for a modified decarboxylation procedure in which polysaccharide samples are heated with 57% HI and the CO₂ evolved is assayed by gas-liquid chromatography (GLC)⁷⁹ or direct non-aqueous titration.⁸⁰ It is obvious that other uronic acid-containing polysaccharides can interfere with the alginate assays.

Colorimetric assays of polyuronides based on acid degradation of their constituent monosaccharides have found much wider

application. The main reaction product formed upon heating of uronic acid derivatives with concentrated sulfuric acid is 5-formylfuran-2-carboxylic acid, which is rather stable under these conditions.⁸¹ The formation of degradation products of neutral sugars (5-hydroxymethylfurfural and furfural) from hexoses and pentoses, respectively, prevents its direct spectrophotometric analysis. It is therefore more expedient to use the ability of 5-formylfuran-2-carboxylic acid to form coloured products with various organic reagents, particularly with some aromatic nitrogen heterocycles and phenols, e.g., carbazole,^{82, 83} indole,⁸⁴ 3-hydroxybiphenyl⁸⁵ and 3,5-dimethylphenol.⁸⁶

Along with indisputable advantages (in the first place, the possibility to experiment with microquantities of material), colorimetric assays have obvious drawbacks, such as interference due to neutral sugars and different reactivities of individual uronic acids. This is the reason why the analytical procedure was repeatedly modified, although the reaction with carbazole had long been used for the determination of polyuronides including alginic acids.⁸⁷ Thus it was proposed to supplement the reaction mixture with boric acid in order to intensify the colour formation and to equalise the reactivities of different uronic acids.^{88, 89} The addition of sulfamate^{90, 91} or different temperature regimes⁹² were used in order to minimise the effects of neutral sugars. It was demonstrated that the composition of a specimen containing three uronic acids (glucuronic, galacturonic and mannuronic) can be calculated by conducting the reaction with carbazole in four different regimes.⁹³

The effect of ballast neutral sugars was estimated during the elaboration of a procedure for pectin assays.^{94, 95} It was found that 3,5-dimethylphenol⁸⁶ and 3-hydroxybiphenyl⁹⁶ have salient advantages over carbazole in pectin and hemicellulose assays.

In a more recent study,⁹⁷ Filisetti-Cozzi and Carpita proposed a method for the colorimetric assay of polyuronides including alginic acids, which took account of recommendations from previous investigations. This method utilised 3-hydroxybiphenyl in combination with the borate anion and sulfamate. Our recent studies have shown that 3,5-dimethylphenol is a more preferable specific reagent for alginic acids.⁸ We modified the procedure proposed by Scott⁸⁶ for the analysis of pectins and hemicelluloses to fit with the specific composition of alginates using greater amounts of borate and more prolonged heating of reaction mixtures at 70 °C. The results of these experiments weakly depended on changes in the ratios of D-mannuronic and L-guluronic acids in different alginate specimens.

The problem of selectivity of the colour reaction and the necessity to eliminate interference due to the presence of neutral sugars in the specimen under study is of prime importance in the analysis of heteropolysaccharides, such as plant hemicelluloses and complex pectins, animal mucopolysaccharides and many bacterial and fungal polysaccharides. In the case of alginic acids, the effect of neutral sugars can be eliminated by preliminary removal of ballast substances,⁹⁸ although this procedure complicates the experimental protocol. For example, ion-exchange chromatography on Dowex 1 × 2 was used for purification of an alginate isolated from the extracellular material of mucoid strains of *Pseudomonas aeruginosa*,⁹⁹ although DEAE-cellulose or DEAE-Sephadex are evidently more suitable.^{100, 101} In alginate assays in food products, it is recommended to conduct enzymic deproteination with subsequent precipitation of calcium alginate. The latter is carefully washed off from soluble carbohydrates and dissolved in cold 80% sulfuric acid or in hot sodium hexameta-phosphate solution; alginates are assayed in the resulting solutions using naphthoresorcinol,¹⁰² phenol^{103, 104} or trivalent iron sulfate¹⁰⁵ in concentrated sulfuric acid. The selectivity of these reagents is lower than that of 3-hydroxybiphenyl, 3,5-dimethylphenol and carbazole. The reaction with Fe₂(SO₄)₃ was successfully used for the study of seasonal changes and anatomic distribution of alginates in some species of brown algae.¹⁰⁶ In a more complicated procedure described by Toyoda *et al.*,¹⁰⁷ naphthoresorcinol-HCl was added to an alginate after its

precipitation as Cu^{2+} salt; the coloured reaction product formed thereupon was extracted with butyl acetate and quantitatively assayed using HPLC.

In the majority of the above-described reactions, concentrated sulfuric acid was used to destroy uronic acids; however, similar results can be obtained in polyuronide assays utilising the Bial reagent (orcinol in concentrated hydrochloric acid, usually supplemented with FeCl_3 ¹⁰⁸). In the case of alginates, the reaction with orcinol has certain advantages over the reaction with carbazole,¹⁰⁹ although analytical results also depend on the composition of the original polymer.¹¹⁰ Obviously, this dependence is the main limitation of the majority of alginic acid assays, since chemical properties of uronic acid residues strongly depend on whether it forms a part of a homo- or a heteropolymeric block. This circumstance is the main obstacle on the way to the design of versatile calibration curves for the determination of alginic acids with any ratio and any distribution of β -D-mannuronic and α -L-guluronic acids along the polymeric chain.

3. Assays based on acid hydrolysis of glycosidic bonds

As mentioned above, alginic acids, like other polyuronides, are hydrolysed with difficulty and under drastic conditions. This leads to partial degradation of the monosaccharides liberated, in the first place, of guluronic acid. In the hydrolysis products, the monomeric uronic acids are in an equilibrium with lactones. This all makes the analysis of alginic acid hydrolysates a rather complicated procedure. The method for determining the M/G ratio by polarimetry of the total hydrolysate of alginates in the form of brucine salts¹¹¹ has not found wide application, since it requires large quantities of the starting material and its high purity, for ballast carbohydrates significantly distort the results of polarimetric analysis. Therefore, in the overwhelming majority of cases the hydrolysates are analysed following preliminary separation of the hydrolysis products.

Some time ago, it was proposed to use paper chromatography for separation of the hydrolysis products; this procedure allowed for the first time the proof of the presence of guluronic acid residues in the polymers.¹² Later, conditions were elaborated for the separation of guluronic, mannuronic, galacturonic and glucuronic acids by paper electrophoresis.¹¹² However, these methods are suitable for qualitative rather than for quantitative analysis of hydrolysates. In more recent studies, thin-layer chromatography (TLC) on silica gel was used for the identification of depolymerisation products of alginic acids. This method is especially convenient for detecting small amounts of alginates in beer^{113–115} and other foodstuff; acid methanolysis is more preferable than hydrolysis. Thus TLC of the methanolysis products allows unambiguous identification of alginates even in the presence of other uronic acid-containing food polysaccharides.^{116,117} High-performance TLC was used to study alginate biosynthesis in *Pseudomonas aeruginosa*.¹¹⁸

A procedure based on ion-exchange chromatography has been developed for quantitative determination of uronic acids in hydrolysates and, correspondingly, for the calculation of the M/G ratio.^{110,119} The conditions of hydrolysis proposed by Haug and Larsen^{110,119} were used (almost without modification) in a great number of more recent studies. After treatment of alginate with 80% sulfuric acid at 0 °C, the mixture was incubated for 18 h at 20 °C, then water was added up to the acid concentration of 1 mol litre⁻¹ and the resulting mixture was heated for 5 h at 100 °C. After cooling, the hydrolysate was neutralised with calcium carbonate, alkalinised to pH 8.0, incubated for 30 min for lactone opening and chromatographed on a Dowex-1 column (acetate form) in a linear gradient of acetic acid (from 0.5 to 2 mol litre⁻¹). Under these conditions, guluronic acid was eluted from the column before mannuronic acid. The uronic acid content in the fractions was determined using the reaction with orcinol; the experimental value of M/G was multiplied by 0.66 in order to correct for guluronic acid losses due to its predominant degrada-

tion during hydrolysis. This method was used to characterise the alginates isolated from a great number of algal species.²⁵

Some more recent modifications were aimed at the improvement of hydrolysis conditions¹²⁰ and refinement of the correction coefficients.¹²¹ In particular, it was proposed to use 88% formic acid instead of sulfuric acid for diminishing the degradation of monomeric uronic acids.²² However, the main progress in this field is connected with elaboration of new technologies for separation and identification of the hydrolysis products. Thus high-performance liquid chromatography was widely used for ion-exchange separation of uronic acids;^{122–128} quantification of these compounds in the eluate can efficiently be performed by measuring intrinsic absorption at 210 nm,¹²⁷ by using refractometric¹²⁴ or pulse amperometric detectors¹²⁵ or in a reaction with cyanoacetamide¹²⁶ with subsequent spectrophotometry or spectrofluorimetry.¹²⁹

The new separation technique for uronic acids markedly accelerated and simplified the experimental procedure, but did not eliminate the distortions introduced by hydrolysis of alginates. A method for the analysis of real specimens of alginic acids isolated from different brown algal species¹²⁷ which utilises ion-exchange chromatography in an isocratic regime and UV-detection for monitoring elution, has gained especially wide popularity.

Yet another popular procedure for the quantification of hydrolysis of products of alginic acids is GLC, which requires additional chemical conversion of uronic acids into their volatile derivatives. Hydrolysis products normally represent a mixture of uronic acids with lactones. Substitution of methanolysis for hydrolysis yields a multicomponent mixture of methyl esters of methyl glycosides. Analysis of such mixtures (e.g., in the form of trimethylsilyl derivatives) is a rather complex problem,^{130–132} and the results obtained are of limited value for quantitative assays.

In order to simplify the composition of the mixtures to be separated, it was proposed to convert uronic acids into aldonic acid lactones (by reduction of the aldehyde groups with subsequent lactonisation^{133,134}) or alditols (by more profound reduction) with subsequent chromatographic separation as acetates.^{134–136} In the latter case, several approaches are used to distinguish uronic acid derivatives from the reduction products of neutral monosaccharides. For example, uronic acids are separated by treatment of hydrolysates with ion-exchange resins prior to reduction,¹³⁶ otherwise sodium borodeuteride is used for reduction followed by chromatomass spectrometry for the identification of reaction products.¹³⁷ It was also recommended to separate hydrolysates into two portions, in one of which neutral sugars are converted into aldononitrile acetates (the procedure employed results in degradation of uronic acids), and the other portion is used for complete reduction. Comparison of analytical data allows one to calculate the amounts of both neutral monosaccharides and uronic acids.¹³⁸ Neutral sugars and uronic acids can also be assayed simultaneously by converting the former into alditol acetates and the latter into *N*-propylaldonamide acetates *via* aldonolactones.¹³⁹

Attempts have been made to circumvent difficulties in alginic acid hydrolysis by reducing the carboxy groups in the polymeric molecule. This can be done either by preliminary esterification of the carboxy groups^{140,141} or by their activation with water-soluble carbodiimide with subsequent treatment with sodium borohydride at controlled pH.¹⁴² The reduction procedure for the determination of the composition of alginic acids was proposed in 1981;¹⁴³ however, further studies of the preparative reduction of alginic acids with water-soluble carbodiimide revealed that this reaction cannot be brought to completion.^{144,145} Thus treatment with an excess of carbodiimide caused a significant destruction of the original polysaccharide¹⁴⁴ concomitantly with the preferential reduction of the L-guluronic acid carboxy groups;¹⁴⁵ in the deficiency of this reagent, preferential reduction of the D-mannuronic acid carboxy groups took place.¹⁴⁴

A more recent study was specially devoted to comparison of different methods of reduction of the carboxy groups in polymers containing uronic acids.¹⁴⁶ The method based on activation of the carboxy groups with 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide *metho-p*-toluenesulfonate in 8 M urea¹⁴⁷ was found to be the most efficient procedure; however, in this case subsequent treatment with sodium borohydride caused only partial reduction of the carboxy groups and the results obtained for polysaccharides yielding viscous solutions were poorly reproducible. We have simplified the reduction procedure⁸ by using prolonged treatment of alginates with the so-called 'magic methanol'¹⁴⁰ (a methanol–chloroform–concentrated HCl mixture, 10:1:1) for esterification and by reducing the formed ester with a large excess of sodium borohydride in a concentrated imidazole buffer (pH 7.0, 0 °C), by analogy with a method proposed for the identification of esterified galacturonic acid residues in pectins.¹⁴⁸ The hydrolysis products of reduced polysaccharides were converted into aldono-nitrile acetates and analysed by GLC. The chromatograms revealed two peaks corresponding to gulose derivatives (1,6-anhydro- β -L-gulose and L-gulononitrile acetates) and a peak of acetylated D-mannononitrile. Despite incomplete esterification and, correspondingly, incomplete reduction, the M/G values calculated from the peak areas of the corresponding mannose and gulose derivatives coincided with the results of analysis of the ¹³C NMR spectra.

A procedure for the determination of the M/G ratio which consists in the reduction of the carboxy groups with subsequent methylation, reductive splitting of the polymer with triethylsilane in the presence of trimethylsilyl methanesulfonate and boron trifluoride etherate and identification of the anhydroalditols (in the form of the corresponding derivatives) using HPLC or GLC, proposed by Zeller and Gray,¹⁴⁹ seems to be too complicated for routine assays of alginic acids.

4. Partial hydrolysis for determining the block composition

As stated in the introduction, physicochemical properties of alginates are largely determined by the mode of distribution of the two uronic acid residues along the polymeric chain. This distribution pattern can be characterised chemically using partial acid hydrolysis.^{26,27} After short-term heating of alginic acid suspensions in dilute mineral acids (20 min, 100 °C, 0.3 M HCl), an oligomeric fraction with an average degree of polymerisation of ~ 20 and containing approximately equal amounts of both uronic acid residues (MG-blocks) passes into the solution. The insoluble residue additionally heated for 20 h with acid is separated into two fractions, *viz.*, a fraction soluble at pH 2.85 and insoluble one. These fractions also represent oligomers with average degrees of polymerisation of ~ 20 , but the former contains exclusively M-blocks (the mannuronic acid content exceeds 90%), while the latter consists of G-blocks (the mannuronic acid content is less than 10%). From the yields of all the three fractions, one can establish the distribution pattern of uronic acid residues in the linear chain of alginates. Using partial hydrolysis, it was demonstrated for the first time that alginates of different origin differ in fact in their block composition.¹⁵⁰ In subsequent studies, a similar approach was repeatedly used for characterisation of alginates (see, *e.g.*, Ref. 151).

A simplified procedure for the determination of the block composition of alginates was described by Penman and Sanderson.¹⁸ These authors proposed to use a one-step treatment of alginates with an acid (5 h, 100 °C, 0.3 M HCl) instead of two-step hydrolysis and to determine the yields of soluble and insoluble fractions colorimetrically, by reaction with phenol and concentrated sulfuric acid. The insoluble fraction obtained was analysed by ¹H NMR spectroscopy as a solution in D₂O at 80 °C rather than separated into blocks of different composition. The low-field region of the spectrum has a singlet for H(1) of the residue M at $\tau = 5.34$ (peak B), a doublet for H(1) of the residue G at $\tau = 4.96$ (peak A) and a singlet for H(5) of the residue G at $\tau = 5.56$ (peak C). The ratios of integral intensities B/A or B/C (these

values can be averaged) and the yield of the soluble fraction permit one to calculate the block composition of the original polysaccharide.

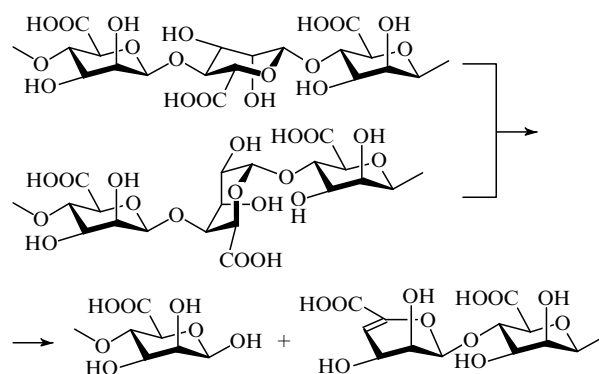
Yet another modification of the partial hydrolysis procedure is the use of ion-exchange and gel-permeation chromatography for the separation of oligomeric products.^{152,153} Using several commercial alginate preparations as examples, it was shown that the size of M-blocks varies in the range of 3–10, that of G-blocks varies in the range of 4–15 monosaccharide residues, while the distribution of monomers within MG-blocks is random.¹⁵²

Electrophoresis in polyacrylamide gel¹⁵⁵ was recommended for separation and quantitative determination of oligomannuronic and oligoguluronic acids with a degree of polymerisation varying from 2 to 9 obtained by partial hydrolysis of alginates.¹⁵⁴ In order to increase the electrophoretic mobility of the oligosaccharides and sensitivity of their assays, these were fluorescently labelled by reductive amination with 8-aminonaphthalene-1,3,6-trisulfonic acid.

III. Enzymic and immunological methods

All currently known enzymes able to depolymerise alginate molecules are lyases, *i.e.*, they catalyse β -elimination of the substituent from position 4 of the uronic acid residue rather than hydrolysis of glycosidic bonds.^{156–158} This cleavage results in the formation of a 4,5-unsaturated uronic acid residue (Scheme 1) at the newly formed end of one of the fragments. Since elimination results in disappearance of asymmetric centres at C(4) and C(5), the same unsaturated uronic acid is formed from both β -D-mannuronic and α -L-guluronic acids. This unsaturated residue has an intense absorption band at 230–240 nm, and the increase in optical density at 230 nm can be used as a convenient method for determining the enzymic activity of alginate lyases.¹⁵⁹ A mixture of oligomers with low degrees of polymerisation is a final product of enzymic treatment of polymeric alginic acids with alginate lyases.¹⁶⁰

Scheme 1



Alginate lyases have been detected in many organisms, *e.g.*, sea molluscs, echinoderms, bacteria and fungi.¹⁶¹ Molluscs (Gastropoda)¹⁶² and bacteria^{163–165} are the most convenient sources for the isolation of these enzymes. Alginate lyases of different origin differ essentially in their stabilities,¹⁶⁶ specificities^{167–169} and abilities to hydrolyse acetylated bacterial alginates.^{170,171} Thus M-lyases (polymannuronate lyases) normally isolated from molluscs are endoenzymes, which easily hydrolyse M- and MG-blocks without any effect on G-blocks.^{172,173} In contrast, G-lyases (polyguluronate lyases) hydrolyse G- and MG-blocks but are inert with respect to M-blocks.¹⁶² The substrate specificities of alginate lyases can be examined using a recently proposed procedure for depolymerisation of alginates on agar plates in the presence of calcium chloride¹⁷⁴ or using homopolymeric substrates containing a terminal fluorescent label.¹⁷⁵

A convenient and versatile procedure which takes into account the specificity of alginate lyases and is suitable for detection and analysis of alginates in solutions at concentrations

of 0.01 to 1 mg ml⁻¹ (see Ref. 176) was developed for quantitative determination of various alginic acids. The material under study was treated with a mixture of two enzymes of different origin, viz., a mixture of poly-M-lyase isolated from the mollusc *Haliotis tuberculata* and poly-G-lyase isolated from the bacterium *Klebsiella pneumoniae*; the absorption of reaction products was measured at 230 nm. With the use of an excess of enzymes it was shown that the final values of optical density were proportional to the initial concentration of the substrate. A combination of two enzymes made it possible to eliminate the effect of the variable composition of different alginates. It is noteworthy that the separate application of these enzymes can provide information about the block structure of various alginates. This recently developed procedure holds much promise, especially for future studies provided alginate lyases become commercially available.

Alginate lyases of known specificity are also used for obtaining information about the distribution of uronic acid residues and the sizes of individual blocks in alginates. It is bacterial enzymes that made it possible to establish, for the first time, the deviation of the uronic acid sequence in poly-MG from a strictly alternating pattern.^{160, 177} Some alginates were found to contain poly-M-blocks that are homogenous in size and have an average degree of polymerisation of 24;¹⁶⁰ however, more recent studies with other subjects established more variable distribution patterns of poly-G- and poly-M-blocks according to their size.^{178, 179}

The specificity of action of the enzyme isolated from the sea mollusc *Haliotis tuberculata* was studied in most detail. High-performance liquid chromatography was specially adapted for the separation of saturated and unsaturated oligoguluronates and oligomannuronates formed upon enzymic hydrolysis of alginates¹⁸⁰ and different procedures of NMR spectroscopy¹⁸¹ were specially developed for the elucidation of the structure of these oligosaccharides. It was found that alginate lyase effectively cleaves M–M and G–M bonds (but not G–G or M–G bonds) and that the pentamer of mannuronic acid is best bound to the enzyme active centre.

In an analogous study of recombinant bacterial alginate lyase,¹⁸² it was established that the enzyme cleaved exclusively M–M bonds. The enzymic action is blocked by the presence of the acetyl groups in mannuronic acid residues, which is characteristic of bacterial alginates. This enzyme was recommended for the preparative isolation of poly-M-blocks from acetylated polymanuronate of *Pseudomonas aeruginosa* and of poly-MG-blocks from another bacterial alginate containing residues of both uronic acids.¹⁸³

Alginates possess antigenic activity. Several attempts were undertaken to raise antibodies against definite structural elements of alginate molecules and to use these antibodies for the analysis of alginates by standard immunological procedures.¹⁸⁴ Specific antibodies (both polyclonal^{185, 186} and monoclonal¹⁸⁷) against alginates were used to localise the polysaccharide in various algal tissues; however, this assay was complicated by gel formation. Considering that gel formation decreases the ability of the corresponding sites in the alginate molecule to bind to antibodies and that the reaction conditions (pH, temperature, accessibility of Ca²⁺ ions and the nature of other buffer components) can strongly influence the results of immunological assays,¹⁸⁸ it may be concluded that these studies are still far from being completed and that the immunological behaviour of alginates and the specificity of the corresponding antibodies need additional investigation.

IV. Nondestructive physicochemical methods

1. IR spectroscopy

The total amount of polymers consisting of uronic acids can be determined from the intensity of the absorption band of the ionised carboxyl at 1607 cm⁻¹ in the IR spectrum of a sample solution in a D₂O-phosphate buffer.¹⁸⁹ It was recommended to determine semi-quantitatively the M/G value in alginates by

measuring the ratio of absorption band intensities at 808 (M) and 787 cm⁻¹ (G) in the IR spectra of specially prepared films.¹⁹⁰ Comparison of band intensities at 1320 (M) and 1290 cm⁻¹ (G) can also be used for this purpose.¹⁹¹ However, because of low precision and interference due to different factors these two methods have not found wide application. On the other hand, IR spectra provide valuable information about the presence of acetyl groups in bacterial alginates^{22, 99, 101} judging from intense absorption bands at 1250 and 1730 cm⁻¹.

Recently, it was proposed to use spectroscopy in the near IR region (400–2500 nm) for determination of the alginate content in brown algae biomass.¹⁹² The reflectance spectra recorded for powdered biomass samples are computer-processed at 9 parameters. The experimentally determined calibration curves allow the determination of alginate in the starting material with high precision. This method was successfully used for characterisation of biodegradation of the alga *Laminaria hyperborea* in which the alginate content varies from 2.2% to 40.8%. Horn *et al.*,¹⁹² who have developed this procedure, gave it a high estimate, although this analysis requires the use of a specially designed spectrophotometer. It was noted also that variable content of moisture and polyphenols in the specimens under study interfere with the analysis of alginates.

2. Circular dichroism

The three types of blocks present in alginate molecules differ essentially in their circular dichroism (CD) spectra; the poly-G spectrum lies completely in the region of negative molar ellipticity values, $[\theta]$, the poly-M spectrum has an intense positive band, while the poly-MG spectrum is characterised by intermediate values of $[\theta]$.^{193, 194} The CD spectra of natural alginates are characterised by a peak at 200 nm and a trough at 215 nm. It was found that the M/G ratio may be calculated from the observed ratio of peak height to trough depth using simple equations.¹⁹⁵ Therefore, this important parameter can be determined from the CD spectra even for milligram quantities of the alginate without any destruction of the polymer.

Since the CD spectra of mixed blocks (poly-MG) are not identical with the spectra of equimolar poly-M and poly-G mixtures, the determination of the block composition of alginates from their CD spectra is possible. A relatively simple computer-assisted calculation was proposed which mimics the real spectrum owing to a linear combination of three types of spectra characteristic of isolated blocks.¹⁹⁵ Although the shape of poly-MG spectra depends on the distribution of uronic acid residues within the blocks, which is not taken into consideration in the calculation procedure, the results obtained with known alginate specimens showed good coincidence with those earlier established using partial hydrolysis or NMR spectra. The CD spectra were subsequently used to characterise the block composition of alginates isolated from many species of brown algae or from different types of algal tissues.^{47, 196, 197}

3. ¹³C NMR Spectroscopy

A preliminary report concerning the interpretation of ¹³C NMR spectra of alginates was published in 1977 by Grasdalen *et al.*²⁰ who showed that the alginate spectra recorded at 25 MHz contained four signals in the anomeric resonance region rather than two signals, as might be expected for a polysaccharide made up of two uronic acid residues. This implies that the position of C(1) signals of both monosaccharides (M and G) depends on the nature of the neighbouring residue. The intensities of these signals could be used for estimating both M/G and the relative content (*F*) of pairs of monomers (MM, MG, GM and GG). Moreover, the signal corresponding to the C(5) atom of the residue M was represented in the spectrum by three lines, which suggests the dependence of the signal position on the nature of both neighbouring residues. This phenomenon could be used for quantification of the number of triplets with a central M residue within the polymer. It was found that the central line of the signal corre-

sponds to the central residues M of the MMM and GMG triplets, whereas the low-field and high-field lines represent the corresponding signals for GMM and MMG, respectively. Thus, the relative content of the latter two triplets in the alginate molecule can be measured directly, from the intensity of the corresponding signals, and the probability of the presence of triplets MMM and GMG in the polymeric chain can be calculated from the ratios: $F_{MMM} + F_{GMM} = F_{MM}$ and $F_{GMG} + F_{MMG} = F_{MG}$. The data calculated for several alginates showed good correlation with the results of chemical analysis. However, no possibility to determine the number of triplets with a central (G) residue was found in this pioneering study.

Later, in detailed studies Grasdalen *et al.*²¹ used a higher-resolution NMR spectrometer (50 MHz) and carefully selected the conditions for recording NMR spectra. The signals for the anomeric carbon atoms gave eight lines corresponding to the central units of eight theoretically possible triplets of the primary structure. The intensities of these lines were used to calculate the content of each type of triplets in several specimens of natural alginates. The validity of these calculations was partially confirmed by an analysis of signals corresponding to the carboxyl carbon atoms and to C(4) and C(5) atoms of the residue M, which also have multiplet structures, and by comparison of these data with the results of chemical assays. The average lengths of homopolymeric blocks can be calculated from the triplet content: $N_{G>1} = (F_G - F_{MG})/F_{GM}$ and $N_{M>1} = (F_M - F_{GM})/F_{MM}$.

It is of note that the most probable distribution of residues along the polymeric chain in synthetic binary copolymers formed by polymerisation of two different monomers can be calculated, taking into account the initial concentrations and relative reactivities of the monomers. However, the block composition of alginates usually differs from the calculated sequence, which is at variance with the mechanism of formation of these polysaccharides by copolymerisation of two monosaccharide precursors and is a convincing argument in favour of an alternative route of their biosynthesis involving mannuronan-C(5)-epimerase.^{198, 199}

¹³C NMR spectroscopy is an extremely convenient procedure for structural characterisation of alginates isolated from different natural sources (see, *e.g.*, Refs 8, 9, 200) or modified by enzymic treatment.²⁰¹ This was also used to monitor alginate biosynthesis in bacteria.²⁰² However, recent experiments have shown^{49, 203} that the reliability of determination of the block composition depends on M/G of the specimen under study. More adequate results were obtained for alginates with a high content of one of the monomers; if M/G is close to unity, the calculated values of individual block lengths can differ substantially from the results obtained upon chemical or enzymic hydrolysis.

¹³C NMR spectra were obtained not only for solutions but also for solid alginate samples.²⁰⁴ In the latter case, the resolution of peaks was much lower, especially for the anomeric carbon signals. Nevertheless, a complex spectral pattern could be represented as a sum of individual symmetric signals corresponding to the C(2)–C(5) atoms of both uronic acid residues, which made it possible to estimate the M/G ratio with a sufficiently high accuracy.²⁰⁴

4. ¹H NMR spectroscopy

The ¹H NMR spectra of alginates were studied in parallel with ¹³C NMR spectra in the hope to elaborate a more sensitive and accurate method for the determination of the content of monomers and their block distribution. It was shown¹⁹ that informative spectra of alginates can be obtained using a 100 MHz spectrometer after short-term mild acid treatment of samples, which reduces the viscosity of solutions. Although not all signals could be resolved in these spectra, the low-field region contained three well-defined peaks, *viz.*, A [H(1) of the residue G], B [a sum of H(1) of the residue M and H(5) of the residue MG] and C [H(5) of the residue GG], which made it possible to calculate the following values: $F_G = I_A/(I_B + I_C)$ and $F_{GG} = I_C/(I_B + I_C)$. Taking into

account that $F_G + F_M = 1$, $F_{GG} + F_{GM} = F_G$ and $F_{MM} + F_{MG} = F_M$ (for lengthy chains, $F_{MG} = F_{GM}$), the M/G ratio and the content of the four possible monomeric pairs in alginate molecules can be calculated. The parameters established for well-known specimens coincided with the results obtained by chemical methods and ¹³C NMR spectroscopy.

In a continuation of these studies, ¹H NMR spectra of alginates and their fractions were recorded at 400 MHz.²⁰⁵ As in the above-cited paper,¹⁹ the M/G values and contributions of the dimeric sequences (MM, MG = GM and GG) were calculated from the analysis of ¹H NMR spectra. In addition, higher resolution made it possible to isolate four signals corresponding to the H(5) atom of the central residue of α -L-guluronic acid in the four possible triads (GGG, MGG, GGM and MGM). The content of these trimers showed a good correlation with the values obtained by other analytical methods.

The ¹H NMR spectra of poly-M and poly-G, the components of a bacterial alginate produced by *Azotobacter vinelandii*, were further analysed using both one-dimensional and modern two-dimensional NMR techniques.^{206, 207} The unambiguous assignment of signals was performed on the basis of chemical shift theory, analysis of spin–spin coupling constants and measurements of the nuclear Overhauser effects. These data were used to study the interaction of poly-M- and poly-G-blocks with Ca²⁺ ions in aqueous media. A model for binding of calcium ions was proposed, which is based on the measurement of the relative intensity of cross-peaks in the two-dimensional spectra (NOESY) of the free polymer and its calcium salt. The experimental results are important for interpreting the gel-forming ability of alginates in the presence of calcium ions and elucidation of the role of calcium as a cofactor essential for the functioning of mannuronan-C(5)-epimerase.

High-resolution ¹H NMR spectroscopy was efficiently used for characterisation of many natural alginates, of both algal^{196, 208} and bacterial^{209, 210} origin, particularly for establishing the degree of acetylation and localisation of acetyl groups in bacterial alginates.²⁴ It was noted, however,²⁰⁴ that partial hydrolysis traditionally used for decreasing the viscosity of solutions of high-molecular-weight alginates prior to recording their proton NMR spectra can induce the precipitation of a portion of alginate and thus significantly distort the experimental results (M/G ratio).

V. Conclusion

As may be inferred from the survey, the analytical chemistry of alginic acids is a well-grounded and well-studied field. Numerous approaches have been proposed for the solution of analytical problems of different degrees of complexity, from quantitative determination of alginates in mixtures with other natural compounds to the analysis of uronic acid sequences in the linear molecules of these polysaccharides.

Alginate acids differ from other natural polyuronides in that they are made up of unique monosaccharides and are characterised by a peculiar distribution of monomers along the polymeric chain. Special approaches were elaborated for investigation of these structural features among which partial acid hydrolysis, enzymic degradation and some nondestructive physicochemical methods (in the first place, NMR spectroscopy) have proved to be especially efficient. The experimental findings have made it possible to formulate a concept of the primary block structure of alginic acids and to gain a deeper insight into the pathways of their biosynthesis leading to this structure. These results not only have a great theoretical significance, but are of great practical value, since they permit direct alteration of physicochemical properties of alginates by enzymic treatment.^{201, 211} However, it should be remembered that specific analytical approaches were elaborated for the solution of concrete practical problems and have certain limitations which have been mentioned in the review. Further in-depth studies into the structure and properties of alginates will

probably demand further improvement of existing methods of structural analysis of these polysaccharides.

The significance of analytical chemistry of alginates goes far beyond the confines of this class of biopolymers. As uronic acid-containing polysaccharides are widely spread in nature, many chemical methods designed for the detection and quantitative determination of alginates, particularly, the approaches based on specific degradation of uronic acids or chromatography of acid hydrolysates, are equally efficient in the analysis of plant mucilages, pectins, hemicelluloses, bacterial and fungal polysaccharides and animal glycuronoglycans.

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Site-specific photosensitised modification of nucleic acids with biradical and electrophilic reagents

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Abstract. Photosensitised oxygen-independent chemical modification of nucleic acids including free-radical cycloaddition and electrophilic addition (type III photodynamic effect) are considered. The main attention is given to site-specific photomodification. New approaches to highly specific affinity modification of nucleic acids, *viz.*, sensitised photomodification with binary photoreagent–sensitiser systems and two-photon photosensitised reactions, are described. The prospects for application of electrophilic photoreagents for *in vivo* modification of nucleic acids are discussed. The bibliography includes 119 references.

I. Introduction

The development of methods for targeted chemical modification of nucleic acids (NA) at definite nucleotide sequences is of great importance for the study of cellular processes connected with gene expression,^{1,2} design of gene-addressed biologically active substances³ and the development of new technologies based on the use of oligonucleotide chips and microelements for new generations of computers.⁴

The targeted modification of NA is carried out with affinity reagents which can bind specifically to definite nucleotide sequences and contain reactive groups bringing about NA modification upon binding. Fragments of antibiotics,^{5,6} oligonucleotides^{3,7,8} and their derivatives^{2,9} are used for the recognition of definite nucleotide sequences. Compounds generating free radicals,^{3,10} alkylating reagents^{3,8} and photoreactive compounds^{2,3,7,11} are used as the affinity reagents.

Chemically reactive oligonucleotide derivatives can react with different cell components, which results in undesirable toxicity and considerable expenditure of reagents in side reactions. Photoreactive derivatives possess considerable advantages, *viz.*, they are nontoxic in the dark and their photoactivation is easily controlled. Considerable experience has been gained in the last few years in the area of synthesis, studies of physicochemical properties, biological application of novel reagents containing photoreactive groups and the determination of the structure of NA photomodification products under the action of these reagents.

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The design of DNA-cleaving reagents which are chemically stable and can be photoactivated is a topical problem. These reagents are helpful tools in the study of DNA structure when used as photonucleases, photofootprinting reagents and potential photoreagents in the phototherapy of cancer and various viral infections.^{11–13}

Photosensitised NA modification reactions are commonly referred to as photoinduced reactions occurring at wavelengths greater than the intrinsic absorption of NA.¹⁴ These reactions involve three main types,^{15,16} *viz.*, photooxidation with radical species or by photoinduced electron transfer (type I photodynamic effect), photooxidation with singlet oxygen (type II photodynamic effect) and oxygen-independent free-radical and electrophilic addition (type III photodynamic effect).

The classification of photosensitised reactions of NA is problematic and any description of them is ambiguous, for photochemical reactions are numerous, they occur in parallel and in low quantum yields. Their study is complicated by the fact that the same photomodification end products are formed by different mechanisms.⁷

This review is devoted to the analysis of the most important photosensitised, oxygen-independent free-radical and electrophilic addition reactions. One-photon^{17,18} and two-photon^{19,20} photochemical reactions of NA induced by far UV light (190–300 nm), photooxidation of DNA with singlet oxygen^{3,7,21} and radical species^{22–24} as well as oxidation caused by photoinduced electron transfer^{11,25,26} have been studied in sufficiently great detail and will not be considered in this review.

II. Free-radical cycloaddition and electrophilic addition photoreactions of nucleic acids

Several types of oxygen-independent photosensitised chemical modifications of NA are known,^{14,16} *e.g.*, free-radical photocycloaddition to the double bonds of bases,^{27–45} photoinduced alkylation,^{46–58} arylation,^{59–63} acylation^{27,64} and other electrophilic addition reactions. Modification of NA with highly electrophilic species formed during photochemical reactions is especially attractive, since the electrophilic species manifest pronounced selectivity with respect to nucleophilic bases, such as guanine and adenine. In turn, photocycloaddition reactions occur with high selectivity at the double bonds of the pyrimidine bases.²⁷

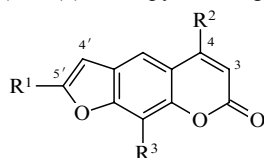
1. Free-radical photocycloaddition

Excitation of most ketones and thioketones gives rise to biradical species which initiate radical cycloaddition reactions involving the double bonds of the heterocyclic bases of NA. Psoralen and

thiopyrimidine derivatives are the most popular and efficient photoreagents of this type.

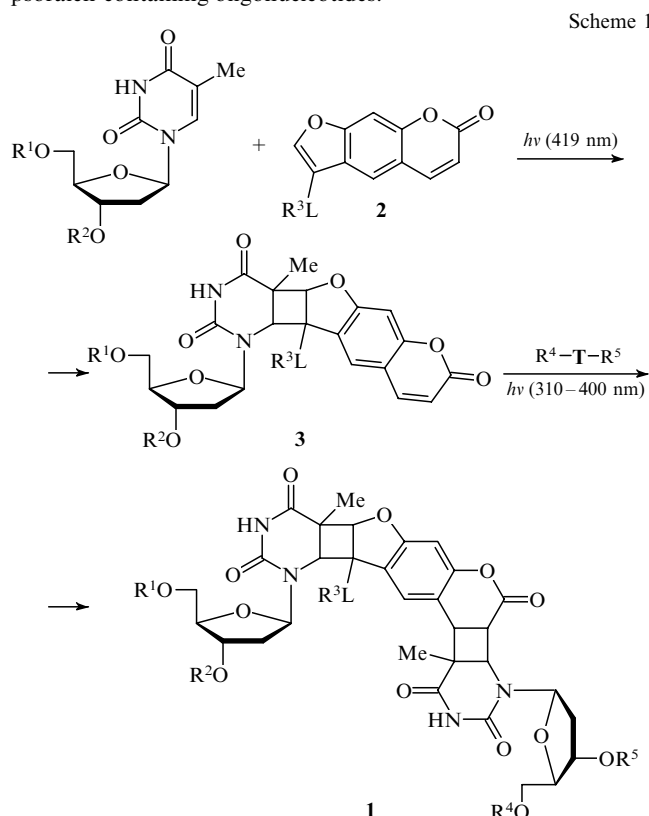
a. Photomodification of nucleic acids with psoralen derivatives

Psoralens (7*H*-furo[3,2-*g*][1]benzopyran-7-ones) are tricyclic aromatic compounds, which have a planar structure and can intercalate between base pairs of double-stranded DNA (ds-DNA). They contain two photoreactive double bonds, *viz.*, C(3)=C(4) in the pyrone ring and C(4')=C(5') in the furan ring.



R¹, R², R³ = H, Alk.

Irradiation of DNA duplexes at 310–420 nm in the presence of psoralens results in covalent binding of the latter to pyrimidine bases of DNA (preferentially, to thymine) at the C(5)=C(6) bond to give cyclobutane adducts (Scheme 1). Photoaddition reaction of psoralens to cytidine occurs 15-fold more slowly than that to thymidine.¹ Psoralens are bifunctional photoreagents; they can cross-link both DNA strands, especially when intercalating in the 5'-TpA-3' sequence.^{1, 28–38} 5'-TpA/3'-ApT fragments are present in signal sequences of many genes as potential targets for psoralen-containing oligonucleotides.



L is CH₂NH(CH₂)₂NH-p, R¹–R⁵ are fragments of oligonucleotide chains.

Using molecular modelling methods, it was shown¹ that psoralen incorporates between the nucleotides of a target in two different ways, *viz.*, between nucleosides N_{n+1} and N_n or between nucleosides N_n and N_{n-1}, where N_n is the nucleoside complementary to the 5'-terminal nucleoside of the psoralen conjugate. Spatial structure of the reaction centre which is the most favourable for photoaddition, is realised in the former case. The incorporation of psoralen is especially efficient where thymidine residues occupy positions *n* + 1 and *n* – 1, and adenosine residues occupy position *n* of the target. In this case, the reaction occurs

simultaneously in both directions. The yield of the cross-linked product of the type **1** amounts to 95%.

In recent years, psoralen-containing oligonucleotide derivatives have been used mostly for photomodification of ds-DNA.

Studies of Gunther *et al.*²⁹ have shown that the 16-membered conjugate Pso-CH₂NH(CH₂)₂NH-p-5'-TTTTCTTTTCCCCCT **2** forms a triplex with DNA regions of HIV-1 containing homopurine–homopyrimidine sequences. Psoralen intercalates into ds-DNA thus increasing the melting temperature of the triplex from 20 to 29 °C. Irradiation with UV light at wavelengths > 310 nm yields mono- and bis-adducts **3** and **1**, which is confirmed by their electrophoretic mobility. The addition of the furan ring of psoralen to the C(5)=C(6) bond of thymine next to the 5'-end of the homopurine sequence of the DNA-target gives the cyclobutane adduct **3**. This is followed by photochemical cycloaddition of the pyrone ring of the adduct **3** to the C(5)=C(6) bond of 3'-terminal thymine in the homopyrimidine chain, resulting in the bisadduct **1**.

The DNA region of HIV-1 contains two sequences which can serve as targets for the conjugate **2**. Both sequences are involved in cross-linkage with high efficiency. Besides, at higher exposures and higher concentrations of the oligonucleotide reagent **2**, cross-linking occurs in the regions where the 5'-terminal 8-membered fragment (T₄CT₃) of the conjugate **2** binds to ds-DNA. The reason for such modification is that the sequence (pC)₆ of the conjugate **2** cannot be fully protonated under physiological conditions, and the overall specificity of the 16-membered conjugate **2** is determined by the fragment (T₄CT₄). Substitution of (pG)₆ for (pC)₆ results in photomodification at only two specific sequences.²⁹

The dependence of the length of the oligonucleotide address on the degree of modification of target ds-DNA *in vitro* was studied.²⁹ It was shown that 10- and 16-membered psoralen-containing oligonucleotide conjugates were effective in sequence-specific photocross-linking of mouse ds-DNA, while an 8-membered oligonucleotide reagent had little effect. Binding of the 10-membered conjugate to ds-DNA occurred rapidly (in less than 10 min).

A conjugate of 5-alkoxypsoralen and 5'-pTTTTTC*C*TC*T-C*C*C*TC*T, where C* is 5-methylcytosine residue introduced for increasing the triplex stability, was used to inhibit the expression of the interleukin 2 α-chain receptor gene.³⁰ The conjugate bound to the promoter homopurine–homopyrimidine sequence to yield a triplex. The mutant form of the promoter containing a transversion of three nucleotides in the centre of the homopurine–homopyrimidine sequence was used as a control. The conjugate did not bind to the mutant promoter.

Irradiation with UV light (365 nm) was accompanied by photocycloaddition of the psoralen 3,4- and 4',5'-double bonds to the C(5)=C(6) bonds of the sequence 5'-TpA-3' at the duplex–triplex junction, resulting in the bisadduct **1**. The formation of a covalently bound triplex inhibited transcription *in vitro*, while transcription of the mutant form of the promoter was not inhibited. After *in vitro* photomodification of DNA, the photocross-linked triplex was transfected into human HeLa cells. The irradiated mutant promoter was transcribed with the same efficiency as the nonirradiated one; the activity of the irradiated promoter was inhibited by 80% (according to the photocross-linkage yield).

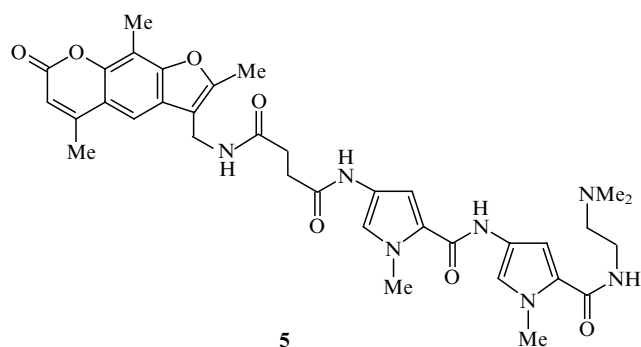
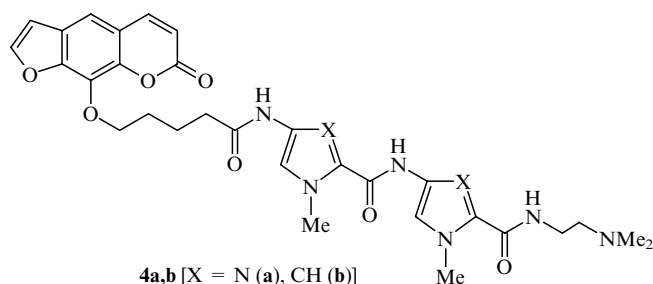
The formation of photoadducts in a triplex of a bacteriophage λ ds-DNA with a conjugate 4'-hydroxymethyl-4,5',8'-trimethyl-Pso-pAGGAAGGGGG was most extensively studied by Gasparro *et al.*³¹ The quantum yield (φ) of the monoadduct **3** was 0.0065, while that of the bisadduct **1** was 5 times as great. The formation of the bisadduct **1** implies that the C(4')=C(5') bond of the furan ring of psoralen reacted first and then the C(3)=C(4) bond of the pyrone ring. Otherwise, the bisadduct is not formed. It was therefore proposed to carry out the irradiation in a stepwise manner, *viz.*, first, with visible light (419–447 nm) and then with UV light (> 310 nm). The efficiency of photomodification upon irradiation with visible light was 400 times lower than with UV

light, but in this case the monoadduct **3** is formed at the T166 residue (yield 40%). Subsequent UV irradiation gives the bisadduct **1** (yield 62%) and monoadducts (yields at pyrimidine and purine residues were 9% and 22%, respectively). In this two-step irradiation, the total degree of photomodification of ds-DNA reached 95%.

Irradiation with visible light (419 nm, 30 min) of ds-DNA within a complex with a triplex-forming psoralen conjugate **2** yielded the monoadduct **3** in 87% yield. Further irradiation with UV light for 5 min resulted in the bisadduct **1** (in up to 92% yield).³¹ A conjugate 4'-hydroxymethyl-Pso-4,5',8-trimethyl-pAGGAAGGGG was used for site-specific injury of the supF-gene incorporated into vectors of *E.coli* phage λ ³² and virus SV40.³³ It was shown that the formation and photocross-linking of the triplex can also occur *in vivo*.³⁴

Inhibition of gene expression with a conjugate 5-hydroxy-Pso-pTC*TTC*TTC*C*TC*T-C*TT, where C* is 5-methylcytosine, in transfected HeLa cells is reported.³⁸ After UV irradiation (> 310 nm) of the triplex *in vitro*, the amplification of a DNA fragment was inhibited by 95%. Plasmid pCH110 was photo-modified and incorporated into HeLa cells. The activity of the gene of the incorporated β -galactosidase 5 h after transfection was 5%.

Penetration of psoralen derivatives through hydrophobic cell membranes and their resistance to nuclease hydrolysis could be enhanced if psoralen was coupled to distamycin-like imidazole (**4a**) and pyrrole (**4b** and **5**) derivatives.^{35–37}



The imidazole analogues of distamycin **4a** can deliver psoralen to GC-rich DNA regions, while the pyrrole analogues **4b** and **5**, to AT-rich DNA regions. The imidazole analogue **4a** photomodifies DNA 10 times more efficiently than the original psoralen. The efficiency of photomodification of ds-DNA with the pyrrole analogue **4b** is 1000 times greater than that with psoralen and 100 times greater than that with the imidazole analogue.¹

These data suggest that psoralen conjugates are promising reagents for photomodification of NA *in vivo*. High phototoxicity of psoralens as regards modification of ds-DNA is determined by the formation of bisadducts **1**.

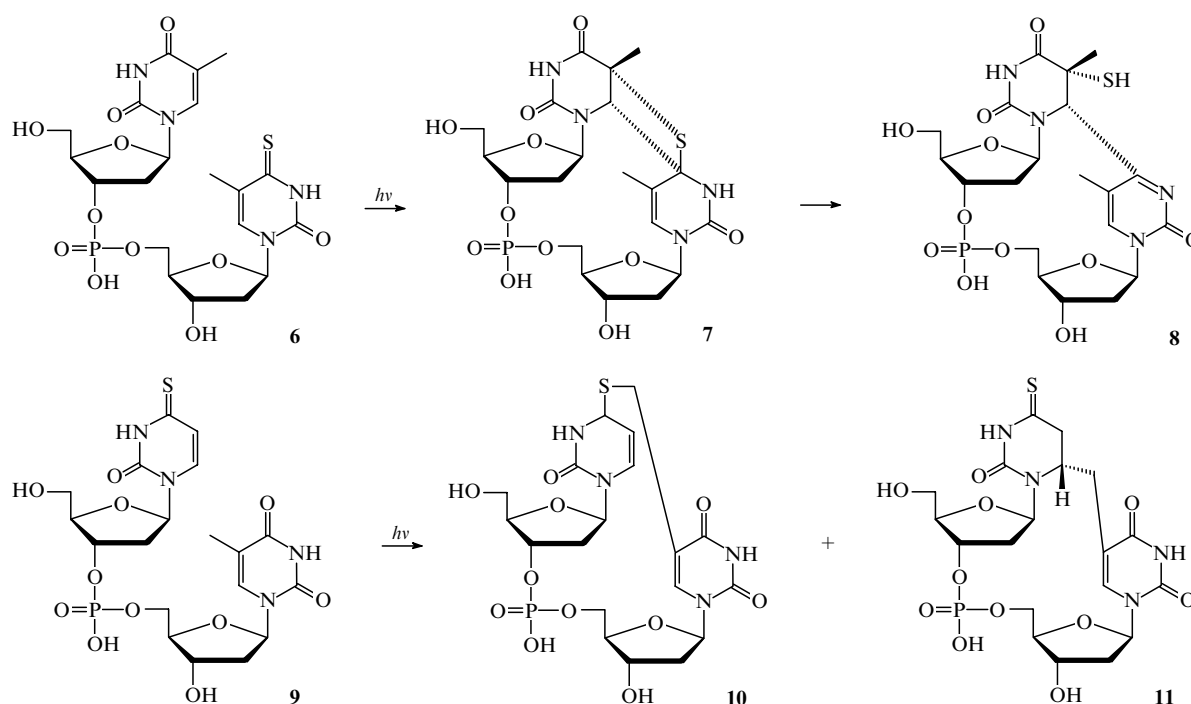
b. Photomodification of nucleic acids with 4-thiopyrimidine derivatives

Along with psoralens, thiopyrimidine nucleotides, *e.g.*, 4-thiouridine (s⁴U) and 4-thiothymidine (s⁴T), are used as photoreagents able to undergo free-radical cycloaddition. The presence of a sulfur atom instead of an oxygen atom at position 4 causes a shift of the absorption spectrum towards the long-wave region ($\lambda = 330$ nm) and the appearance of new photochemical properties.^{39, 40}

Irradiation of thiopyrimidines with UV light (330 nm) leads to the population of the excited state S_2 which is rapidly (within 5 ps) and in high quantum yield ($\phi = 0.9$) converted into state T_1 . Photolysis of d(s⁴U) in water in the presence of oxygen yields dU.⁴⁰

Thiopyrimidine nucleotides can form covalent adducts with all natural nucleic bases, but the quantum yield of the photo-reaction with pyrimidine bases is higher than that with purines. Irradiation of the dinucleotide dTp(s⁴U) (**6**) gives two stable products **7** and **8** (quantum yield 0.02) (Scheme 2). It is assumed

Scheme 2



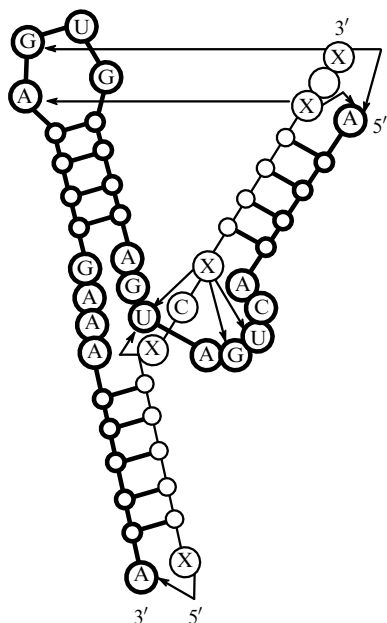


Figure 1. The structure of a ribozyme complex (bold-type) containing an RNA fragment.

that the [2+2]-cycloaddition of thiopyrimidine involving the excited C=S bond to the C(5)=C(6) bond of a pyrimidine results in the adduct **7** and subsequent chemical reactions yield the final product **8**.⁴⁰

Irradiation of the dinucleotide d(s⁴U)pT (**9**) afforded the adducts **10** and **11** (Scheme 2). In all probability, they are formed due to hydrogen abstraction from the methyl group of thymine by photoexcited thiouridine followed by recombination of radical species.⁴⁰

A significant advantage of thiopyrimidines as photoreagents is that the van der Waals radius of the sulfur atom is by only 0.45 Å larger than that of the oxygen atom. This does not affect the structure of oligo- and polynucleotides with incorporated thiopyrimidine residues.³⁹ The photochemical properties of thiopyrimidines were most completely employed in the study of the tertiary structure and mechanism of action of ribozymes (Fig. 1).^{39–45} Thiouridine residues were introduced into the RNA substrate at positions X. Irradiation of the ribozyme complex with RNA was accompanied by the formation of cross-links (indicated by arrows in Fig. 1). The photoaffinity modification data suggest that several alternative conformations appear in the ribozyme complex with RNA in different stages of a catalytic cycle of RNA hydrolysis.^{40–42}

2. Photoinduced alkylation of DNA

Numerous photochemical methods for the generation of electrophilic species that alkylate DNA have been described.^{27, 46–58} These methods involve the preparation of azacycloheptatetraene *via* an intermediate singlet nitrene by photodecomposition of aromatic azides,^{46–52} generation of quinolylmethylcarbocations by heterolytic photodecomposition of quinolylmethylisothiuronium salts,⁵³ preparation of quinonemethide by photoenolisation of 5- and 2-methylnaphthoquinone derivatives^{54–57} and generation of oxonium cations from monothioacetals by photoinduced electron transfer.⁵⁸

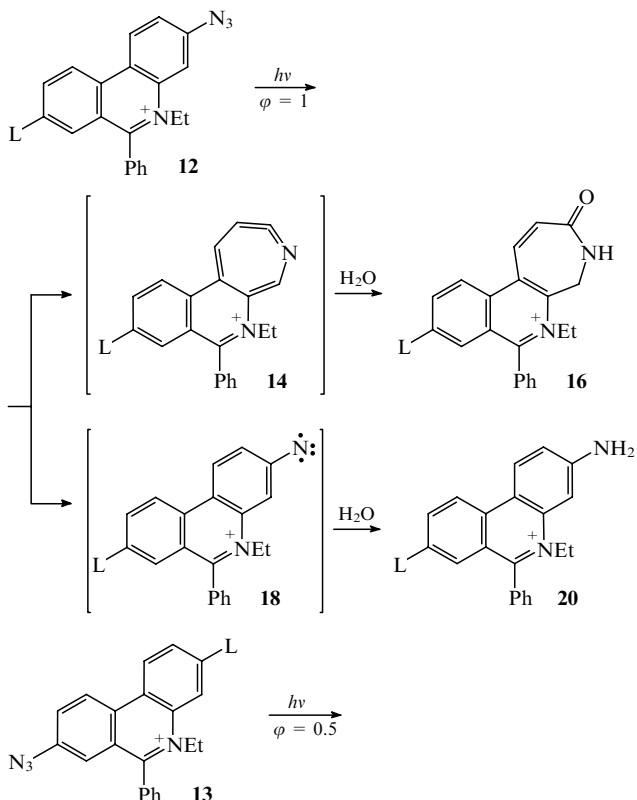
a. Photomodification of nucleic acids by aromatic azides

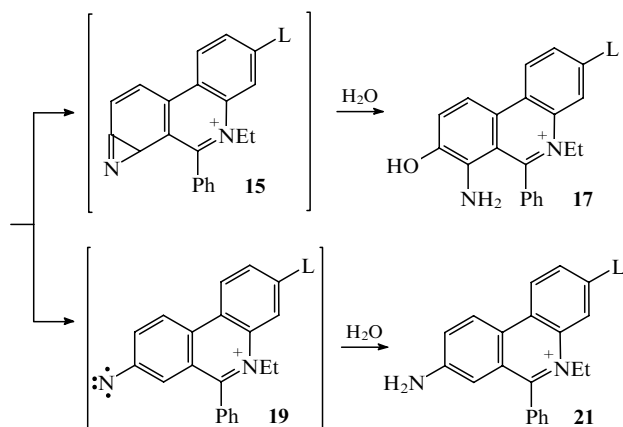
Oligonucleotide derivatives of aromatic azides are widely used in photomodification of DNA^{46, 47, 50–52} and RNA^{48, 49} owing to their high photoreactivity and accessibility.

Conformational changes of a *p*-azidophenacyl 5'-thiophosphate derivative of ribozyme L-21 Sca I were studied in different stages of binding and catalytic cleavage of an RNA-substrate.^{48, 49} Irradiation of the photoreactive ribozyme derivative with UV light (312 nm) in the absence of the RNA-substrate gives covalent adducts at the A88\A89\A90 residues (yield 12%). The photomodification affected the A114\A115 residues of ribozyme (yield 34%) within the complex with the fragment GGCCCU-CUAAAAA where ribozyme hydrolysed the phosphodiester bond between the uridine and adenine residues; in the absence of Mg²⁺ cations, the C102\A103\A104 residues were photomodified in 38% yield.⁴⁸ The data obtained made it possible to establish the position of the ribozyme internal guide sequence (IGS) containing the *p*-azidophenacyl residue in different stages of the catalytic cycle of RNA hydrolysis.^{48, 49}

Ethidium derivatives **12** and **13** proved to be the most efficient photoreagents for DNA modification.^{50, 51} In all probability, this is associated with the ability of these residues to intercalate into DNA and with the photochemical properties of aromatic azides. The photolysis products of the azides **12** and **13** in water have been studied.⁵¹ This reaction yields intermediate electrophilic species, *viz.*, the azacycloheptatetraene **14** and the aziridine **15**; which add water to give the adducts **16** and **17**. In both cases, the triplet nitrenes **18** and **19** were formed, which underwent nonproductive decomposition as regards NA photomodification, *viz.*, reduction to the amines **20** and **21**, respectively.

Formally, photolysis of the azide **13** in the presence of nucleophiles should give arylation products of the type **17**; however, these products have not been obtained and this azide is considered for convenience of comparison.





L = $\text{NHCO}(\text{CH}_2)_2\text{NH}_2$.

Heptanucleotide pCCAACA conjugates with the azides **12** and **13** linked through 5'-phosphate were used for site-specific photomodification of the ^{32}P -labelled complementary octanucleotide 5'-*pTGT TTGGC.⁵¹ The introduction of azidoethidium residues strongly stabilises the complementary complexes by increasing their melting temperature by 20–30 °C.



Irradiation of these duplexes with UV light (320 nm) results in covalent adducts in 40% and 60% yields, respectively. After treatment with piperidine which results in the cleavage of the DNA chain at the modified bases, the total degree of the octanucleotide photomodification increased up to 70% and 80%, respectively. The results of piperidine-catalysed cleavage led the authors to conclude that modification predominantly affected the C8 residue and, to a lesser degree, the G7 residue (indicated by arrows). The formation of up to 10 different adducts (many of which are unstable) was established by HPLC, but the attempts to isolate these adducts and to determine their structure were unsuccessful.

The oligonucleotides p(TC)₆Tp containing the azides **12** and **13** at their terminal phosphates were used for photomodification of ds-DNA in the triplex **22**.⁵⁰



22

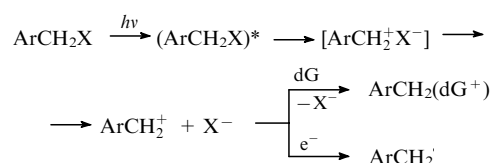
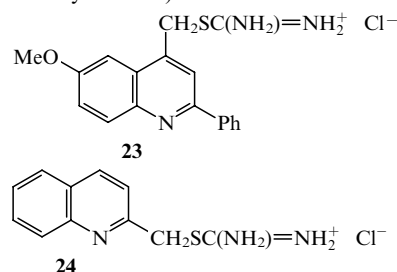
Irradiation of the triplex **22** (320–420 nm) containing the conjugate 5'-(**12**)p(TC)₆T as a photoreagent resulted in spontaneous cleavage of the purine-rich chain at the residue G3 (the degree of photomodification was 15%) as well as in the formation of covalent adducts with this residue (yield 30%). The pyrimidine-rich chain was photomodified to a far lesser degree; this was accompanied by the formation of covalent adducts with the residue T4 (yield 10%).

With the 3'-(**12**)p(TC)₆T derivative as a photoreagent, the total degree of photomodification of both chains did not exceed 10%.

Irradiation of the triplex **22** with the 5'-(**13**)p(TC)₆T reagent resulted in highly selective photomodification of the pyrimidine-rich chain. No direct cleavage was observed in this case; the covalent adducts (yield 35%) and the product of modification of the residue T4 were detected using treatment with piperidine.

b. Photomodification of DNA with benzylisothiuronium salts

A study of photolysis of a series of benzyl compounds of the type ArCH_2X capable of generating carbocations revealed that the quinolyl-2(4)-methylisothiuronium salts **23** and **24** manifested the highest photoreactivity. Their irradiation with UV light (350 nm) in water gave the carbocations ArCH_2^+ (yield 90%, quantum yield 0.09).⁵³



dG is deoxyguanosine.

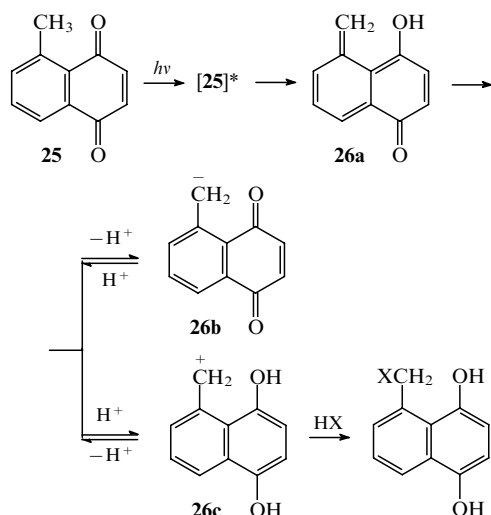
Photomodification of ds-DNA with the salts **23** and **24** resulted in insignificant cleavage of the target independent of its sequence. Most probably, the reaction occurs as hydrogen abstraction from deoxyribose by a benzyl radical ($\text{ArCH}_2^\bullet$) formed simultaneously with subsequent oxygen-dependent cleavage of the DNA-target. After treatment with piperidine, the degree of DNA modification increased 10-fold due to G-specific cleavage. It is assumed that quinoline residues intercalate into DNA in such a way that the positively charged isothiuronium residues of the reagents **23** and **24** are located on the duplex surface. Alkylation of guanine residues with a photoinduced quinolymethylcarbocation at position N(7) is considered to be the most probable mechanism of G-specific modification. The quantum yield of photoalkylation product formation is rather low [$\phi = (5-6) \times 10^{-6}$]; the yield of adducts with respect to the photoreagent does not exceed 1%.⁵³ Because of low efficiency of photoalkylation, these photoreagents have not found wide application.

c. Photoalkylation of nucleic acids with methylnaphthoquinones

Modification of single-stranded DNA (ss-DNA) with an oligonucleotide derivative of 5-methyl-1,4-naphthoquinone upon irradiation with UV light (> 345 nm) is the best studied example of photoinduced alkylation of NA.^{54–56} Unlike photomodification with the isothiuronium salts **23** and **24**, the products of oxidative cleavage of the DNA-target were not found and the alkylation product was exclusively formed in ~20% yield. Neither piperidine (DNA cleavage at the sites of bases alkylated at the nitrogen atoms of a heterocycle), nor sodium borohydride [cleavage at the sites of pyrimidine bases with a saturated C(5)–C(6) bond] effected cleavage of the DNA-target. Pre-irradiation of the photoreagent resulted in its complete inactivation due to the photodegradation of the substituted naphthoquinone.⁵⁴ It was shown that photogenerated quinonemethides alkylate G and C residues at the exocyclic amino groups. Such adducts are more resistant to alkaline hydrolysis of DNA than the ordinary alkylation products.⁵⁶

The efficiency of photoalkylation of DNA with oligonucleotide derivatives of 3-(1,4-naphthoquinonyl)thiopropionic acid with substituents at positions 2, 5 and 6 has been studied.^{55,56} 5-Methyl-substituted naphthoquinones proved to be the most photoreactive agents, the degree of alkylation of ss-DNA regions reached 27%. The yields of products of DNA alkylation with 2- and 6-methylnaphthoquinones did not exceed 6%–8%.

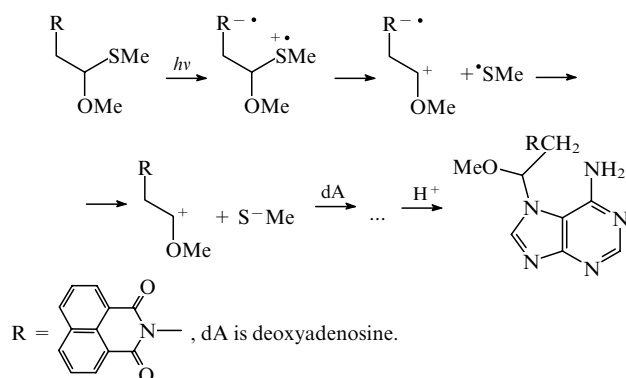
The mechanism of photoalkylation of DNA with 5-methylnaphthoquinone (**25**) in aqueous solutions has not been studied until very recently.⁵⁷ Upon photoexcitation, the naphthoquinone **25** is converted into 4-hydroxy-5-methylenenaphthalen-1(5*H*)-one (**26a**), which can be deprotonated to give the naphthoquinone-5-carbanion (**26b**) or protonated to give the corresponding carbocation **26c**. The reaction of the carbocation **26c** with nucleophiles (HX) is the limiting step of photoinduced alkylation.



Photolysis under physiological conditions results predominantly in the carbanion **26b** ($pK_a = 6.5$); the corresponding value for the carbocation **26c** is 1.1. This fact is the main reason for the low efficiency of DNA photoalkylation with methylnaphthoquinones.

d. Photomodification of nucleic acids with monothioacetals

Irradiation of 1,8-naphthalimidoacetaldehyde monothioacetals with UV light (> 330 nm) generates S-centred radical cations due to intramolecular electron transfer to the photoexcited naphthalimide. The radical cation dissociates into a carbocation and an alkylthio radical, which is rapidly reduced by the naphthalimide radical anion.⁵⁸



The carbocation reacts with nucleophiles (e.g., the reaction with MeOH in the absence of oxygen occurs with a 98% yield and a quantum yield of 0.038) to give alkylation products.

1,8-Naphthalimidoacetaldehyde monothioacetal was irradiated with UV light (366 nm) in the presence of a triplet sensitizer (acetophenone); in this case, 99% of the light was absorbed by acetophenone. It was thus demonstrated that the electron transfer occurs *via* the triplet state of naphthalimide.

Irradiation of supercoiled DNA of pBR 322 with UV light (365 nm) in the presence of this monothioacetal resulted in its conversion into cyclic DNA after heating. Adenine alkylated at position N(7) was the main DNA photomodification product.⁵⁸

Thus, several types of electrophilic photoreagents are currently known which can be used for photoalkylation of NA upon

irradiation with proximal UV light (320–400 nm). However, low efficiency of these reagents and the lack of photoreactivity in the visible region of the spectrum restricts their application for the *in vivo* photomodification of NA.

3. Photoarylation of DNA

Ruthenium(II) polypyridyl complexes photosensitize the formation of single-strand breaks in ds-DNA in low quantum yields [$\phi = (1-7) \times 10^{-6}$].^{59,60} The mechanism of cleavage was investigated with short 5'-labelled oligonucleotides, which were irradiated with visible light (436 nm) together with a $Ru(TAP)_3$ complex, where TAP is 1,4,5,8-tetraazaphenanthrene. It was found that the main photosensitized reaction is not the cleavage of oligonucleotide chains, but rather the formation of covalent adducts of the $Ru(II)$ complex with the oligonucleotide.^{59,61} The yield of adducts in the $Ru(bipy)_nL_{3-n}$ series, where $L = TAP$ or HAT, bipy is 2,2'-bipyridyl and HAT is 1,4,5,8,9,12-hexaazatriphenylene was rather high for $n = 0,1$, while no covalent adducts were formed for $n = 2,3$.

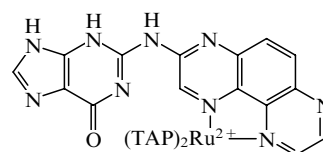
With an increase in n , the photochemical properties of $Ru(II)$ and $Os(II)$ complexes change, which is manifested in a bathochromic shift of absorption and fluorescence maxima and a decrease in the reducing potential (E_{red}^*) of the excited state (Table 1). Covalent adducts with the DNA-target are formed only in the case of $Ru(II)$ and $Os(II)$ complexes the E_{red}^* values of which exceed the redox potential of guanosine monophosphate ($E_{ox} = 0.92$ V).

Table 1. Photochemical properties of $Ru(II)$ and $Os(II)$ complexes: the absorption (λ_{max}) and fluorescence maxima (λ_{fl}); the values of the reduction potential (E_{red}^*) of photoexcited triplet states and the possibility of formation of covalent adducts with DNA.⁶¹

Complexes	λ_{max} /nm	λ_{fl} /nm	E_{red}^* /V	Adducts
$Ru(HAT)_3$	440	596	1.46	+
$Ru(bipy)(HAT)_2$	472	661	1.12	+
$Ru(bipy)_2(HAT)$	484	742	0.83	—
$Ru(TAP)_3$	437	608	1.32	+
$Ru(bipy)(TAP)_2$	465	649	1.06	+
$Ru(bipy)_2(TAP)$	484	714	0.86	—
$[Ru(bipy)_2]_2HAT$	572	800	1.03	+
$[Ru(phen)_2]_2HAT$	564	820	1.02	+
$Os(TAP)_3$	—	—	1.11	+

The bimetallic complexes $[Ru(bipy)_2]_2HAT$ and $[Ru(phen)_2]_2HAT$ (where phen is *o*-phenanthroline) attract substantial interest as electrophilic photoreagents, since they also form covalent adducts with DNA; their absorption maxima show bathochromic shifts by about 100 nm relative to monometallic complexes.

The covalent adduct formed by photomodification of ds-DNA with the $Ru(TAP)_3$ complex was isolated and characterized. The exocyclic 2-amino group of guanine was covalently bound to the C(2) position of TAP. Photomodification of DNA with $Ru(bpz)_3$ (bpz is 2,2'-bipyridaziny), $Ru(TAP)_2bipy$,⁶¹ $[Ru(phen)_2]_2HAT$ ⁶⁰ and $Os(TAP)_3$ ⁵⁹ complexes gave similar photoadducts.



Although the $Ru(II)$ polypyridyl complexes intercalate into ds-DNA through the major groove, the formation of covalent adducts takes place in the minor groove.

The mechanism of photosensitized arylation of DNA with $Ru(II)$ complexes has not been finally elucidated; however, it is

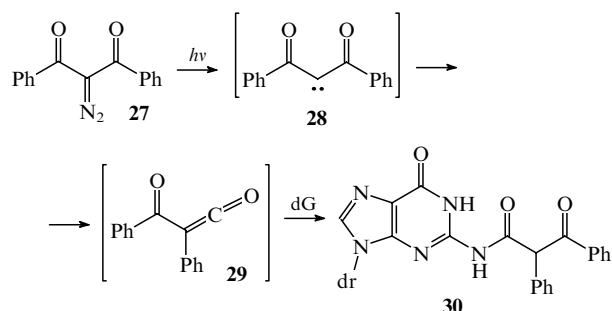
believed that the photoinduced electron transfer from the guanine residue to the excited ligand (TAP*) is followed by proton transfer from the radical cation $G^{+\bullet}$ to the radical anion $TAP^{-\bullet}$ as well as by recombination of radicals and oxidative rearomatisation of the TAPH₂ residue.^{59, 61}

Oligonucleotide conjugates of Ru(II) polypyridyl complexes were used to study photoinduced electron transfer,^{62, 63} but experimental support for complementarily addressed photomodification of DNA by these derivatives is lacking.

It should be noted that metal polypyridyl complexes open up new opportunities for the design of photoreagents that can be employed for the *in vivo* modification of NA. This is due to the fact that the properties of such complexes can be varied within a very wide range by changing the central metal atom and the ligands.

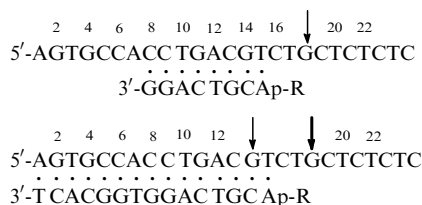
4. Photoacylation of DNA

It is known that photoinduced dissociation of dibenzoyldiazomethane (**27**) results in dibenzoylcarbene (**28**), which is converted into the electrophilic ketene **29** capable of reacting with nucleophiles following the Wolff rearrangement.^{27, 64} Thus its photolysis (366 nm) in the presence of 3',5'-di-*O*-(*tert*-butyldiphenylsilyl)-2'-deoxyguanosine gives a guanosine derivative **30** with an acylated exocyclic amino group.²⁷



Irradiation of dibenzoyldiazomethane (**27**) together with ss-DNA in the presence of the singlet oxygen trap, NaN₃, gave covalent adducts. Treatment of the latter with piperidine is accompanied by G-specific cleavage owing to the reaction with the ketene **29** and insignificant nonspecific cleavage due to hydrogen abstraction from deoxyribose by the carbene **28**.²⁷

Site-specific photomodification of a 25-membered fragment of ss-DNA with 8- and 15-membered complementary oligonucleotide conjugates having a substituent (R) at the 5'-terminal phosphate in the presence of NaN₃ results exclusively in covalent adducts in 32% and 47% yields, respectively.



R = 4-(PhC(O)C(=N₂)CO)C₆H₄CH₂OC(O)NH(CH₂)₆NH.

In both cases, treatment of photomodification products with piperidine caused cleavage of the DNA-target at the residue G18 located in the single-stranded fragment of the duplexes; in the case of the 15-membered reagent, additional cleavage occurred at the residue G14 (indicated by arrows). The greater part of the adducts is not cleaved with piperidine. The total degree of modification after treatment with piperidine increased up to 33% and 56%, respectively. The formation of piperidine-labile adducts is due to the acylation at the N(7) position of guanine, whereas that of piperidine-stable adducts, by the acylation at the exocyclic amino group.²⁷

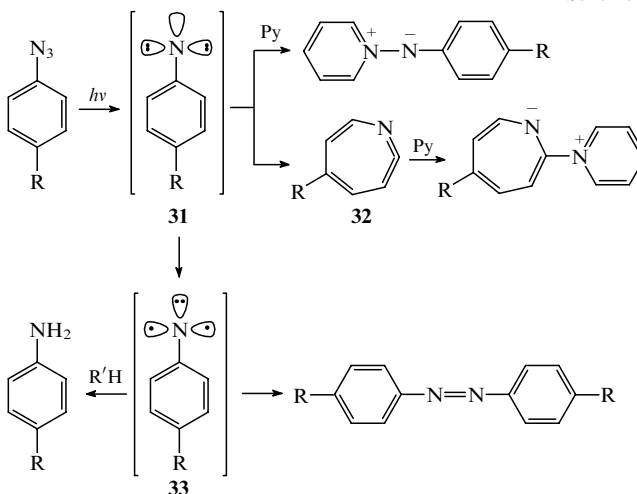
Thus, substituted diazo ketones are promising reagents for G-specific photoacylation of NA.

5. Other electrophilic addition reactions

A series of 8-alkoxy-5-azidopsoralens were synthesised with the aim of integrating the photochemical properties of aromatic azides and psoralens and investigating their ability in the photomodification of NA. Irradiation of azidopsoralens in acetonitrile with UV light (351 nm) affords a triplet nitrene and an azacyclo-tetraene, whereas irradiation in water yields exclusively a triplet nitrene. The reactivity of these species is insufficient for efficient photomodification of DNA. Being a triplet sensitizer, psoralen favours the formation of a triplet nitrene. Such a detrimental effect of the psoralen residue on the photochemistry of the azido group is the reason for the inability of pBR322 DNA to undergo cleavage with 8-alkoxy-5-azidopsoralens upon UV irradiation.⁶⁵

Oligonucleotide reagents containing aromatic azido groups were also fairly inefficient in the photomodification of NA due to numerous side reactions. In the case of aromatic azides, the reaction does not occur *via* the highly reactive singlet nitrene **31** but rather *via* the much less reactive azacycloheptatetraene **32** formed from the nitrene **31** by rapid intramolecular ring expansion. Besides, nitro-, cyano-, formyl-, acyl- and, particularly, amino-substituents in aromatic azides accelerate intersystem crossing into a more stable but less reactive triplet nitrene **33** upon irradiation.⁵² The nitrene **33** is usually consumed in radical dimerisation reactions to give azo derivatives or is reduced to the corresponding aniline without formation of NA modification products (Scheme 3).

Scheme 3

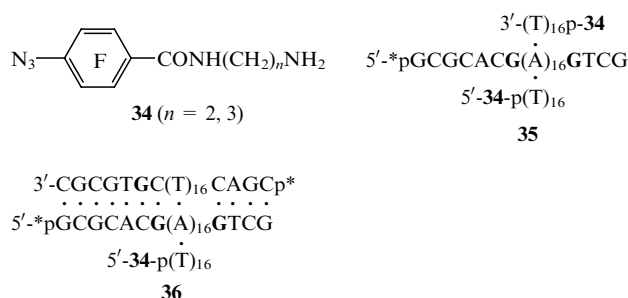


Perfluoroaromatic azides represent a more promising class of photoreagents, since their photodissociation predominantly results in the singlet nitrene **31**.^{52, 66–68} The presence of fluorine atoms in *o*-positions relative to the azido group decreases the rate of azacycloheptatetraene formation 1700-fold.⁶⁶ In addition, the acceptor fluorine atoms increase the electrophilicity of the singlet nitrene 10-fold⁶⁷ and reactivities of the triplet nitrene and the azacycloheptatetraene, 1000 and 10 000-fold, respectively,⁶⁸ in comparison with nonfluorinated derivatives.

Dobrikov *et al.*^{46, 47} studied the effect of the aryl azide structure on the efficiency of site-specific photomodification of DNA by comparing the reactivities of oligonucleotide derivatives of 4-azido-, 5-azido-2-nitro- and 4-azidotetrafluorobenzamides. Upon irradiation with UV light, these compounds generate different species, *viz.*, azacycloheptatetraene **32**, the triplet (**33**) and the singlet (**31**) nitrenes, respectively; the yields of covalent adducts in site-specific photomodification were 5%, 15% and 70%, respectively.⁶⁷ The reactivity of the species **32** and **33** is insufficient for modification of NA. The specificity of photomodification of DNA-targets containing T, C, A or G residues opposite to the photoreagent was studied with an example of an

oligonucleotide reagent containing a perfluoroaryl azide residue **34** coupled through 5'-phosphate. Treatment of modification products with piperidine showed that the degree of modification of these residues was ~50%, the largest degree of modification being 40%, 45%, 45% and 65%, respectively.^{46,47,69} The reactions of the singlet nitrene **31** with the nitrogen atoms of the pyridine type of the heterocycles result in N-amination (Scheme 3). Photomodification of ss-DNA is most probably accompanied by electrophilic addition at position N(7) of guanine. The use of two oligonucleotide reagents complementary to the neighbouring regions of the DNA-target and containing two perfluoroaryl azide residues **34** at the contact site made it possible to increase the yield of covalent photomodification adducts to 80%.⁷⁰

A highly efficient site-specific photomodification of 27-membered fragments of ss- and ds-DNA with a 4-azidotetrafluorobenzamide derivative of p(T)₁₆ has been carried out.^{71,72}



Photomodification of ss-DNA within the triplex **35** occurred mainly at the bases G7 and G24 (bold-typed); the yields of covalent adducts amounted to 77%. Residues G7 of A-rich and G-22 of T-rich strands (the yields of covalent adducts were 37% and 16%, respectively) were the main sites of photomodification of ds-DNA within the triplet **36**. After piperidine treatment, the total degree of modification of the triplex **36** increased up to 50% in A-rich and up to 42% in T-rich strands due to noncovalent modification at pyrimidine bases.^{71,72}

The effects of *p*-substituents in perfluoroaromatic azides on the efficiency of site-specific photomodification of ss-DNA was also studied. The increase in the conjugation chain in substituted perfluoroaryl azides accelerates the intersystem crossing of the singlet nitrene into the triplet one and decreases the efficiency of DNA photomodification. Studies with pyridines as the chemical trap for the singlet nitrene **31** revealed that the yield of covalent adducts with DNA correlates with the yield of pyridine ylides in the photolysis of perfluoroaryl azides in 6 M pyridine. It was assumed that the electrophilic addition of the singlet nitrene to the nitrogen atoms of the pyridine type in NA bases is the most feasible mechanism of covalent adduct formation.⁷³

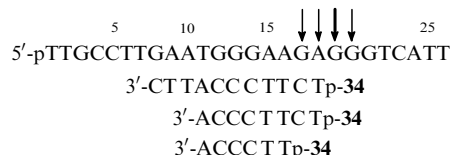
The efficiency of site-specific photomodification (irradiation with UV light, $\lambda = 303\text{--}370$ nm, irradiation power 0.5 mW cm^{-2} , 5 min, 4 °C, pH 7.0) of ss-RNA and ss-DNA fragments (5 mmol litre^{-1}) with oligonucleotide conjugates of perfluoroaryl azide **34** ($50\text{ mmol litre}^{-1}$) was compared by Levina *et al.*⁷⁴

Reagent	Yield of covalent adducts for targets (%)	
	5'-d(TGTTGGC)	5'-UGUUUGGC
5'- 34 -pd(AAACA)	~5	~5
5'- 34 -pd(CAAACA)	65	30
5'- 34 -pd(CCAAACA)	75	55

The efficiency of photomodification increases with an increase in the length of the oligonucleotide address. Photomodification of RNA occurs less efficiently than that of DNA, which most probably depends on the structures and stabilities of duplexes. Nevertheless, 6–7-membered ribonucleotide conjugates carrying a perfluoroaryl azide residue **34** at the 5'-terminal phosphate were

used to study the decoding centre of human 80S ribosomes.⁷⁵ Irradiation of a ribosome–tRNA–photoreactive mRNA analogue complex with UV light (270–380 nm) resulted in binding of the analogue to the 40S subunit (45%–55%) and 18S sRNA (8%–22%). Only one base, *viz.*, the residue G1207, underwent photomodification within sRNA.

Kazantsev *et al.*⁷⁶ studied the kinetics of site-specific photomodification of 26-membered ss-DNA with oligonucleotide conjugates of perfluoroaryl azide **34**. Irradiation with UV light (> 300 nm) resulted in the formation of covalent adducts; upon treatment with piperidine, cleavage (predominantly, at residue G19 and, to a lesser degree, at residues G17, A18 and G20) (indicated by arrows) occurred.



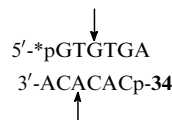
The kinetic data shown in Table 2 suggest that the efficiency of photomodification with 5'-*p*-azidotetrafluorobenzamide conjugates is not very high. The maximum degree of photomodification with a 11-membered conjugate was higher than that with 6- and 8-membered ones due to the higher value of the constant K_x . Irradiation of the conjugates in the absence of a DNA target resulted in photodeactivation and an approximately 200-fold decrease in affinity for the target.⁷⁶

Table 2. The association constants (K_x) of the conjugates with the target, the efficiency of photomodification within the duplexes (γ_{eff}) and maximum degrees of photomodifications (PZ) at 37 °C.

Photoreagent	$K_x/\text{mol litre}^{-1}$	γ_{eff}	PZ (%)
CTTACCCTTCTp- 34	8.4×10^6	0.2	70
ACCCTTCTp- 34	1.1×10^5	0.33	55
ACCCTTCTp- 34	1×10^5	0.27	40

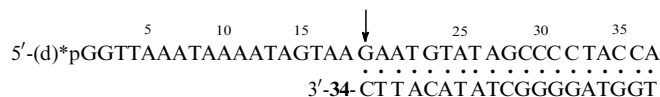
Note. The concentrations of a DNA-target and the conjugates are $10\text{ mmol litre}^{-1}$ and $60\text{ mmol litre}^{-1}$, respectively (see Ref. 76).

Site-specific photomodification of a ss-DNA fragment with an oligonucleotide conjugate containing the azide **34** was carried out in order to elucidate the possible reasons for such photodeactivation.⁷⁷



Irradiation of a labelled reagent in the absence of the target also resulted in a partial loss of its affinity for the target; treatment with piperidine resulted in cleavage at all the bases of the address, the total degree of cleavage was 44%. Irradiation with an excess of a target and subsequent hydrolysis revealed that the modification of the address occurred at the residue A4 (yield 29%), *i.e.*, the formation of the duplex did not prevent the modification of the address. With a 5000-fold excess of the conjugate, photomodification affected the residue G3 of the target localised in the double-stranded fragment. The maximum yield of photomodification reaches 80%; γ_{eff} is close to unity.⁷⁷

Site-specific photomodification of a 37-membered DNA fragment with an oligonucleotide reagent carrying a perfluoroaryl azide residue at 3'-phosphate in complexes with human immunodeficiency virus reverse transcriptase (HIV RT)^{78,79} or with DNA-polymerase α has been carried out.⁸⁰



Irradiation of these complexes with UV light (> 300 nm) has led to cross-linking of the primer to matrices with 60%^{78,79} and 70%⁸⁰ efficiency. Treatment with piperidine resulted in cleavage of the target at the residue G19 which is located opposite the photoreagent incorporated into the primer.

Thus, by virtue of high reactivity of the species formed upon irradiation of perfluorinated azides, these have found wide application in photomodification of NA. The main disadvantage of these photoreagents is the lack of noticeable photoreactivity in the visible region of the spectrum, which restricts their application in complex biological systems.

III. Sensitised photomodification of DNA with binary systems

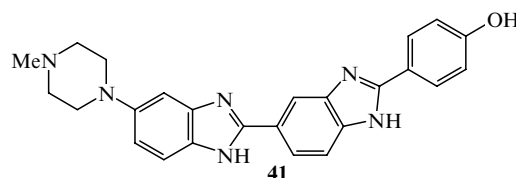
1. Photomodification of DNA with two-component (sensitiser – photoreagent) systems

Irradiation of DNA containing 5-bromo- or 5-iododeoxyuridine residues with UV light (302–313 nm) induces numerous photochemical reactions, *viz.*, modification of bases, cross-linking, single- and double-strand breaks, *etc.* (Scheme 4).^{23,81–88}

The mechanism of formation of single-strand breaks initiated by photolysis of halogenated pyrimidines was studied in detail for oligonucleotides **37** containing 5'-A^{Br}U sequences.^{23,81,82} Irradiation with UV light (302 nm) resulted in photoinduced electron transfer from adenine to the excited triplet state of bromouridine ³(BrU)* with the formation of a radical cation of adenine Ade^{•+}, and a radical anion of uridine (compound **38**). This is followed by elimination of Br[−] from the radical anion; the 5-uracil radical formed abstracts hydrogen from the adjacent C(1') atom to give the carbocation **39**.⁸¹ Addition of water to the C(1') atom of the carbocation **39** results in the 1'-hydroxy derivative **40**. Apurinisation of compound **40** and subsequent reactions bring about cleavage of the DNA chain. The structure of stable DNA cleavage products has been considered in a review of Pratiel *et al.*⁸¹ Similar reactions take place in self-complementary duplexes of the type 5'-d(GCA^{Br}UGC)₂ containing 5'-A^{Br}U sequences.⁸³

Irradiation (313 nm) of DNA containing 5-d¹U fragments results in alkali-dependent single-strand cleavage with the efficiency 0.5; its mechanism is somewhat different.⁸⁴ The photo-reaction occurs *via* the homolytic cleavage of the C(5)–I bond of uridine. The 5-uracil radical formed competitively abstracts hydrogen atoms from the C(1') or C(2') atoms of deoxyribose on its 5'-side.⁸¹ The efficiency of analogous cleavage induced by irradiation with UV light ($\lambda = 365$ nm) in the presence of Hoechst

33258 bisbenzimidazole **41** reaches 0.9. Under these conditions, the initial rate of sensitised photomodification is 4–5 times greater than the rate of photomodification in the absence of bisbenzimidazole. Binding of compound **41** to DNA occurs in the minor groove, where it strongly absorbs UV light (365 nm, 23 000 mol^{−1} litre cm^{−1}) and undergoes excitation. The electron transfer from bisbenzimidazole **41** to 5-d¹U induces elimination of I[−] and the formation of an uracil radical; reactions of the latter bring about photomodification of DNA.⁸⁴ Similar results were obtained in the photo-induced cleavage of DNA containing 5-dBrU fragments sensitised to long-wave UV light with bisbenzimidazole **41**.⁸⁵



It is believed that bisbenzimidazole dyes bind preferentially to (AT)₄- and (AT₃)A(5-BrU) sequences of DNA⁸⁶ and thus ensure high efficiency of electron transfer to the adjacent residues of halogenated pyrimidines.

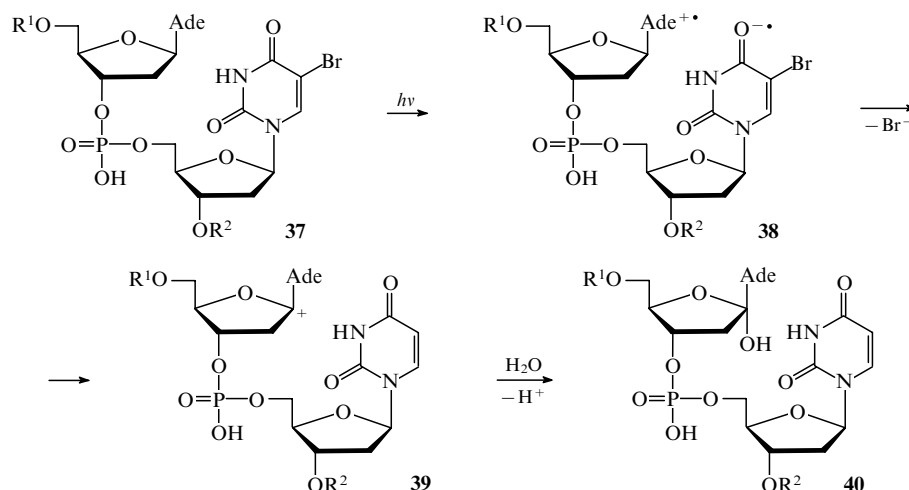
In cells cultured on 5-dBrU-containing media, one 5-dBrU residue per ~ 200 nucleotides is incorporated into DNA. Irradiation of cells with UV light (365 nm) in the presence of bisbenzimidazole **41** induces the formation of protein – nucleic acid cross-links as well as single- and double-strand breaks of DNA and modification of bases,^{87,88} resulting in multiple aberrations of chromosomes and cell death. The death of cells irradiated in the presence of the photoreagent 5-dBrU and the sensitiser **41** occurs 30 000 times more efficiently than in the case of UV-irradiated native cells and 20 times more efficiently than in the case of 5-dBrU-containing cells irradiated in the absence of the sensitiser.⁸⁷

The use of two-component sensitiser – photoreagent systems has made it possible to combine high reactivity of the photoreagent with spectral-luminescent properties of the sensitiser.

2. Sensitised photomodification of DNA with binary systems of oligonucleotide reagents

For the majority of photoreactive derivatives, light absorption and dark reactions within a complementary complex with a DNA-target and in solution occur at the same rate. At best, this results in nonproductive decomposition of the photoreagent in solution and triggers undesirable side reactions.

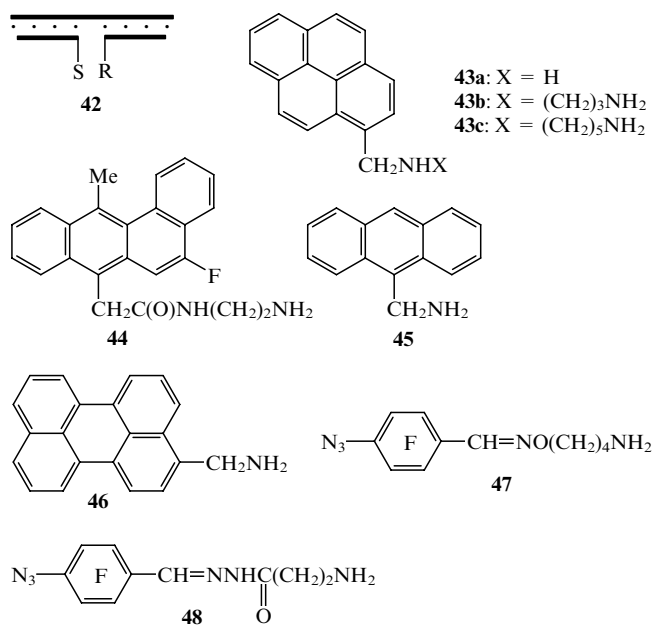
However, the specificity of oligonucleotide derivatives is insufficient for modification of nucleic acids *in vivo*, since under physiological conditions (37 °C) stable complexes are formed at



Scheme 4

the oligonucleotide lengths of 12–13 bases. Oligonucleotides having the lengths of 18–20 bases, which is necessary for highly specific recognition of unique nucleotide sequences within the DNA structure, can form numerous imperfect complexes with incompletely complementary sequences.⁸⁹

To overcome these drawbacks, the separation of light absorption and photomodification was suggested. For this purpose, binary systems of the oligonucleotide conjugates **42** complementary to the adjacent sequences of a DNA-target and containing chemically inert groups, *viz.*, a sensitiser (S) and a photoreagent (R), have been developed. The groups S and R being brought together within the structure of the complementary complex form a photoreactive centre which can be activated by irradiation with long-wave UV or visible light due to a non-radiative transfer of the electron excitation energy from the sensitiser to the photoreagent. The thus excited photoreagent induces photomodification of only that DNA-target which is an integral part of the complementary complex.^{90–100} The lengths of both nucleotide addresses (both were decanucleotides) were chosen so that the melting temperature of the duplexes was $\sim 37^\circ\text{C}$; such short oligonucleotides cannot form imperfect duplexes with incomplete complementary sequences under physiological conditions.⁸⁹



Pyren-1-yl-methylamines (**43a–c**),^{89, 94–96} *N*-(5-fluoro-12-methylbenzo[*a*]anthracen-7-ylacetyl)ethylenediamine (**44**),^{90–93} anthracen-9-ylmethylamine (**45**)⁹⁸ and perylen-1-ylmethylamine (**46**)^{97, 99, 101, 102} derivatives were used as sensitisers, whereas perfluoroaromatic azides (*p*-azidotetrafluorobenzamides **34**,^{94, 95} *O*-(4-aminobutyl)-*p*-azidotetrafluorobenzaldoxime (**47**)⁹⁶ and *N*-(4-azidotetrafluorobenzylidene)-*N'*-(3-aminopropionyl)hydrazine (**48**)^{89–93, 101, 102} were used as photoreagents.

Several sensitisation mechanisms, *e.g.*, singlet–singlet energy transfer from a photoexcited sensitiser to a photoreagent,^{89–94, 98} a two-quantum triplet–triplet energy transfer^{95, 96} and photo-induced electron transfer from a photoreagent to an excited sensitiser,^{97, 99, 101, 102} have been suggested.

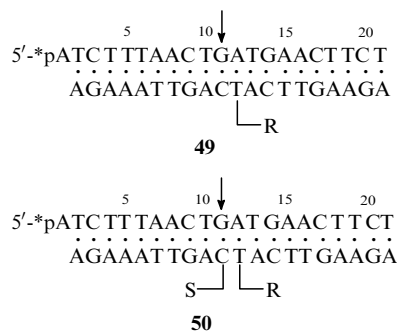
a. Singlet–singlet energy transfer

Singlet–singlet energy transfer occurs provided the energy of the 0,0-transition between the lowest vibrational levels of the ground and the first electronically excited states in the sensitiser molecule is greater than the energy of the corresponding transition in the photoreagent R molecule and the emission spectrum of the excited sensitiser (S*) overlaps with the absorption spectrum of the photoreagent R.¹⁰³

The energy of the 0,0-transition in aromatic azides is $\sim 70\text{ kcal mol}^{-1}$ and their weak $n\pi^*$ -absorption is observed at 450 nm.¹⁰⁴ Derivatives of polyaromatic hydrocarbons, *viz.*, pyrene **43**, benzoanthracene **44** and anthracene **45**, have high quantum yields of fluorescence and low Stokes shifts (*i.e.*, the minimum energy losses in photoexcitation and subsequent fluorescence). The energies of 0,0-transitions in unsubstituted pyrene, benzoanthracene and anthracene are equal to 76,¹⁰⁴ 72¹⁰⁵ and 73 kcal mol^{−1} (see Ref. 104) and exceed those of 0,0-transitions in the azides **34**, **47** and **48**. Thus, the fluorescence spectra of compounds **43–45** overlap with the absorption spectra of these azides.⁹¹

The efficiency of the energy transfer strongly depends on the distance between the sensitiser and the photoreagent and at commonly used micromolar concentrations of oligonucleotide derivatives the energy transfer from the sensitiser to the photoreagent does not occur in solution.

UV irradiation (365–390 nm) of ss-DNA complexes with an oligonucleotide conjugate containing a photoreagent in the absence (complex **49**) and in the presence (complex **50**) of a sensitiser results in covalent adducts. The azide **34** was used as a photoreagent (R), while the pyrene derivatives **43a–c** were used as sensitisers (S). Treatment of reaction products with piperidine showed that direct (within the complex **49**) and sensitised (within the complex **50**) photomodification affects the residue G11.⁸⁹



The initial rate and efficiency of direct (within the complex **49**) and sensitised (within the complex **50**) photomodification of the target depended on the localisation of the photoreagent and the sensitiser on the 3'- or 5'-phosphates as well as on the length of the linker between the sensitiser and the oligonucleotide address. Oligonucleotide derivatives containing a photoreagent at 3'-phosphate appeared to be more efficient, *viz.*, the yield of covalent adducts amounted to 70%. The rate of photomodification sensitised to UV light (365–390 nm) was 100–1500 times higher than that of direct complementarily addressed modification and decreased with an increase in the linker length in the series of the pyrenyl derivatives **43a–c**.⁹⁴

Photomodification of ss-DNA in the complexes **49** and **50** with the oligonucleotide azide derivative **48** has been carried out. At equimolar ratios of conjugate and target, the largest yields of covalent adducts of direct photomodification within the complex **49** (Fig. 2, curve 1) and of photomodification sensitised with the oligonucleotide benzoanthracene derivative **44** within the complex **50** (Fig. 2, curve 2) are identical ($\sim 30\%$), but the initial rate of the sensitisation reaction is 120 times greater than that of direct photomodification. The observed increase in the rate of photomodification is due to efficient energy transfer from the photoexcited sensitiser S* to the photoreagent R. With a 50-fold excess of oligonucleotide conjugates (curve 3), the initial rate of sensitised photomodification was not practically changed in comparison with the rate of sensitised modification represented by the curve 2, but the yield of covalent adducts increases up to 72%. The yield of direct photomodification products increases insignificantly under these conditions.^{90, 93}

To account for these results, the dependence of the yields of covalent adducts was studied with a deficit of the sensitiser and an excess of the photoreagent on the concentration ratio of the

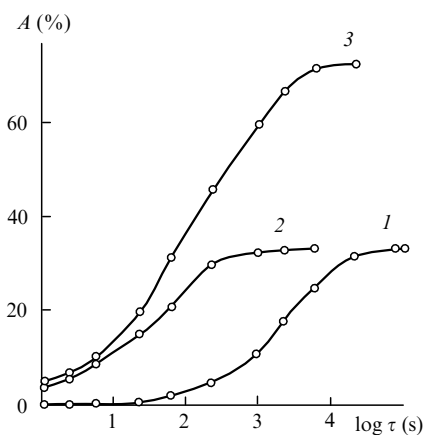


Figure 2. The yield (A) of covalent adducts of an oligonucleotide conjugate containing an azide residue **48** to a complementary DNA-target upon irradiation with UV light (365–390 nm) of the complexes **49** (1) and **50** (2, 3); concentrations/ $\mu\text{mol litre}^{-1}$; oligonucleotide conjugates, 50 (1–3), DNA-target, 50 (1, 2), 1 (3).

sensitiser to the DNA-target (Fig. 3). In the absence of the catalytic effect of the sensitiser it should be linear as in the case of irradiation under such conditions (10 min, 4 °C) where the components of the complex **50** are not exchanged for the solution components (curve 1). With an increase in the irradiation time and in temperature, each sensitiser molecule initiates the modification of several target molecules (curves 2 and 3). Thus with a 100-fold deficit of the sensitiser (irradiation at 42 °C), each sensitiser molecule induces photomodification of up to 24 target molecules.⁹³

The specificity of direct and sensitised photomodification of a natural DNA-target was studied.^{91,92} A mixture of 18 fragments of ss-DNA of M13BMR4 was obtained by enzymatic hydrolysis. One of these fragments having the length of ~ 150 bases contained a sequence-target complementary to oligonucleotide addresses (similar to the complexes **49** and **50**); while other fragments did not contain this sequence. The results of direct and sensitised photomodification of a mixture of DNA restricts with an oligonucleotide conjugate carrying an azide residue **48** at ^{32}P -labelled 5'-phosphate are shown in Fig. 4.

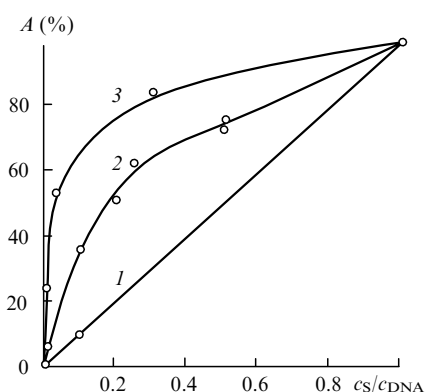


Figure 3. The dependence of the relative yields (A) of the covalent adducts of sensitised photomodification within the complex **50** on the concentration ratio of the sensitiser (c_s) and DNA-target (c_{DNA}) upon irradiation with UV light (365–390 nm). The yield of adducts at an equimolar c_s/c_{DNA} ratio is taken as 100%. The concentration of the DNA-target and the oligonucleotide photoreagent is 50 $\mu\text{mol litre}^{-1}$. The irradiation was performed for 10 min, 4 °C (1); 90 min, 42 °C (2) and 300 min, 42 °C (3).

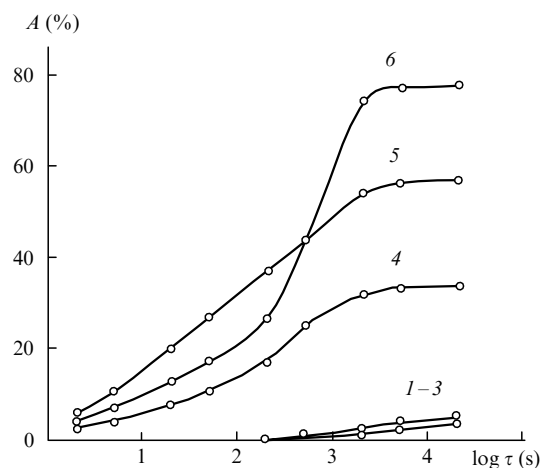


Figure 4. The temperature dependence of the yields of the covalent adducts (A) upon photomodification of a mixture of M13BMR4 ss-DNA restricts within the complexes **49** (1–3) and **50** (4–6) upon irradiation with visible light (400–480 nm)/°C: (1, 4) 4; (2, 5) 20; (3, 6) 37.

An excess of noncomplementary DNA fragments has practically no effect on γ_{eff} of sensitised modification (curve 6) in comparison with modification within the model complex **50**. The efficiency of direct photomodification of a mixture of restricts is noticeably decreased (curves 1–3) in comparison with γ_{eff} for the complex **49**, apparently due to the competition with partially complementary sequences of different fragments of M13 DNA. The efficiency and rate of direct photomodification weakly depend on temperature (curves 1–3). In the case of sensitised photomodification, its efficiency increases sharply with an increase in temperature from 4 to 37 °C (curves 4–6). In this case, the rate of the reaction increases first (curves 4, 5) and then decreases 2-fold as the melting temperature of the complex has been reached (curve 6).

Such a temperature dependence is due to the ability of the single-stranded fragment to form hairpins near the modification site; at low temperatures, the target sequence becomes inaccessible for oligonucleotide conjugates. The accessibility of the target sequence and the efficiency of sensitised photomodification increase with an increase in temperature, which causes the unwinding of the structured sites of ss-DNA.

At 37 °C, the initial rate of sensitised photomodification is four orders of magnitude higher (curve 6), and the degree of modification is 60 times greater than in the case of a direct reaction (curve 1). At the same temperature, the level of nonspecific modification of fragments of M13 DNA containing no complementary insert is ~ 1.5 times lower for the photosensitised reaction than for the direct one.⁹² It was found that the selectivity of sensitised photomodification determined as a ratio, γ_{eff} , of specific to nonspecific modification is 90 times greater than that of the direct reaction.^{91,92}

Modifications predominantly affect the G residues, the PZ value being dependent on their number in the $(\text{pG})_n$ -sequence of DNA-targets at the modification site. The yields of covalent adducts of direct modification at $n = 1, 2$ and 4 are 33%–41%, 68%–72% and 82%–85%, respectively, whereas those of photosensitised modification products are 62%–68%,^{89,98} 75%–82%^{94,98} and 98%–99%,⁹⁸ respectively.

The photomodification of a DNA-target (5'-*pATGGATT-CTTGAAGGGGACCGCATT) with a binary system of conjugates complementary to the underlined regions and containing anthracene **45** and azide **48** residues has been carried out. The results of treatment of the reaction products with piperidine show that photomodification predominantly affected the residues G15 and G16 and, to a lesser degree, the residues G14 and G17.⁹⁸ This finding made it possible to establish the structure of the binary

system of oligonucleotide conjugates with the DNA-target (data from two-dimensional ^1H NMR).¹⁰⁰ The probabilities of the contacts of perfluoroaryl azide residues with bases G14–G17 of the DNA-target were as follows: G14:G15:G16:G17 = 12:40:40:8.⁹⁸

b. Photoinduced electron transfer

In the foregoing section, it was demonstrated that the use of binary systems of oligonucleotide conjugates increases the initial rate of photosensitised photomodification of ss-DNA (100–10 000-fold in comparison with the rate of direct photomodification) and the efficiency of the specific reaction (by nearly two orders of magnitude). However, sensitisation due to singlet–singlet energy transfer does not fully prevent nonspecific modification, as is the case with long-chain (≥ 7500 bases) sequences. The occurrence of nonspecific reactions is due to the following. A conjugate containing a photoreagent binds to those complementary sequences of a DNA-target which have no adjacent sequences complementary to the conjugate containing a sensitizer.⁹⁰

In order to prevent nonspecific modification in the formation of imperfect complexes, each of the groups in the photoreactive centre should be inactive under irradiation conditions.

With this in mind, Dobrikov *et al.*^{97,99} developed a binary system of oligonucleotide derivatives of the sensitizer **46** and the photoreagent **48** complementary to the neighbouring regions of a DNA-target within the complex **50**; this system can be activated with visible light (440–580 nm).

The excitation energy ($E_{0,0}$) of the perylene derivative **46**, which was chosen as a sensitizer, is less (64 kcal mol^{-1})¹⁰⁴ than the energy of the 0,0-transition in aromatic azides, but perylene is capable of sensitising their photodecomposition due to photoinduced electron transfer from the azido group to the photoexcited sensitizer.¹⁰⁴

Figure 5 shows the results of direct photomodification of a DNA-target within the complex **49** upon irradiation with visible light (420–580 nm) (curve 1) and photomodification within the complex **50** sensitised with oligonucleotide derivatives of benzoanthracene **44** (curve 2) and perylene **46** (curve 3). The initial rate of perylene-sensitised photomodification is nearly 300 000 times higher and that of benzoanthracene-sensitised reactions is nearly 10 times higher in comparison to direct photomodification. Irradiation of the complex **49** with UV light (365–390 nm) results

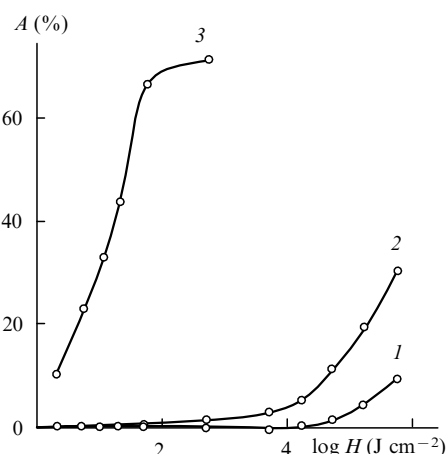
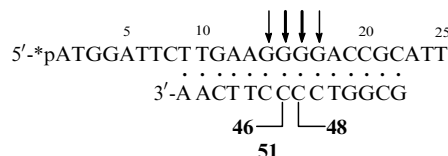


Figure 5. The dependence of the yields of the covalent adducts of DNA photomodification in the complexes **49** (1) and **50** (2, 3) upon irradiation with visible light on exposure (H). The concentration of the DNA target is $1 \mu\text{mol litre}^{-1}$, that of oligonucleotide conjugates is $50 \mu\text{mol litre}^{-1}$. The irradiation was performed at the wavelengths/nm: 420–580 (1), 450–580 (2, 3). The oligonucleotide conjugate containing a benzoanthracene **44** (2) or perylene **46** (3) residue was used as a sensitizer.

in adducts (yield $\sim 30\%$) which are cleaved by piperidine at the guanosine residue G14 of the DNA-target (marked by an arrow). The visible light-induced photomodification within the complex **50** with a conjugate of perylene **46** gives covalent adducts (yield $\sim 70\%$) cleaved at the same guanosine residue, which is most likely due to electron transfer from the lone electron pair of the nitrogen atom in the azido group of the photoreagent to the photoexcited perylene.^{97,104} The perylene residue generates a radical anion which is rapidly oxidised by atmospheric oxygen to the corresponding 1,12-perylenequinone.⁹⁷ This is accompanied by a simultaneous formation of a radical cation from perfluoroaryl azide, which after a series of dark conversions induces DNA photomodification similar to that triggered by the singlet nitrene.



Sensitised photomodification (450–580 nm, 15 min) of a DNA sequence from the promoter region of the multiple drug resistance gene (MDR-1) containing four G residues in the region of the photoreactive centre with a binary system of oligonucleotide conjugates (complex **51**) occurs with nearly quantitative yield.^{101,102} Treatment of the reaction products with piperidine revealed that modification affected predominantly residues G15 and G16 and, to a lesser degree, residues G14 and G17. Photomodification did not take place in the absence of the sensitizer.

Thus, binary systems of oligonucleotide reagents containing perylene **46** and perfluoroaryl azide **48** residues can be used for quantitative photomodification of a DNA-target upon irradiation with visible light in the blue-green region of the spectrum (450–580 nm) where both components of the system are singly practically inactive.

IV. Two-quantum photosensitised modification of DNA

The $\cdot\text{OH}$ radical and singlet $^1\text{O}_2$ are the main reagents for nucleic acid photooxidation and possess high toxicity. It was therefore proposed to use photoreagents, which do not form active diffusing species. The chemical activity of photoreagents can be triggered by two-quantum excitation of higher electronic states.^{106,107} The progress in picosecond laser technologies has made it possible to conduct multiquantum reactions. Two-quantum excitation can be mediated by two different mechanisms, *viz.*, resonant two-quantum excitation and nonresonant two-photon excitation.

The former consists in a consecutive absorption of two photons *via* a real intermediate state of the absorbing species. This is populated in the absorption of the first quantum and is a starting point for the absorption of the second quantum. The real excited state has a definite lifetime (normally, 10^{-4} – 10^{-9} s). Photochemical modification of DNA can be performed both from higher singlet and triplet excited states.^{15,106,108}

The second mechanism, *viz.*, nonresonant two-quantum excitation, does not involve any real intermediate state. In this case, the second photon will be absorbed simultaneously with the first one, *i.e.*, within $\sim 10^{-15}$ s. Two-quantum (especially, nonresonant) excitation requires high light intensities ($I \geq 3 \times 10^{14} \text{ W m}^{-2}$).¹⁰⁸

Summation of light quantum energy needed for a photochemical reaction to take place is an important feature of two-quantum excitation mechanisms. Yet another peculiarity of two-quantum reactions is their correspondence to spectroscopic selection rules. If a photosensitizer molecule has a centre of symmetry, the absorption of each light quantum changes the parity of the wave function. Hence, two-quantum excitation can generate reactive states which are forbidden in single-quantum excitation.^{108,109}

1. Two-quantum nonresonant excitation

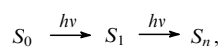
Two-quantum excitation is a promising field for practical application of known photoreagents, since it allows one to trigger photochemical reactions by irradiation with red and infrared light instead of ultraviolet and violet light. IR irradiation (750–1000 nm) can penetrate deeply into tissues, is not absorbed by cell components and does not induce cell injuries. The specificity of its action can thus be significantly increased.¹⁰⁸

Psoralens belong to the most promising candidates for photoreagents, but their spectral photosensitivity was limited by the range of 320–436 nm.^{108,110} Considerable progress was achieved in the past few years in overcoming this obstacle. Thus irradiation of 8-methoxy-, 4'-amino-4,5,8-trimethyl-¹⁰⁹ and 4'-hydroxymethyl-4,5',8-trimethylpsoralens¹¹¹ with a titanium-sapphire laser (730 nm) was accompanied by nonresonant two-quantum excitation and anti-Stokes fluorescence at 452 nm the intensity of which showed a quadratic dependence on the peak power of the laser.¹⁰⁸ The same photochemical reactions were triggered as in the case of single-quantum activation of psoralens with UV light (365 nm).

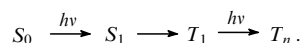
Photobiological properties of psoralen in two-quantum excitation were studied *in vivo* in inactivation of *Salmonella typhimurium* His-operon. Short-pulse ($\tau \sim 0.2$ ns), high-flux laser irradiation ($I = 3 \times 10^{14}$ W m⁻²) in the absence of psoralen was characterised by low mutagenicity; in the presence of psoralen, laser irradiation (730 nm) fully suppressed the expression of the His-operon due to the formation of covalent psoralen bisadducts with ds-DNA.¹⁰⁸

2. Two-quantum resonant excitation

Two-quantum resonant excitation consists in sequential absorption of two quanta of light, resulting in both higher excited singlet states (S_n):



and higher excited triplet states (T_n):



a. Two-quantum resonant singlet–singlet excitation

Photoexcitation generates primarily singlet states, S_n , characterised by higher energy but several orders of magnitude shorter lifetimes than the corresponding triplet states. Thus the lifetime of state S_n is less than 10^{-11} s, while that of state S_1 is usually 10^{-8} s. The appropriate conditions for bimolecular reactions from states S_n are attained in the case where the sensitiser forms a donor–acceptor complex with the molecule-target in the ground state or an exciplex in an excited state.¹¹¹

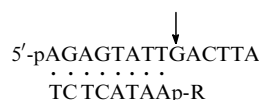
For realisation of this mechanism, the photoreagents should have a low yield of intersystem crossing (ISC) into the triplet state and the corresponding $S_1 \rightarrow S_n$ conversions. Some polymethine dyes ($\phi_{ISC} \leq 0.03$), tetraazaporphyrins ($\phi_{ISC} \leq 0.15$), Mg²⁺- and Zn²⁺-phthalocyanines (MPC²⁺, M = Mg, Zn) ($\phi_{ISC} \leq 0.06$), etc., meet these requirements.^{106,112}

Nonlinear absorption of MgPC²⁺ ($\epsilon_{681} = 2.2 \times 10^5$, $\phi_{\text{fl}} = 0.6$, $\tau_{\text{fl}} = 5$ ns) was observed in pulse ($\tau = 1.6$ ns) laser excitation (680 nm) with a pulse density of $> 10^{24}$ Einstein cm⁻² s⁻¹. The yield of two-quantum excited molecules reached $\sim 100\%$ at the pulse density of 10^{27} Einstein cm⁻² s⁻¹. The absorption spectrum of *MgPC²⁺ from state S_1 has a long-wave maximum at $\lambda = 710$ nm. Simultaneous irradiation of MgPC²⁺ with light of two different wavelengths ($\lambda = 680$ and 710 nm) results in efficient population of state S_n ($\tau \sim 15$ ps), which is insufficient for the normal course of bimolecular reactions but sufficient for a photoinduced electron transfer which is completed within 0.3 ps.¹⁰⁶

Laser-induced two-quantum photomodification of DNA sensitised by different intercalating dyes among which ethidium

bromide proved to be the most efficient one has been studied.^{113–115}

Site-specific two-quantum photomodification of ss- and ds-DNA with oligonucleotide conjugates of ethidium derivatives **20** and **21** has been carried out. Irradiation with a nitrogen laser (337 nm, $I = 150$ W m⁻²) results in stepwise two-quantum excitation of the chromophore intercalated into DNA with subsequent modification of the target. The energy of two quanta was sufficient for initiating different photomodification reactions including the cleavage of phosphodiester bonds.^{113,114} The focussed laser irradiation of the duplex



resulted in a spontaneous cleavage of the DNA-target at the residue G9 (yield $\sim 10\%$) and the formation of covalent adducts (yields 20%–40%).

The efficiency of spontaneous cleavage of the DNA-target showed a quadratic dependence on the irradiation power density. After piperidine-induced cleavage, the total degree of modification of the DNA-target increased due to cryptic modification and reached 90%. Unfocussed laser irradiation (2 W m⁻²) of the duplex gave exclusively covalent adducts (yield 40%).¹¹⁵

The mechanism of two-quantum cleavage is not finally elucidated yet. However, it was shown that an addition of chemical traps of radicals and ¹O₂ did not decrease substantially the efficiency of spontaneous cleavage. The majority of breaks are at a distance of not more than one base from the ethidium residue. Consequently, the migration radius of two-quantum excitation along the DNA chain does not exceed 4–5 Å.^{113,114}

The attachment of ethidium **20** to the heptanucleotide 5'-ACAAACCP caused an increase in the melting temperature of the duplex with the complementary octanucleotide 5'-pTGTTTGGC from 23 to 50 °C. Irradiation of the duplex with a nitrogen laser (337 nm, $\tau = 8$ ns, $I = 1200$ W m⁻², 4 h) up to complete photodegradation of the ethidium residue in the case of the 5'-ACAAACCP-**20** conjugate gives rise to covalent adducts (yield 40%). Their treatment with piperidine induced the cleavage at the residues G6 and G7 and increased the degree of injury of the target to 65% due to cryptic modification.⁵⁰ Irradiation of the octanucleotide 5'-pTGTTTGGC duplex with the 5'-ACAAACCP-**21** conjugate yields 55% of covalent adducts and 5% of direct cleavage products. Treatment with piperidine induces cleavage at the same residues (G6 and G7) (total yield 70%).

Irradiation of a ds-DNA triplex with the 5'-(TC)₆T derivative of ethidium **20** results in a direct cleavage (yield 10%) of the polypurine chain at residues G(–1), A(0), A(1) and G(2) relative to the position of ethidium within the triplex. This was not accompanied by any noticeable photomodification of the polypuridine chain.⁵⁰

The type of injuries and noticeable specificity of photomodification with respect to the electron-donor purine bases is consistent with the following mechanism. In the case of nano-second duration of the laser pulse, the triplet state cannot be formed and a two-quantum excitation passes into state S_n and is accompanied by ionisation and formation of an ethidium radical cation and a free electron. The former causes the electron abstraction from the purine bases of DNA or hydrogen atoms from deoxyribose. The quantum yield of ethidium bromide-sensitised photodegradation of DNA is very low ($\phi = 5 \times 10^{-8}$) due to a reverse electron transfer; however, in the presence of the chemical trap of electrons, *viz.*, methyl viologen, it increases by an order of magnitude.¹¹⁶

b. Two-quantum resonant triplet–triplet excitation

Binary systems of oligonucleotide reagents open up broad opportunities for the application of different mechanisms of two-quantum sensitisation in site-specific photomodification of

directionality of photomodification in the two-quantum sensitisation can be more useful in the study of biological complexes than with one-quantum sensitisation.

The use of nonresonant two-quantum excitation makes it possible to initiate photochemical reactions by irradiation with red and IR light but will hardly increase the specificity of photomodification. At such high peak intensities, all cell components which absorb in the UV region at a double frequency will be excited in a two-quantum mode. In this respect, two-quantum resonant excitation at two different wavelengths seems to be a more promising approach. In this case, only compounds the absorption of which is close to that of photosensitisers in both ground and excited states will be excited together with them, but the probability of this reaction is rather low.

The results described in the review suggest that a combination of binary systems of oligonucleotide conjugates with two-quantum excitation methods is the most helpful tool for selective photomodification of nucleic acids *in vivo*.

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Micellar liquid chromatography

E M Basova, V M Ivanov, O A Shpigun

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Abstract. Background and possibilities of practical applications of micellar liquid chromatography (MLC) are considered. Various retention models in MLC, the effects of the nature and concentration of surfactants and organic modifiers, pH, temperature and ionic strength on the MLC efficiency and selectivity are discussed. The advantages and limitations of MLC are demonstrated. The performance of MLC is critically evaluated in relationship to the reversed-phase HPLC and ion-pair chromatography. The potential of application of MLC for the analysis of pharmaceuticals including that in biological fluids and separation of inorganic anions, transition metal cations, metal chelates and heteropoly compounds is described. The bibliography includes 146 references.

I. Introduction

Studies of secondary chemical equilibria (acid–base, complexation, formation of ion pairs and solubilisation) in reversed-phase high-performance liquid chromatography (RP HPLC) have been gaining momentum in recent years since their consideration leads to a higher selectivity of separation. The application of surfactant solutions at concentrations above the critical micellar concentration (CMC) as mobile phases in RP HPLC has given birth to micellar liquid chromatography (MLC), which is an alternative to the classical RP HPLC with aqueous-organic eluents.^{1–4}

Micellar liquid chromatography offers a number of advantages compared to other chromatographic methods. First, owing to the dual nature of surfactants possessing both hydrophobic and hydrophilic properties, it is possible to carry out simultaneous separation of a mixture of ionic and non-ionic sorbates. Second, owing to the ability of micelles to increase solubility of uncharged sorbates in water, they can act as organic modifiers; it is noteworthy that micellar eluents are inexpensive and non-toxic. Third, it is possible to influence effectively the selectivity of MLC because

it depends on a large number of parameters: the nature of surfactants (*viz.*, their types and charges) and concentrations, additives of various organic modifiers, ionic strength (salt additives) and pH of the mobile phase and the nature of the stationary phase. Fourth, biological fluids can be injected directly into a chromatographic column without preliminary precipitation of proteins, because both anionic and non-ionic surfactants are capable of solubilising proteins. This simplifies preparation of samples and accelerates analysis of various medicinal preparations. Fifth, the sensitivity of determination is increased since the intensity of luminescence, low-temperature phosphorescence and absorption are enhanced for many substances in the presence of surfactants. Sixth, the use of micellar gradients makes it possible to carry out fast separations because there is no need for column conditioning upon replacement of the mobile phase as the concentration of the free surfactant in solution is virtually constant after equilibration of the column with the surfactant at concentrations above CMC. Seventh, many authors have demonstrated the existence of a correlation between the retention and partition coefficients in the octanol–water system and biological activity. In this context, MLC may be useful for estimating hydrophobicity of sorbates and predicting biological activity.

A substantial drawback of this method is lesser efficiency of separation compared to that in classical RP HPLC. Two ways have been proposed to overcome this drawback: to use the so-called hybrid eluents, *i.e.*, mobile phases with addition of small amounts of organic modifiers (usually, short-chain alcohols), or to raise the working temperature. The addition of alcohols to the micellar mobile phases leads not only to enhancement of the efficiency of separation, but also to changes in selectivity and to a faster analysis. Therefore, special attention has been paid in recent years to the MLC techniques using hybrid eluents.

Despite the fact that this method has been developing for only two decades (the first paper appeared in 1980⁵), several reviews^{2,6–9} devoted to the discussion of basic theoretical problems of MLC and to the most recent achievements⁷ have been published. However, in the Russian-language literature none of the numerous monographs or reviews devoted to HPLC make any mention of this method (except for Ref. 1 where only the notion of MLC is given).

The aim of this review is to fill this gap. The review generalises the retention models in MLC described in the relevant literature, discusses causes of low efficiency of separation and ways of its increase and the possibilities of modifying the selectivity of separation and gives examples of the use of MLC for the analysis

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and determination of inorganic, medicinal and biologically active compounds.

II. Retention models for micellar liquid chromatography

Micellar liquid chromatography is a variant of partition chromatography where the sorbate molecules are partitioned between three phases: stationary phase, micellar and non-micellar (aqueous) mobile phases. In MLC, three equilibria are taken into consideration: sorbate partition between the micelle and the aqueous phase characterised by the partition coefficient P_{MW} , sorbate partition between the micelle and the stationary phase with the partition coefficient P_{SM} and sorbate partition between the stationary phase and the mobile aqueous phase with the partition coefficient P_{SW} . Several equations have been proposed to relate the retention of sorbates in MLC to the concentration of micelles.^{10–12} Armstrong and Nome¹⁰ express this dependence as

$$\frac{V_s}{V_e - V_0} = \frac{V(P_{MW} - 1)}{P_{SW}} [M] + \frac{1}{P_{SW}}, \quad (1)$$

where V_s , V_e and V_0 are the volume of stationary phase, the volume of sorbate elution and the void volume of the column, respectively; V is the molar volume of the surfactant, $[M]$ is the concentration of the surfactant in form of micelles in solution, which is calculated as $[M] = c - c_{cr}$, where c is the total surfactant concentration in solution and c_{cr} is the critical micelle concentration. The dependence $V_s/(V_e - V_0)$ on $[M]$ should be linear, whereas the value of $V(P_{MW} - 1)$ is equal to the constant of sorbate association with the micelles⁹ and may be obtained experimentally from the slope of the straight line and the magnitude of the intercept of this line on the ordinate.

Arunyanart and Cline Love¹¹ have proposed the equation relating the basic chromatographic parameter — capacity factor (k') — to the concentration of surfactant micelles.

$$\frac{1}{k'} = \frac{K_2}{\phi[L_s]K_1} [M] + \frac{1}{\phi[L_s]K_1}, \quad (2)$$

where K_2 is the constant of sorbate association with the micelle, ϕ is the phase ratio, $[L_s]$ is the ligand concentration in the stationary phase, and K_1 is the binding (adsorption) constant of sorbate from the mobile aqueous phase to the stationary phase.

In this case, the dependence of $1/k'$ on $[M]$ should be linear, while the constants of sorbate–micelle association can also be easily derived from experimental data. Equations (1) and (2) are therefore equivalent.¹³

Proceeding from the general model of secondary equilibria in chromatography,^{14, 15} Foley¹² has deduced the equation

$$k' = \left(\frac{K_{SM}[M]}{1 + K_{SM}[M]} \right) k'_{SM} + \left(\frac{1}{1 + K_{SM}[M]} \right) k'_S, \quad (3)$$

where K_{SM} is the constant of sorbate–micelle association, k'_S and k'_{SM} are the capacity factors of the sorbate and the sorbate–micelle complex.

Transformation of Eqn (2) with consideration of the fact that the sorbate–micelle complex is not retained, since the micelle is a component of the mobile phase, gives the equations

$$k' = \left(\frac{1}{1 + K_{SM}[M]} \right) k'_S \quad (4)$$

or

$$\frac{1}{k'} = \frac{K_{SM}}{k'_S} [M] + \frac{1}{k'_S}. \quad (5)$$

Equation (5) is equivalent to Eqns (1) and (2).

It should be noted that the constant of sorbate–micelle association derived from any equation — (1), (2) or (5) — is called the constant of association per monomer. As the concentration of micelles is expressed by the equation

$$[M] = (c - c_{cr})/n, \quad (6)$$

where n is the aggregation number, the multiplication of the constant K_2/K_{SM} or $V(P_{MW} - 1)$ by n gives the constant of association per micelle.

In the studies of the retention mechanism of hydrophobic, poorly water-soluble alkylbenzenes in MLC with non-ionogenic surfactants polyoxyethylene [10]- or -[23]-lauryl ethers (Brij-22 or Brij-35, respectively), Borgerding¹⁶ has modernised Eqn (1) and proposed a model of limited solubility. Assuming that $P_{MW} - 1 \approx P_{MW}$ and denoting the coefficient of sorbate partition between the stationary and mobile phase as $P_{SM} = P_{SW}/P_{MW}$, the equation

$$\frac{1}{k'} = \frac{1}{\phi} \left(\frac{V[M]}{P_{SM}} \right) + \frac{1}{\phi P_{SW}}, \quad (7)$$

was obtained, which in the extreme case (insolubility in water) is transformed into the equation

$$k' = P_{SM} \left(\frac{\phi}{V[M]} \right). \quad (8)$$

Analysis of Eqns (1) and (2) shows that as the concentration of micelles in the mobile phase increases the retention decreases ($1/k'$ increases), *i.e.*, the eluting strength increases with the concentration of micelles.

Equations (1) and (2) were both used for the determination of the constants of sorbate association with different surfactants in purely micellar as well as in hybrid eluents.^{10, 11, 17–20} In both cases, straight lines with good correlation coefficients were obtained;¹⁸ the values of association constants calculated by the two methods are also in good agreement.

It was noted that in the presence of the cationic surfactant cetyltrimethylammonium bromide the constants of association of a number of benzene and naphthalene derivatives with micelles are larger than those in the presence of the anionic surfactant sodium dodecyl sulfate,¹⁸ which can be explained by the preferred electrostatic interactions between the positively charged head groups of cetyltrimethylammonium bromide micelles and delocalised electrons of the aromatic ring of sorbates. However, still higher values of the constant of sorbate–micelle association were obtained in the case of the non-ionogenic surfactant Brij-35, which is difficult to explain if one considers solely the hydrophobic interactions.

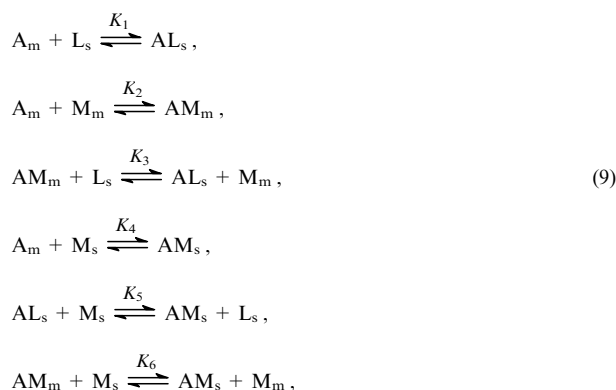
As it follows from the basic equilibria taken into consideration in the deduction of Eqns (1) and (2), the values of P_{MW} and K_2 depend only on the nature of the sorbate and the micellar system used and are independent of the nature of the stationary phase.¹⁷ It should be noted that the error in the determination of dissociation constants also depends on the nature of the sorbate and is increased with its higher hydrophobicity [the P_{SW} values are large and the $1/P_{SW}$ value in Eqn (1) is small].

The addition of organic modifiers to a micellar system leads to changes in its characteristics (CMC and the aggregation number),^{21, 22} which should in turn result in the modification of sorbate–micelle interactions and, consequently, in changes in the retention.^{21, 22} The sorbate–micelle interactions are as a rule decreased in a medium modified by alcohols.⁹ Indeed, the constants of sorbate–micelle association calculated for a number of benzene and naphthalene derivatives are larger for sodium dodecyl sulfate and cetyltrimethylammonium bromide in purely aqueous micellar solutions than in solutions containing 5 vol.% or 10 vol.% of *n*-butanol as the modifier, which is related, according to Garcia *et al.*,²⁰ to the competition between the sorbate and modifier molecules for the interaction with the

micelles. Addition of salts (e.g., NaCl) to the system enhances the interaction between the sorbate and the sodium dodecyl sulfate micelle; in this case, the values of association constants are even higher than those in the purely micellar mobile phases.²⁰

Thus, the ability of micelles for selective solubilisation of the sorbate or interaction with it is the basis of separation in MLC using grafted alkyl stationary phases. It is known that the molecules of monomeric surfactants are easily adsorbed on such stationary phases thereby modifying their properties and making a definite contribution to the retention and selectivity in MLC. However, the equilibrium adsorption of surfactants on the stationary phase was not taken into account in the deduction of Eqns (1), (2) and (5).

Hu *et al.*^{23, 24} have given an explanation of the mechanism of chiral recognition in the separation of enantiomers of 2,2'-dihydroxy-1,1'-dinaphthyl- and -1,1'-dinaphthyl-2,2'-diyl hydrophosphates by MLC with the use of different salts of bile acids (e.g., sodium cholate) in the mobile phases. A three-phase system proved to be ineffective for this purpose. A new model of the heterogeneous stationary phase has been proposed: the ODS (octadecyl sulfate) stationary phase adsorbs micelles, and it is into these micelles that the analytes are distributed. Based on the existence of the following equilibria in the system



where A, M and L are the sorbate, the micelle and the solvated stationary phase, respectively, whereas the subscripts 'm' and 's' refer to the mobile and stationary phases, respectively, the following equation was deduced

$$\frac{1}{k'} = \frac{V_m}{K_3 K_4 V^L [L_s] + K_4 V_s^M [M_s]} + \frac{V_m^M [M_m]}{K_3 V^L [L_s] + V_s^M [M_s]}, \quad (10)$$

where V^L , V_s^M , V_m and V_m^M are the volumes of solvated stationary phase, micelles adsorbed on the stationary phase, micelles of solvent and micelles in the mobile phase, respectively; $[M] = c - c_{cr}$.

The retention mechanism depends on the concentration of a co-solvent (acetonitrile) in the mobile phase: at low concentrations of acetonitrile, its partition between the micelles in the mobile and stationary phases is dominant. At higher acetonitrile concentrations, the mechanism of chiral recognition is determined by the partition between the bulk of mobile phase solution and the micelles adsorbed on the stationary phase. However, consideration of the equilibrium of micelle adsorption on the stationary phase did not result in the modification of the general relationship between the retention and the concentration of micellised surfactant: as in the case of Eqns (1) and (2), the dependence of $1/k'$ on $[M]$ is linear.

In the deduction of equations, neutral organic compounds, mainly aromatic hydrocarbons, were used as model sorbates. The distribution of a sorbate in a micelle is determined by the nature of the micelle and the balance of hydrophilic and hydrophobic properties of the sorbate. The micelle has a lamellar structure. In

aqueous solution, it consists of a hydrocarbon nucleus, a water-hydrocarbon layer the thickness of which is usually 2 or 3 CH_2 groups and corresponds to the depth of penetration of water molecules inside the hydrocarbon part of the micelle or, conversely, of the hydrocarbon chains inside the aqueous phase (here, the hydrophilic-hydrophobic balance is established), a layer of hydrated polar groups and a heterogeneous layer of solution (the diffusive part of the double electrical layer in the case of ionic micelles) adjoining the micelle.²² Since the micelle is regarded as the macroscopically homogeneous medium, it cannot be indicated unequivocally where the sorbate is localised. As the existence of a correlation between the capacity factors and partition coefficients in the octanol-water system^{8, 9} has been demonstrated for many neutral organic compounds, it is believed that the basic interactions are hydrophobic; in this case, the sorbate is either in the hydrophobic hydrocarbon nucleus or in the layer nearest to it. In the course of partition of charged organic sorbates, in addition to hydrophobic interactions, electrostatic interactions should also be observed, including those with the stationary phase surface modified due to the adsorption of monomeric surfactants.

The retention of monoprotic,²⁵⁻²⁸ diprotic and zwitterionic (amino acids and peptides)²⁶⁻²⁸ compounds in MLC have been systematically studied. The retention of monoprotic compounds is described²⁶ by the equation

$$k' = \frac{\phi L_s (K_s^{\text{HA}} + K_s^{\text{A}} - K_a / [\text{H}^+])}{1 + K_m^{\text{HA}} [\text{M}] + (1 + K_m^{\text{A}} - [\text{M}] K_a / [\text{H}^+])}, \quad (11)$$

where K_s^{HA} , K_s^{A} , K_m^{HA} and K_m^{A} are the binding constants of a weak acid HA and the conjugate base A with the stationary phase ligands L_s and the micelle M, K_a is the constant of HA dissociation in aqueous solution, $[\text{M}]$ is the concentration of micelles calculated as the stoichiometric concentration of surfactant minus CMC. Equation (11) allows prediction of the retention at any concentration of micelles and protons.

For the diprotic sorbates in the mobile phase, the following equilibrium is established:

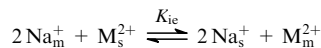


Each particle interacts with a micelle with the equilibrium constants K_{mc} , K_{mz} and K_{ma} , respectively, and with the stationary phase with the equilibrium constants K_{sc} , K_{sz} and K_{sa} , respectively. The following equation was proposed for calculating the capacity factor

$$\begin{aligned} k' = & \left[\frac{k'_c (1 + K_{mc} [\text{M}]) + k'_z (1 + K_{mz} [\text{M}]) K_{a1}}{[\text{H}^+]} + \frac{k'_a (1 + K_{ma} [\text{M}]) K_{a1} K_{a2}}{[\text{H}^+]^2} \right] / \\ & \left[\frac{1 + K_{mc} [\text{M}] + (1 + K_{mz} [\text{M}]) K_{a1}}{[\text{H}^+]} + \frac{(1 + K_{ma} [\text{M}]) K_{a1} K_{a2}}{[\text{H}^+]^2} \right], \end{aligned} \quad (12)$$

where k'_c , k'_z and k'_a are the capacity factors of the ions HABH^+ , $^-\text{ABH}^+$ and ^-AB , respectively; K_{ma} is the apparent dissociation constant in a micellar solution. Equations (11) and (12) are useful for studying the dependence of selectivity on pH of the mobile phase. They were deduced assuming the occurrence of only hydrophobic interactions of various particles (charged, uncharged, zwitterionic) with the micelle and the mobile phase with the consideration of secondary acid-base equilibria in the mobile phase.²⁶ Sorbate-micelle interactions in micellar chromatography of zwitterions were studied by Zibas.²⁷ Carmelo²⁸ used the example of cephalosporin to study the retention mechanism in the micellar liquid chromatography of zwitterions.

Since the hydrophobicity of inorganic anions is usually low and the main interactions in such systems are electrostatic, an ion-exchange model²⁹ was proposed for explaining the mechanism of separation of transition metal cations in MLC. In this model, ionic micelles (and the stationary phase coated with sodium dodecyl sulfate) are regarded as ion exchangers; retention is determined by the concentrations of micelles and counter-ions. For the ion exchange equilibrium



(Na^+ ions are counter-ions in the sodium dodecyl sulfate micelle, whereas the subscripts 'm' and 's' refer to the phases of micelles and solution, respectively; K_{ie} is constant), the following equation was obtained

$$\log K_{MW}^{\text{app}} = \log ([\text{Na}_m^+]^2 K_{ie}) - 2 \log [\text{Na}_s^+], \quad (13)$$

where K_{MW}^{app} is the apparent coefficient of sorbate partition between the aqueous and micellar phases. The value of K_{MW} was calculated using Eqn (11) proposed earlier by Okada^{30,31} for the retention in the exclusion MLC and simplified assuming that the inner volume of the ODS stationary phase is negligibly small

$$\frac{1}{V_r - V_0} = \frac{(K_{MW} - 1)v c_m + 1}{K_{SW} V_s}, \quad (14)$$

where V_r , V_0 and V_s are the volume of sorbate retention (elution), the void volume of the column and the stationary phase volume, respectively; v is the partial molar volume of micelle; c_m is the concentration of micelles equal, as in all the cases discussed above, to the surfactant concentration minus CMC; K_{MW} and K_{SW} are the coefficients of sorbate partition from the aqueous phase into the micelle and the stationary phase, respectively. Equation (14) is analogous to Eqn (1).

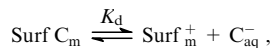
In order to minimise partition of sorbates into the stationary phase, it is recommended to supplement the eluent with salts and also with tartaric acid, which is a complexation agent.³² If the retention fits the ion-exchange model, the dependence of $\log K_{MW}^{\text{app}}$ on $\log [\text{Na}_s^+]$ should be linear, and this was confirmed for all metals, the slope of the straight line being equal to 2.

If complexation of metal ions with tartrate ions in the mobile phase (the complexes ML with the stability constant β_L and MHL^+ with the stability constant β_{HL}) is taken into consideration, Eqn (13) is transformed into (15) (K_2 is the constant of tartaric acid dissociation).

$$\begin{aligned} \frac{1}{K_{MW}^{\text{app}}} &= [\text{Na}_s^+]^2 \left(1 + \beta_{HL} [\text{HL}^-] + \frac{\beta_L [\text{L}^{2-}]}{K_{ie} [\text{Na}_m^+]^2} \right) = \\ &= [\text{Na}_s^+]^2 \left[\frac{1 + (\beta_{HL} [\text{H}^+]/K_2 + \beta_L) [\text{L}^{2-}]}{K_{ie} [\text{Na}_m^+]^2} \right] \end{aligned} \quad (15)$$

In this case too, a linear dependence of $\log K_{MW}^{\text{app}}$ on $\log [\text{Na}_s^+]$ was obtained for all metal ions, which implies that complexation does not influence the partition of sorbate into the micellar phase. This is understandable since in the presence of micelles the ionisation constants of weak acids (pK_a) increase,²¹ which leads to a lower concentration of the reactive ligand L^{2-} in the system. Thus for tartaric acid at pH 4.35, 50% of L^{2-} is present in the aqueous solution, whereas in the presence of sodium dodecyl sulfate its content is as low as 4%.²⁹

A mechanism based on the stoichiometric ion-exchange model for anions in the system with a cationic surfactant was proposed by Okada and Shimizu.³³ Based on the existence of equilibria of the analyte A and the counter-ion C



where the subscripts 'aq', 's' and 'm' refer to the aqueous solution, the stationary phase and the micellar phase, respectively; K_d is the equilibrium constant of the counter-ion transition from the micelle to the aqueous phase; K_{ies} and K_{iem} are the constants of ion-exchange equilibrium between the solution-resin and solution-micelle systems, the following equations were deduced

$$\frac{\phi}{k'} = \frac{[\text{C}_{\text{aq}}^-]}{K_{ies} [\text{C}_s^-]} \left(1 + \frac{K_{iem} c_m}{[\text{C}_{\text{aq}}^-] + K_d} \right), \quad (16)$$

$$\frac{n_s^c}{(V_r - V_0)[\text{C}_{\text{aq}}^-]} = \frac{1}{K_{ies}} \left(1 + \frac{K_{iem} c_m}{[\text{C}_{\text{aq}}^-]} \right), \quad (17)$$

where n_s^c is the number of counter-ion moles in the stationary phase, which is equal to the number of moles of hexadecyltrimethylammonium bromide adsorbed on the stationary phase; c_m is the concentration of micelles; V_r and V_0 are the volume of analyte retention and the void volume of the column, respectively. The concentration of the counter-ion in the aqueous phase $[\text{C}_{\text{aq}}^-]$ is determined as the sum of concentrations of the added counter-ion C^- (due to dissociation of micelles) and of the counter-ions of monomeric surfactants ($c - c_{\text{cr}}$). The retention of ions in ionic micellar chromatography can be described by the stoichiometric ion-exchange model, and it formally fits the pseudophase model where the concentration of the added counter-ion is sufficiently high; in this case, the concentration of the counter-ion formed upon dissociation of micelles may be neglected.

The model of micellar exclusion chromatography^{30,31} is based on Eqn (1) and takes into account that the micelles of cetyltrimethylammonium and dodecyltrimethylammonium chlorides³⁰ or sodium dodecyl sulfate can penetrate partly into the stationary phase (external solution). Micelles do not penetrate into the inner part of the stationary phase, but the latter contains surfactant monomers (internal solution) and ions are retained there owing to ionic interactions. In this case, the retention is described by the equation

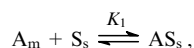
$$\frac{1}{V_r - V_e} = \frac{(K_{MW} - 1)V c_m + 1}{V_i + V_s K_{SW}}, \quad (18)$$

where V_r , V_e , V_i and V_s are the volumes of sorbate retention, external solution, inner solution and stationary phase, respectively; K_{MW} is the coefficient of sorbate partition (ratio of concentrations) between the micellar phase and the internal solution phase; K_{SW} is the coefficient of sorbate partition (ratio of concentrations) between the stationary phase and the internal solution phase; V is the molar volume of surfactant; c_m is the concentration of micelles in the eluent. The dependence of $1/(V_r - V_e)$ on c_m is linear for both anions (IO_3^- , I^- , Br^- , NO_3^- , NO_2^-)³⁰ and cations (Pb^{2+} , Zn^{2+} , Co^{2+}).³¹

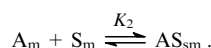
Thus, there are two basic models for describing MLC, viz., Eqns (1) and (2); they describe adequately the dependence of sorbate retention on the concentration of micellised surfactant and are based on three equilibria: sorbate partition between the micellar mobile phase and the aqueous mobile phase, between the micellar mobile phase and the stationary phase and between the stationary phase and the aqueous mobile phase. The major types of interactions are hydrophobic in the case of organic uncharged and charged sorbates and electrostatic for transition metal cations. The stationary phase is always modified due to the adsorption of monomeric surfactant molecules; this effect, however, was taken into account only qualitatively. In many cases, irreversible surfactant adsorption on various commercial silica gels with grafted C_{18} groups was observed.³⁴⁻³⁶ As shown in the example of cetyltrimethylammonium bromide, the amount of surfactant sorbed depends irreversibly on the sorbent character-

istics, the type of eluent and temperature.³⁶ In the case of sodium dodecyl sulfate, 6% of this compound initially adsorbed on the C₁₄ stationary phase is sorbed irreversibly.³⁵ On the whole, irreversible adsorption is more probable for monomeric stationary phases with a high density of grafted ligands and surfactants with a small polar head group (when both the surfactant and the grafted ligand have the alkyl chain length of more than 8 carbon atoms).³⁵ In the early stages of MLC studies it was believed that the surfactant adsorption is arrested after reaching CMC. In 1989, Borgerding *et al.*,³⁷ showed that more than 58% of the total amount of sodium dodecyl sulfate is adsorbed on Resolve C₁₈ when its concentration in the mobile phase varies in the range of 2 to 70 CMC. For Brij-22 and Brij-35, more than 50% of the total amount of adsorbed surfactant is sorbed on Resolve C₁₈ from solutions with the initial concentration > 50 CMC. Thus, the adsorption of both non-ionogenic surfactant and anionic surfactant continues after attaining CMC.

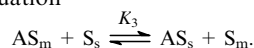
In their recent study, Hu and Haddad³⁸ tried to take into account the surfactant adsorption on the stationary phase surface. They also used a three-phase model. The stationary phase consisted of a surfactant adsorbed on an ODS sorbent. The sorbate localised in the extramolecular mobile phase A_m can bind to the surfactant on the stationary phase S_s in the form of an AS_s complex in conformity with the equation



and to the surfactant in the mobile phase S_m in the form of a complex AS_m in accordance with the equation



Direct transfer to the stationary phase of the sorbate bound to the surfactant in the mobile phase AS_m can also take place by the equation



The capacity factor can be expressed by the equation

$$k' = \frac{K_1 V_s^S [S_s]}{V_m + K_2 V_m^S [S_m]}, \quad (19)$$

where V_s^S , V_m and V_m^S are the volumes of surfactant adsorbed on the stationary phase bulk, of the solvent and of surfactant in the mobile phase, respectively.

It follows from Eqn (19) that

$$\frac{1}{k'} = \frac{V_0'}{K_1 W_s} + \frac{K_2 V_m^S [S_m]}{K_1 W_s}, \quad (20)$$

where $W_s = V_s^S [S_s]$ is the mass of surfactant adsorbed on the stationary phase; $V_m = V_m^S - V_0$. The dependence of $1/k'$ on $[S_m]$ (determined as the total surfactant concentration in the mobile phase) should be linear. The content of sodium dodecyl sulfate on the stationary phase was determined (16.5%) and found to be almost equal to the carbon:silicon ratio in the initial sorbent (17.1%). In other words, the octadecyl groups of the sorbent are covered to a large extent with the adsorbed surfactant, and the stationary phase may be regarded as the adsorbed surfactant. The dependence of $1/k'$ on $[S_s]$ is linear for the model sorbents studied, *viz.*, benzyltriethylammonium chloride and phenylalanine. It should be noted that Eqn (20) is analogous to Eqn (2), the only difference consisting in that Eqn (2) includes the surfactant concentration in the form of micelles in solution (minus CMC), while Eqn (20) contains the overall surfactant concentration in solution.

Consideration of some other equilibria (acid–base equilibria in the mobile phase or adsorption of micelles on the stationary phase) does not modify the dependence of retention on the concentration of micelles. Electrostatic interactions (ion

exchange between metal cations and the cations of the diffusive part of the double electrical layer) are taken into consideration in the MLC model in which retention is dependent on both the concentration of micelles and the concentration of counter-ions.

III. Efficiency of micellar liquid chromatography

One of the major drawbacks of the MLC method is its low efficiency compared to that of RP HPLC. There are several explanations of this phenomenon in the relevant literature. One of these³⁹ suggests that the main factor of the band blurring is the resistance to the sorbate mass transfer because of the poor wetting of the stationary phase. Yarmchuk *et al.*⁴⁰ presume that the resistance to the sorbate mass transfer exists due to both low rates of the sorbate efflux from the micelle and its slow desorption from the stationary phase. When constructing their model, these authors⁴⁰ took into account kinetics of sorbate adsorption onto, and desorption from, the stationary phase, on the one hand, and kinetics of the sorbate influx to, and efflux from, the micelle into the bulk of the non-micellar mobile phase, on the other. Having calculated the rates of all processes, they have shown⁴⁰ that the rate constants of the influx into the micelle are appreciably higher than the rate constant of the adsorption on the stationary phase (silica gel with the C₁-grafted radicals Supelcosil LC 1) because of the differences in the distance to be covered by the sorbate. Thus 0.10 M sodium dodecyl sulfate solution contains 9.03×10^{17} micelles cm⁻³. Consequently, in order to bring the sorbate from the bulk of solution to the surface of the stationary phase, it is necessary to encounter about 180 micelles, whereas an appreciably shorter distance must be covered for a repeated collision with the micelle. In order to pass from the micelle to the stationary phase, the sorbate should have a definite orientation relative to the stationary phase. No definite orientation is required for the reverse transition; the sorbate can enter the micelle at any point. The rate constants of these four processes depend on the nature of the sorbates.

Relatively small and well water-soluble molecules, having large rate constants of the influx into, and the efflux from, the micelle can move quickly in the bulk of solution, enter and leave micelles multiply before they reach the stationary phase surface. For such hydrophilic sorbates, the efficiency (mass transfer) is not limited by micellar equilibria. For the more hydrophobic sorbates the affinity to the micelle is higher and the rate constants of their efflux from the micelle are much lower (*e.g.*, for pyrene the efflux rate constant is 1000 times as low as that for benzene). Consequently, the hydrophobic sorbates remain in the micelle for an appreciably longer time, decreasing the mass transfer between the micelle and the stationary phase. Since there is an antiparallel correlation between the rate constants of the sorbate efflux from the micelle and the constants of desorption from the stationary phase, the hydrophilic sorbates can return more often to the bulk of aqueous mobile phase and be thereby close to equilibrium. The consequence of the differences in the rates of these processes for the hydrophilic and hydrophobic sorbates is fairly good efficiency for the former and smeared peaks for the latter.

In order to increase the efficiency and to improve the shape of peaks, it was proposed to add small amounts of organic modifiers to the mobile phase and to operate at higher temperatures.⁴⁰ Yarmchuk *et al.*⁴⁰ explain enhanced efficiency in the presence of 2 vol.%–5 vol.% of alcohols by the better mass transfer in the mobile phase owing to the increase in the rate of sorbate efflux from the micelle since the non-micellar part of the mobile phase becomes less polar. These authors relate the higher efficiency after an increase in temperature [for small sorbates of the benzene and phenol type the number of theoretical plates (*N*) is increased by 50%–100% at 50–60 °C] to both upgraded micellar kinetics and lower viscosity of the mobile phase. Addition of 3% of propanol to the mobile phase and an increase in temperature to 40 °C make it possible to attain efficiencies close to that of RP HPLC with aqueous–organic eluents.^{39,41} Enhanced efficiency is promoted

by the decrease in the surfactant concentration.⁴⁰ Indeed, Borgerding *et al.*⁴² have shown that the use of elevated surfactant concentrations can result in the total loss of efficiency. Another factor influencing the height equivalent to a theoretical plate (HETP) is the linear rate.⁴⁰ For small molecules (benzene), the derived dependence was almost analogous to that of usual RP HPLC, whereas for large molecules (naphthalene, anthracene) the efficiency drop with the increasing rate was appreciably larger. Yarmchuk *et al.*⁴⁰ recommend to operate at low flow rates.

The low efficiency of MLC is related^{36, 43–45} to the surfactant adsorption on the stationary phase surface, which results in poor mass transfer in the stationary phase.^{43, 44} Direct relationship between the amount of surfactant in the stationary phase and the decrease in efficiency was observed.⁴³

Based on the determination of diffusion coefficients for a series of sorbates (2-naphthol, *p*-nitroaniline, *p*-nitrophenol, naphthalenedisulfonic and naphthalenetrisulfonic acids) in the absence and the presence of sodium dodecyl sulfate and methanesulfonate in the mobile phase, Borgerding and Hinze⁴³ attempted to elucidate which of the mass transfer processes (in the mobile or the stationary phase) is causative of poor efficiency in MLC. All sorbates may be divided into two groups: the sorbates which interact actively with the micelles (2-naphthol, *p*-nitroaniline and *p*-nitrophenol) and those which do not interact and are repelled or excluded from the micelles (sodium 2,6-naphthalenedisulfonate, sodium 4,5-dihydroxynaphthalenedisulfonate and sodium 1,3,6-naphthalenetrisulfonate). The sorbates of the first group have noticeably lesser diffusion coefficients in the micellar mobile phases. Thus the diffusion coefficients of 2-naphthol and sodium 1,6-naphthalenedisulfonate are 6.0×10^{-6} and $6.71 \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$ in water, 5.67×10^{-6} and $4.73 \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$ in 0.1 M MeSO_3Na solution, and 0.90×10^{-6} and $4.0 \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$ in 0.1 M sodium dodecyl sulfate solution. If the band blurring determined the slow mass transfer in the micellar phase, one would observe different values of efficiency for the two groups of sorbates. Besides, no appreciable variation of *N* was noticed at different surfactant concentrations in the mobile phase. All this indicates that the most probable factor eliciting the deterioration of the efficiency is the resistance to mass transfer in the stationary phase. The MLC efficiency is strongly dependent on the flow rate. For example, in the case of *p*-nitroaniline the value of *N* for a $300 \times 4 \text{ mm}$ column with the cyanopropyl stationary phase increases from 400 to 1300 upon the decrease in the mobile phase flow rate from 1.5 to 0.25 ml min^{-1} . However, this cannot be regarded as the proof in favour of only a decelerated process of mass transfer in the mobile phase because, according to the van Deemter equation, both members contributing to HETP owing to the resistance to the mass transfer in the mobile and the stationary phases are proportional to the linear flow rate.

Borgerding *et al.*⁴² believe that the enhancement of efficiency in MLC with the micelles of ionic surfactants occurs owing to changes in the mobile phase: the repulsion barrier decreases because of the lower density of the electrical charge on the surface of ionic micelles. Indeed, the addition of alkanes has no effect on the surface density of charge and does not lead to higher efficiency for strongly hydrophobic sorbates. Addition of alcohols does not result in higher efficiency of MLC with non-ionogenic surfactants, *e.g.*, Brij-35.

In order to decrease the resistance to the mass transfer and to improve the MLC efficiency, Berthod and Roussel⁴⁶ proposed to use hybrid mobile phases. The addition of short- and medium-chain alcohols induces desorption of surfactants from the stationary phase, which leads to the improvement of mass transfer into the stationary phase (and from the stationary phase) and also ensures better wetting.^{37, 39, 41, 42} This effect is enhanced with increase in the modifier concentration and hydrophobicity.^{19, 37, 47} A study⁴¹ carried out on a broad set of sorbates showed that the higher efficiency of the column is observed not for all sorbates; nonetheless, it was concluded that the cause of

higher efficiency is the decrease in the amount of surfactant sorbed on the stationary phase.

Another mechanism of the effect of alcohols on the efficiency was proposed by Armstrong *et al.*⁴⁴ In their opinion, the use of hybrid eluents makes possible changes in the structure of the stationary phase itself from the block-like to the brush-like one, which can also improve the mass transfer into the stationary phase (and from the stationary phase). It is noted therewith that the use of hybrid eluents increases appreciably the efficiency in the case of hydrophobic rather than hydrophilic sorbates.^{35, 43–45}

As there is no consensus about the cause of poor efficiency in MLC, investigators come continuously back to this problem.^{35, 45, 48} Thus investigation of the effect of the nature of the organic modifier (ethyl acetate, *n*-propanol) on the efficiency of a column packed with different sorbents with the grafted C_{18} , C_8 , C_{18} or cyanopropyl groups in the elution by mobile phases with the surfactant concentrations above or below CMC made it possible to reveal a correlation between the column efficiency and the extent of wetting of the surface of grafted sorbents with an organic solvent.

Bailey and Cassidy⁴⁵ studied the effect of sodium dodecyl sulfate concentration (0–0.35 M) at the ionic strength of 0–0.3 M (NaClO_4) and of *n*-propanol (0–0.8 M) on the column efficiency. In the absence of micelles in the mobile phase, the efficiency of the column varies insignificantly. This suggests that the decrease in the amount of sodium dodecyl sulfate adsorbed on the stationary phase is not the cause of the efficiency increase in the presence of alcohols, contrary to what was thought by some investigators.^{35, 39, 41, 42} In the absence of micelles, at low alcohol concentrations (not exceeding 0.13 M), the column efficiency for benzaldehyde and acetophenone reaches its maximum, and this may be attributed to modification of the structure of the stationary phase surface. However, at high alcohol concentrations, which are commonly used for achieving better efficiency in MLC, the column efficiency remains approximately constant, which may be indicative of the absence of modification of the stationary phase surface in the presence of *n*-propanol. Studies of the factors that influence the mass transfer in the mobile phase in the range of sodium dodecyl concentrations from CMC to 0.3 M showed that at concentrations of 0.005–0.012 M this dependence passes through a maximum, the position of which depends on the sorbate hydrophobicity. At higher concentrations the efficiency decreases, which is consistent with the data reported by Yarmchuk *et al.*⁴⁰ In the presence of *n*-propanol, the maximum is broader and less clearly pronounced, whereas the column efficiency increases from 200–2200 to 700–3700 theoretical plates. These results led the authors to conclude that mass transfer in the stationary phase is not the main cause of low efficiency in MLC; this is apparently related to the processes of micellisation. In a micellar system, two oppositely directed processes take place continuously: desintegration of micelles and their formation. At the same time, two basic processes occur in the micellar system: rapid exchange of the surfactant monomer with the micelle [the lifetime of the surfactant molecule in the micelle is of the order of 10^{-7} s (see Ref. 22)] and the process of formation and disintegration of micelles [the half-life of the micelle is $10^{-3} - 1 \text{ s}$ (see Ref. 22)]. The latter can in turn be split into two processes: (1) a series of stepwise additions of single molecules to the surfactant aggregates with formation of micelles and (2) association of pre-micellar aggregates with formation of micelles. Either of these processes can influence the sorbate mass transfer between the eluent and the stationary phase. The addition of alcohols can influence these processes and enhance the kinetics of mass transfer in the mobile phase.

Villanueva Camanas *et al.*⁴⁹ studied the decrease in the efficiency due to the addition of alcohols to the mobile phase containing sodium dodecyl sulfate micelles in the elution of L-DOPA, 2-methyl-DOPA, norepinephrine, adrenalone, dopamine, isoproterenol on Spherisorb ODS-2 C_{18} . Analogous regularities were revealed earlier in the elution of amines.^{50, 51} It is presumed that the mass transfer is brought about through the

following mechanisms: (1) direct transfer from the micelles to the stationary phase, which is opposed by the electrical repulsion between them and (2) transfer through a continuous aqueous pseudophase. In the presence of alcohol, the polarity of the continuous aqueous pseudophase is decreased. On the one hand, this increases the rate of transfer of hydrophobic sorbates through this pseudophase, while on the other hand, the solubility and the rate of transfer of highly hydrophilic catecholamines is decreased, which accounts for the decrease in the efficiency.

Analysis of the band blurring in MLC was performed^{35,52} using the Knox equation

$$h = Av^{1/3} + B/v + C, \quad (21)$$

where $h = H/d_p$ is the reduced height equivalent to a theoretical plate, H is the height equivalent to a theoretical plate, d_p is the size of stationary phase particles, $v = ud_p/D_m$ is the reduced linear flow rate, u is the linear flow rate of the mobile phase, D_m is the coefficient of sorbate diffusion in the mobile phase, A is the coefficient which characterises the quality of the column packing and the decelerated mass exchange in the mobile phase outside the particles, B is the coefficient accounting for the contribution to the band blurring from the longitudinal diffusion and C is the coefficient describing the decelerated mass exchange in the stationary phase.

The dependences of h on v were determined³³ on one column using first an aqueous–organic mobile phase, then the micellar mobile phase and then again the same aqueous–organic phase. Two types of alkylated silica gels were used, *viz.*, a monomeric C_{18} sorbent and a C_{14} sorbent with high density of grafted alkyl groups ($3.5 \mu\text{mol m}^{-2}$), and two types of surfactants, *viz.*, sodium dodecyl sulfate (anionic surfactant) and Brij-35 (non-ionogenic surfactant). An increase in h was shown to occur mainly due to the higher values of coefficient A : for benzene with the aqueous methanol as a mobile phase, $h = 4.9$ at $v = 10$, whereas in the presence of sodium dodecyl sulfate at $v = 10.9$ the contribution from the coefficient A is 2.36 (48% methanol) and 6.9 (63% methanol), respectively. In micellar eluents, the contribution from the coefficients B and C also increases resulting in a stronger band blurring and lower efficiency. The decrease in the diffusion coefficient of sorbates upon their inclusion into the micelles induces the increase in B . The coefficient of sorbate diffusion in the stationary phase depends on the nature of the sorbate and decreases as the hydrophobicity increases; highly hydrophobic sorbates are transferred from the micelle directly into the stationary phase by-passing the extramolecular aqueous phase in which they are poorly soluble. The value of coefficient C increases in a micellar system (*e.g.*, up to 700% for propylbenzene). The decrease in the mass transfer coefficients may also be associated with poor wetting.^{2,39} The most important reason, however, is believed to be the surfactant adsorption on the stationary phase.^{16, 17, 43, 44, 50}

In the first place, adsorption of a surfactant on the stationary phase surface [a C_{18} sorbent adsorbs 70 mg g^{-1} of Brij-35, and a C_{14} sorbent adsorbs 140 mg g^{-1} (or $2.3 \mu\text{M m}^{-2}$) of sodium dodecyl sulfate] leads to a decrease in the pore volume, obstructs the smallest pores with diameter $< 7 \text{ nm}$ and reduces appreciably the surface area of the stationary phase and its permeability.³⁵ The consequence of this is the increase in the coefficient A values. Secondly, adsorption of a surfactant increases thickness of the organic layer of the stationary phase and decreases the mass transfer rate and the diffusion coefficients in the stationary phase and the coefficients of sorbate diffusion in the mobile phase.^{16, 42, 43, 46} This results in the increased values of the coefficients B and C . The surfactant adsorbed on the stationary phase can be eluted with a pure solvent; however, the adsorption may prove to be partially irreversible.^{32–34} Following operation with the use of micellar phases, the efficiency of a column drops drastically as is evident from the values of the coefficients A , B and C in the Knox equation for benzene. This is also the consequence

of changes in the porosity and permeability of the stationary phase.

Mobile phase	<i>A</i>	<i>B</i>	<i>C</i>
Methanol – water (30 : 70)	1.1	3.1	0.22
1.4% Sodium dodecyl sulfate in water	3.2	20	0.2
Methanol – water (30 : 70) after operation with sodium dodecyl sulfate	5.7	4	–0.7

Lavine and Hendayana⁵² studied the effect of temperature in the range of $25\text{--}45^\circ\text{C}$ on the dependence of h on v for acetophenone, nitrobenzene, benzene, methyl benzoate and toluene in MLC with an aqueous solution of sodium dodecyl sulfate. The values of the coefficients A , B and C for *p*-nitrophenol in 0.02 M sodium dodecyl sulfate solution were found to be 2.34 ± 0.14 , 7.43 ± 0.69 and 0.074 ± 0.013 at 25°C and 1.06 ± 0.13 , 11.4 ± 0.65 and 0.026 ± 0.010 at 45°C , respectively. The decrease in the coefficient B at 35°C (5.16 ± 0.66) is anomalous and inexplicable.⁵²

Noticeable enhancement of chromatographic efficiency with the increase in temperature occurs owing to the decrease in values of both the coefficients A (flow anisotropy) and C (mass transfer in the stationary phase). The decrease in A values with the increase in temperature may be explained by the decrease in the constant of sorbate partition between the micelle and the bulk of solution [K_2 , Eqn (2)] and, consequently, by the decrease in the proportion of sorbate bound to the sodium dodecyl sulfate micelles in the mobile phase. A decrease in the eddy diffusion is eventually attained. The decrease in the values of the coefficient C with the increase in temperature may be explained by the decrease in the adsorption of a surfactant on the stationary phase surface and the higher rate of sorbate mass transfer between the mobile and stationary phases. In addition, the fluidities of the grafted alkyl chains and the adsorbed surfactant are increased at higher temperature, which also decreases the resistance to the mass transfer in the stationary phase.

The values of the coefficient B increase considerably with temperature due to both the lower viscosity of bulk of the solvent and transition of part of the sorbate from the micelle to the solution.

In the example of separation of 12 polycyclic aromatic hydrocarbons on Nova-Pak C_{18} , the influence of the nature and the content of the alcohol and of the column temperature on the efficiency of separation in MLC with the use of sodium dodecyl sulfate was studied.⁵³ The number of theoretical plates increases with the increase in the surfactant concentration in the mobile phase up to 0.13 M. Upon transition from methanol to 2-propanol, the peak becomes more symmetrical, and one observes an increase in the efficiency for less hydrophobic sorbates (fluorene and chrysene). For more hydrophobic dibenzo[*ac*]anthracene, more symmetrical peaks were obtained with *n*-butanol, although in this case the changes in the efficiency were insignificant. It should be noted that in contrast to conventional HPLC, in MLC the number of theoretical plates is commonly calculated by the following formula⁵⁴

$$N = \frac{[41.7(t_R/w_{0.1})^2]}{(B/A + 1.25)}, \quad (22)$$

where t_R is the retention time, $w_{0.1}$ is the peak width at its 10% height, B/A is the factor of peak asymmetry.

An increase in temperature leads to insignificant enhancement of the efficiency and appreciable improvement of the shape of peaks. In this case, the effect of the flow rate on N at different temperatures depends on the sorbate hydrophobicity.

Studies of the effect of alcohols as modifiers of the mobile phase showed that the addition of small amounts of propanol or pentanol led to higher efficiency because of considerable decrease in the values of the coefficients A and C in Eqn (21).⁵² An increase in the coefficient B upon addition of an alcohol seems to occur due

to the lower viscosity of the mobile phase and a shift of sorbate equilibrium in the micelle–solvent volume system. Consequently, the mechanisms of the influence of the increase in temperature and addition of alcohols on the separation efficiency in MLC are similar in many respects.

Thus, Okada³² as well as Lavine and Hendayana⁵² related the deterioration of MLC efficiency to an appreciable increase in the coefficients A and C in the Knox equation. Flow anisotropy, resistance to mass transfer in the stationary phase and molecular diffusion contribute to the band blurring. To enhance the efficiency in MLC, it is recommended to use hybrid eluents.

IV. Selectivity of micellar liquid chromatography

The selectivity of separation in MLC is influenced by the type and concentration of the surfactant, the nature and concentration of the organic modifier, pH, ionic strength, temperature and the nature of the stationary phase. Of these factors, the effects of surfactant and modifier concentrations have been studied most extensively. In MLC, the eluting strength of purely micellar eluents is small, it increases with increase in the micelle concentration in the mobile phase.⁴⁷

1. Effect of surfactant concentration

Foley¹² deduced Eqn (23) for calculating the optimum concentration of micelles [rather than of the micellised surfactant as in Eqns (1) and (2)]

$$\text{pM}_{\text{opt}} \approx \log K_{\text{SM}} - \frac{1}{2} \log \frac{k'_s}{k'_1}, \quad (23)$$

where $\text{pM}_{\text{opt}} = -\log [M]$, K_{SM} is the constant of sorbate association with the micelle calculated per micelle rather than per monomer, k'_s is the factor of sorbate capacity (the extreme value), k'_1 is the sorbate capacity factor at a surfactant concentration of 1 mol litre⁻¹.

The optimum pM values for a broad spectrum of sorbates and three surfactants (sodium dodecyl sulfate, cetyltrimethylammonium bromide and Brij-35) were calculated using Eqn (23). The concentrations of surfactants calculated from Eqn (23) fall into a wide range and are the optima as regards selectivity rather than retention.

For dihydropyridines on a C₁₈ stationary phase, an increase in the surfactant concentration induces a trend towards changes in the retention mechanism from three partition equilibria to direct transfer from the micelles to the stationary phase.^{55,56}

Madamba-Tan *et al.*⁵⁷ used isocratic data to deduce the equation for predicting the retention times in the gradient regime of elution with a gradient of micelle concentration

$$t_R = (t_0/b)\{-1/k'_0 + [(1/k'_0)^2 + 2b(1-f)]^{1/2}\} + t_0 + t_D \quad (24)$$

where t_0 is the dead time of the column; b is the parameter of the gradient steepness; k'_0 is the capacity factor in the initial mobile phase; t_D is the delay time, *i.e.*, the time interval before the gradient does reach the upper part of the column; f is the part of the column through which the sorbate band has already passed and which is calculated from the equation

$$f = t'_D/t_R = \frac{[t_D(1 + 1/k'_0)]}{t_R}. \quad (25)$$

2. Effect of organic modifier concentration

The addition of an organic solvent to micellar eluents leads to simultaneous increase in the eluting strength and selectivity for some ionic and non-ionic sorbates.^{47,58,59} The increase in selectivity is related to the existence of competitive partition in MLC and to the unique capacity of micelles for solubilising separately molecules of sorbates and organic solvents.

Subsequent studies of the role of organic modifiers and micelles in the control of the eluting strength and selectivity in MLC in the example of small peptides, phenols, substituted benzenes and benzoic acids in a sodium dodecyl sulfate–water–

2-propanol system confirmed simultaneous increase in the eluting strength and selectivity;⁶⁰ in this case, the selectivity varies systematically and monotonically as the concentration of 2-propanol in the mobile phase increases. The concentration of micelles has the opposite effect on selectivity compared to that of 2-propanol. For those ion pairs the selectivity of which decreases as the concentration of 2-propanol increases, one observes enhancement of selectivity with the increase in concentration of micelles and *vice versa*. Thus, although the eluting strength of the mobile phase is increased with the increase in the concentration of micelles and organic solvent, the effects of these parameters may be quite different and even opposite. Micelles and 2-propanol compete for the interaction with sorbates, which influences the selectivity and retention.

The dependence of retention on the volume proportion (φ) of organic modifier is described by the equation⁴⁷

$$\ln k' = -S_{\text{hyb}}\varphi + \ln k'_0, \quad (26)$$

where S_{hyb} is the parameter of solvent strength, $\ln k'_0$ is the apparent (extrapolated) coefficient of sorbate capacity in a purely micellar mobile phase.

Equation (26) is analogous to Eqn (1) used for describing changes in the retention with the variation of the volume proportion of the organic modifier in RP HPLC. Combination of Eqns (26), (1) and (2) gives relations (27) and (28).

$$\ln(P_{\text{SW}}\Phi) = -S_s + \ln(P_{\text{SW}}^0\Phi), \quad (27)$$

$$\ln(K_{\text{MW}}[M] + 1) = -S_m + \ln(K_{\text{MW}}^0[M] + 1), \quad (28)$$

where S_s and S_m are the parameters which characterise the sensitivity to changes in the sorbate partition from the bulk of solution into the stationary phase and the micelles with variation of φ ; K_{MW}^0 is the constant of sorbate binding to a micelle, P_{SW}^0 is the coefficient of sorbate partition between the mobile and stationary phases for aqueous micellar eluents, *i.e.*, in the absence of an organic modifier.

The parameter S_{hyb} depends on S_s and S_m

$$S_{\text{hyb}} = S_s - S_m. \quad (29)$$

Several conclusions can be drawn from Eqns (27)–(29). First, the magnitude of the solvent strength parameter in hybrid eluents is smaller than that in aqueous-organic eluents. Second, S_m and, consequently, S_{hyb} depend on the micelle concentration. For two sorbates (a and b) and at two concentrations of organic solvent (φ_1 and φ_2) in the mobile phase, the following equation is valid

$$\ln \alpha_2 - \ln \alpha_1 = -(S_{\text{hyb}}^b - S_{\text{hyb}}^a)(\varphi_2 - \varphi_1), \quad (30)$$

while combination of Eqns (26), (29) and (30) gives Eqn (31).

$$\ln \alpha = (dS_m - dS_s)\varphi + \ln \alpha_0, \quad (31)$$

where $\alpha = k'_b/k'_a$ is the selectivity coefficient ($k'_b > k'_a$), α_0 is the selectivity coefficient in a purely aqueous micellar eluent, dS_m and dS_s are the differences in S_m and S_s for compounds a and b .

It follows from Eqn (31) that the selectivity ($\ln \alpha$) depends linearly on the volume proportion of the organic modifier in the mobile phase and decreases or increases monotonically depending on the dS_m/dS_s ratio for two sorbates. Thus for the majority of substituted benzenes, amino acids and peptides, the reverse dependence between retention and S_{hyb} is observed: the more strongly compounds are retained, the smaller is the S_{hyb} value. In this case, for most aromatic compounds, amino acids and proteins a direct dependence between retention and S_m and a reverse dependence between retention and S_s are observed. The influence of the sorbate structure on the value of S_{hyb} is reflected mainly on changes in S_s .

The influence of the concentrations of an organic solvent and micelles on different equilibria occurring in the system can clearly be seen if Eqn (1) or (2) is transformed into (32).

$$\alpha = \left(\frac{P_{SW}^b}{P_{SW}^a} \right) / \left(\frac{K_{MW}^a[M] + 1}{K_{MW}^b[M] + 1} \right) = \frac{\alpha_{SW}}{\alpha_{MW}}, \quad (32)$$

where α_{MW} is the parameter characterising the selectivity of binding of sorbates to the micelles, α_{SW} is the parameter characterising the selectivity of partition into the stationary phase.

The values of P_{SW} and K_{MW} decrease as the concentration of 2-propanol increases; however, the extent of decrease in these parameters is different for different sorbates, which leads to changes in selectivity. The concentration of micelles, in turn, influences the selectivity at a fixed concentration of an organic modifier mostly through the parameter α_{MW} : as the concentration of micelles increases the parameter α_{MW} decreases faster than the parameter α_{SW} , which is independent of $[M]$. The selectivity is increased because of this effect.

3. Effect of the nature of the organic modifier

The nature of the organic modifier of the mobile phase influences the selectivity of separation in MLC; however, this effect is not the same as that in RP HPLC. Usually lower alcohols from methanol to pentanol^{9, 35, 39, 41, 42, 47, 55, 57, 58, 60, 61–70} and also a pentanol–heptanol mixture (3 : 1)⁷¹ are used as modifiers in MLC. Diols,⁶¹ dipolar aprotic solvents,⁶¹ acetonitrile and tetrahydrofuran⁶⁷ were also used for this purpose. The principles of the choice of solvent selectivity in RP HPLC are based on the Snyder triangle of selectivity, but this approach proved to be inapplicable to MLC.⁶⁷ The selectivities of separation attainable with 2-propanol, acetonitrile and tetrahydrofuran belonging to different types of solvents are close,⁶⁷ whereas those with 2-propanol and n-butanol belonging to the same type exhibited strong differences.^{9, 65, 67} For example, in a model mixture of 15 polyaromatic hydrocarbons (PAH) in the absence of the modifier (0.15 M sodium dodecyl sulfate) in the mobile phase, many compounds are co-eluted, particularly the most hydrophobic ones.⁶⁵ In the presence of 15 vol.% methanol, the peaks of all compounds are well resolved. The quality of separation with 2-propanol instead of methanol is similar; in this case, the time of analysis is reduced from 45 to 25 min. However, the addition of only 7 vol.% of n-butanol degrades separation.

On the one hand, the addition of alcohols to the micellar mobile phase modifies appreciably the partition of sorbates between the micelles and the bulk of aqueous phase which becomes less polar.⁶⁴ On the other hand, alcohols decrease the amount of surfactant sorbed on the stationary phase and solvate the grafted hydrocarbon phase. Considering that n-butanol is endowed with a higher solvation capacity than methanol or 2-propanol, this should exert stronger effect on the partition of sorbates over three phases. This effect is particularly noticeable for more hydrophobic compounds.

The parameter S_{hyb} reflects the extent of solvation of sorbates by organic solvents, localisation of the molecules of sorbates and organic solvents in the micelles⁹ and hence, should depend on the nature of both the sorbate and the surfactant. Khaledi *et al.*⁴⁷ have found that for 14 aromatic compounds belonging to different classes the values of S_{hyb} in the cetyltrimethylammonium bromide micellar phase, modified by methanol, 2-propanol and n-butanol, vary in the order $S_{n-butanol} > S_{2-propanol} > S_{methanol}$, which coincides with the increase in the eluting strength of these modifiers in RP HPLC. An analogous sequence was obtained by Rodríguez Delgado *et al.*⁶⁵ for 15 PAH in the mobile micellar phase of sodium dodecyl sulfate modified with the same alcohols.⁶⁵ The higher values of the parameter S_{hyb} for 2-butanol indicate that it interacts with the micelles more actively, solvates the sorbates more effectively and can compete better with the micelles for the interaction with sorbates than does methanol.

Variation of S_{hyb} as a function of surfactant concentration is also different for different modifiers: as the concentration of sodium dodecyl sulfate in the mobile phase increases from 0.06 to 0.14 M, the ΔS_m varies by ~ 0.2 for methanol, ~ 0.4 for 2-propanol and ~ 2.0 for n-butanol.⁶⁵

Less hydrophobic sorbates interact strongly with the micelles (e.g., anthracene with cetyltrimethylammonium bromide⁴⁷ or naphthalene, acenaphthylene, fluorene and anthracene with sodium dodecyl sulfate⁶⁵). They are less accessible to such polar solvents as methanol. Consequently, the addition of modifying alcohols will have a weaker effect on their retention compared to that in RP HPLC. The interaction of sorbates with the micelles decreases as the hydrophobicity of alcohols increases. This effect is particularly well manifested for hydrophobic sorbates (having large partition coefficients in a water–micelle system) because of the competition between this alcohol and the micelles for the interaction with the sorbate.

The order of the variation of S_{hyb} as a function of the nature of the alcohol used proved to be the same in the systems with both cetyltrimethylammonium bromide⁴⁷ and sodium dodecyl sulfate.⁶⁵

It should be noted that the proportion of an organic modifier added to hybrid eluents does not usually exceed 10 vol.%. At larger contents of organic solvents, the retention mechanism can be changed to reach eventually that typical of RP HPLC; in this case, the system will lose all its advantages in selectivity. It was shown^{58, 59} that up to 20 vol.% of 1-propanol could be added to the micellar eluent without formation of the usual aqueous-organic system.

Based on the equations deduced for RP HPLC, Madambatan *et al.*⁷¹ have developed a new approach to the gradient elution with organic modifiers in MLC. When such gradients are used, equilibrium is established rapidly owing to a narrow interval of organic modifier concentrations in the gradient. This results in the reduction of the analysis time. Practical applications of propanol and acetonitrile gradients have been described.⁷² For example, separation of dansylated and bisdansylated amino acids in the isocratic regime requires 67 min. A gradient of 2-propanol (from 3 vol.% to 15 vol.%) in 5 min with subsequent isocratic elution for another 20 min allows separation of these compounds (the total separation time is 32.5 min, including the time necessary for the equilibrium onset).

According to Eqn (26), the retention of sorbates in MLC decreases as the concentration of organic modifier increases. This holds for the most systems studied in a narrow range of modifier concentrations (3 vol.%–15 vol.% of 2-propanol).⁶⁷ However, the dependence of $\ln k'$ on ϕ is not linear for some amino acids and alkylbenzenes with mobile phases containing sodium dodecyl sulfate or cetyltrimethylammonium bromide⁴⁷ and for some benzene and naphthalene derivatives in a sodium dodecyl sulfate–n-butanol–water system. For some other compounds, the dependence of $\ln k'$ on ϕ was linear only for the mobile phases supplemented with methanol.⁷² For this reason, a new model was proposed⁷² for describing the variation of the sorbate retention time in MLC with changes in the organic solvent concentration. In the example of separation of a mixture of catecholamines on a column packed with Spherisorb ODS-2, the dependences of k' , $1/k'$ and $\log k'$ on $[M]$ and ϕ were approximated using different polynomials up to the second power inclusive using the factor planning method (the factors planned were the surfactant concentration, the micelle concentration $[M]$ (up to 0.15 mol litre^{−1}) and the propanol concentration ϕ (up to 10 vol.%). The dependence of k' on $[M]$ and ϕ was shown to be a poorly expressed asymmetric hyperbolic surface with an extremum situated near the maximum values of $[M]$ and ϕ . The addition of 10 vol.% of propanol and 0.035 M sodium dodecyl sulfate led to a 58%–78% decrease in k' , whereas the increase in surfactant concentration in a purely micellar eluent from 0.035 to 0.15 M resulted in a 81% reduction of k' . The least approximation error was obtained using the equation

$$1/k' = A[M] + B\phi + C[M]\phi + D, \quad (33)$$

where $[M]$ is the micelle concentration, ϕ is the volume proportion of the organic modifier and A , B , C and D are constants.

Equation (33) gives a satisfactory description of the retention of amino acids, peptides, phenols and some other aromatic compounds (the coefficient of correlation between the calculated and experimental k' values is above 0.996).

The following equation was also proposed to describe retention:

$$1/k' = A[M] + B\varphi + C[M]\varphi + D\varphi^2 + E, \quad (34)$$

where A , B , C , D and E are coefficients.

For catecholamines, amino acids and phenols the coefficients of different members of Eqns (33) and (34) are the same, the contribution of the term $D\varphi^2$ to Eqn (34) is insignificant. Equation (33) gives too low values for the most hydrophobic surfactants. Equation (34) provides a better description of the retention.⁷⁰ The following equation was proposed

$$k' = \left[\frac{K_{SW}(1 + K_{SD}\varphi)}{1 + K_{AD}\varphi} \right] \left/ \left[\frac{1 + K_{AM}(1 + K_{MD}\varphi)}{(1 + K_{AD}\varphi)[M]} \right] \right., \quad (35)$$

where K_{AD} , K_{MD} and K_{SD} are constants reflecting the relative variation of the sorbate concentration in the aqueous phase, in the micelles and in the stationary phase, respectively, in the presence of a modifier compared to that in the purely micellar solution. Garcia Alvarez-Coque *et al.*⁷⁰ examined separation of nine sorbates on a column packed with Spherisorb ODS-2 (C_{18}) with a propanol-containing mobile phase of sodium dodecyl sulfate in order to assess the applicabilities of Eqns (33), (34) and (35) for the description of retention. The best results were obtained using Eqn (35). Thus in the description of retention of pyrene, Eqn (35) gives a substantially higher (> 50%) accuracy than does Eqn (33). Analogous mean relative deviations of the calculated k' values from the experimental ones were obtained for other sorbates. For the purely micellar eluents, Eqn (33) is transformed into well-known Eqn (2).

Thus, the simultaneous influence of both the surfactant and the organic modifier concentrations on the retention time was again demonstrated. It is these two factors that play the crucial role in the optimisation of separation conditions in MLC.

Strasters *et al.*⁵⁸ have proposed an iterative-regressive strategy for the choice of optimum conditions for the separation of model mixtures of ionogenic compounds: 13 amino acids and peptides with a sodium dodecyl sulfate–2-propanol–water mobile phase and 15 phenols with a myristyltrimethylammonium bromide–2-propanol–water mobile phase. Prediction of the retention of sorbates proved to be possible on the basis of only five experiments even when the values of parameters were far apart in the parametric space. The time of analysis was decreased 3–7-fold and the selectivity was enhanced.

In order to solve the problems of three-parametric optimisation in MLC where the variables are the concentrations of a surfactant, an organic modifier and pH of the mobile phase, a Turbo-Pascal (version 5.5) programme has been developed.⁵⁹ In the proposed model, it is necessary to derive 15 initial chromatograms in order to plot the function of response–criterion of separation (the resolution of a pair of components which are most difficult to separate and the total time of analysis are regarded as the separation criterion). This model is applicable for optimising the separation of a mixture of 9 amino acids and peptides using a hybrid eluent containing a phosphate buffer, sodium dodecyl sulfate and 2-propanol. Rukhadze *et al.*⁷³ have established the conditions for the separation of a mixture of five barbiturates by the three-factor method using the micelles consisting of sodium dodecyl sulfate and a mixed organic modifier [pentanol–heptanol (1:3)] at pH 2.5; the separation time was 40 min.

Potential advantages of the application of artificial neuronal computational networks instead of classical statistical methods for simulating the dependence of the retention time on the concentrations of surfactant and organic modifier have been demonstrated using a mixture of 27 dihydropyridines⁶⁸ or a

mixture of 23 benzene derivatives and PAH.⁶⁹ The effects of the network architecture (the binding mode of individual neurons), the nodal activation function, the number of layers and the mode of the data processing were studied. The linear activation function was shown to be optimal. It is necessary to use networks with the recurrent bonds; the best results were obtained using the logarithms of capacity factors as the output data.⁶⁹ In the case of dihydropyridines, 1–3 neurons and recurrent networks were used.⁶⁸ Different transmission functions (two sigmoidal, one logarithmic and one linear) were activated in the node of the hidden layer; of these the logarithmic function proved to be the optimum. The optimum number of nodes in the hidden layer was equal to three. The use of the magnitude reciprocal to the capacity factor enhances the performance of neuronal networks. It was shown⁶⁸ that there are appreciable differences between the possibilities of simulation of the retention of dihydropyridines with the aid of neuronal networks and by means of empirical equations.

4. Effect of the nature of the surfactant

The selectivity of separation in MLC may be influenced not only by the variation of the surfactant concentration but also by changes in the nature of the surfactants (*e.g.*, the alkyl chain length and charge). Thus a mixture of six vanillins was successfully separated using a mobile phase of 0.02 M sodium dodecyl sulfate solution (pH 3).⁷⁴ However, when cetyltrimethylammonium bromide was used, the retention time of four of six vanillins proved to be longer than in the case of sodium dodecyl sulfate, although in the latter case the mobile phase contained an appreciably larger number of micelles (the CMC of cetyltrimethylammonium bromide at 30 °C and of sodium dodecyl sulfate at 25 °C in distilled water are 0.9 and 8 mmol litre^{−1}, respectively). Thus, the interaction of the vanillins studied with the stationary phase modified by cetyltrimethylammonium bromide is stronger than that with the stationary phase modified by sodium dodecyl sulfate. Analysis of the regression dependences carried out with the aid of Eqn (2) showed that when sodium dodecyl sulfate is used, the elution order of the sorbates correlates with the magnitude of $\Phi[L_s]K_1$, and hence the selectivity is determined mostly by the stationary phase–sorbate interactions. It should be noted that for a number of compounds the retention time also correlates with K_2 . A decrease in selectivity with the increased concentration of sodium dodecyl sulfate, and hence with the quantity of micelles in the mobile phase, also indicates that the sorbate–micelle interaction begins to play a more important role. For cetyltrimethylammonium bromide, the order of elution correlates with changes in both $\Phi[L_s]K_1$ and K_2 , *i.e.*, the selectivity of separation is determined by the interactions of sorbates with both the micelles and the stationary phase.

The observed differences in selectivities are determined, in the opinion of some investigators,^{33,44,75} by the nature of the surfactant interaction with the stationary phase and by the properties of the modified surface. It follows from the models of surfactant adsorption that in the adsorption of sodium dodecyl sulfate the hydrophobic alkyl radical is inserted into the stationary C_{18} phase, whereas the hydrophilic polar heads are directed towards the bulk of mobile aqueous phase and form a hydrophilic layer, which results in a decrease in the stationary phase polarity. In the case of cetyltrimethylammonium bromide, the head groups seem to be localised nearer to the surface owing to additional hydrophobic interactions of the *N*-methyl groups of ammonium salts with alkyl radicals of the stationary phase. It is possible that they are partially incorporated into the grafted phase. A part of cetyltrimethylammonium bromide can be sorbed irreversibly; the positively charged head groups of the surfactant can form strong hydrogen bonds with the residual silanol groups of the stationary phase and at the sites of defects in the grafted layer. All this leads to an increase in the stationary phase hydrophobicity. Indeed, when aqueous-organic eluents are used before and after work with the micellar phases, the retention times of

compounds where sodium dodecyl sulfate is used are decreased, which points to a decrease in the hydrophobicity of the mobile phase, but they are increased with the use of cetyltrimethylammonium bromide, which suggests an increase in its hydrophobicity. Lavine *et al.*⁷⁴ presume that the irreversible adsorption of cetyltrimethylammonium bromide leads to a reduced activity of the residual silanol groups, which compensates for the increase in the stationary phase polarity associated with the presence of the charged head alkylammonium groups on the surface. On the whole, the stationary phase becomes less polar and more hydrophobic. Since compounds under separation (vanillins) are weak acids ($pK_a = 7.4-8.9$), they are characterised by specific interactions (hydrogen bonding) with the negatively charged layer of the head groups of sodium dodecyl sulfate, which results in higher selectivity than that in the case of cetyltrimethylammonium bromide.

Lavine *et al.*⁷⁶ have shown that the micelles of cetyltrimethylammonium bromide possess better selectivity with regard to compounds containing acidic functional groups. This is explained by the existence of a secondary chemical equilibrium which includes proton transfer from the ionogenic compound to the water molecules in the Stern layer of the surfactant micelle. The decrease in K_a from 0.5 to 3.0 can lead to the incorporation of the guest molecule into the cationic micelle.⁷⁷

The surfactants containing two or more hydrophobic 'tails' in the monomer, *e.g.*, didodecyltrimethylammonium bromide or dihexadecyl phosphate, form vesicles. The selectivity of separation with the use of vesicles in the mobile phase differs from that in MLC, which is associated with the increase in the number of sites accessible for solubilisation from five (in a micelle) to nine (in a vesicle).⁷⁸

5. Effect of pH

The effect of pH on selectivity is determined by the occurrence of different secondary equilibria in the mobile phase and the surfactant-induced shift of the ionisation constants of sorbates.²⁶ The influence of pH on the selectivity of separation of amino acids (*e.g.*, tryptophan and phenylalanine) was studied in aqueous, ion-pair and micellar eluents. The maximum selectivity was observed for the mean pK_a value of a pair of sorbates. The optimum selectivity α_{opt} may be calculated by the equation

$$\alpha_{opt} = \frac{2SS_m + SS_m^{1/2}(SS_m K_i^* + K_j^*)/(K_i^* K_j^*)^{1/2}}{2SS_m + SS_m^{1/2}(SS_m K_j^* + K_i^*)/(K_i^* K_j^*)^{1/2}}, \quad (36)$$

where SS_m is the mean self-selectivity (the ratio of capacity factors of two sorbate forms¹⁴), K_i^* and K_j^* are the apparent dissociation constants of sorbates *i* and *j* in aqueous, non-aqueous and micellar media.

The selectivity of separation of this pair of amino acids is a maximum in aqueous medium, ion-pair chromatography and micellar liquid chromatography at pH 2–2.5, ~4 and 5–5.5, respectively.

It should be noted that the surfactant-induced shifts of pK_a values do not necessarily result in enhanced selectivity. For example, for compounds having different pK_a values and hydrophobicity (isomeric chlorophenols), the micelles influence both parameters.⁷⁹

6. Effect of the nature of the stationary phase

The effect of the nature of the stationary phase is usually considered in MLC as a variation of the column efficiency due to different adsorption of surfactants. Alkylated silica gels C_1 , C_8 , C_{14} and C_{18} with different densities of grafted alkyl groups and cyanopropyl phases were studied. Yang and Khaledi⁸⁰ have demonstrated the advantages (higher selectivity and shorter analysis time) of fluorinated, chemically bound stationary phases compared to the alkyl ones for the separation of mixtures of amino acids, peptides, sulfonamides, phenols and alkylphenols

using the mobile phases containing anionic and cationic surfactants.

Model mixtures of vanillins were separated on columns packed with Apex IC₁₈ and Apex IC₈ (5 μ m) using the same mobile phases (0.02 M surfactant solution).⁷⁴ Both stationary phases provide effective separation upon elution with sodium dodecyl sulfate solutions; in this case, the retention is determined by the interaction of sorbates with the stationary phase. The retention times of sorbates on the C_8 phase are longer than those on the C_{18} phase, despite the fact that the latter is more hydrophobic and contains 13.3% of carbon (the C_8 phase contains 9.0% of carbon). This may be due to poorer sorption of sodium dodecyl sulfate on the C_{18} phase because of the higher density of grafted groups.⁸¹

The use of mobile phases containing the cetyltrimethylammonium bromide micelles also results in a stronger retention on the C_8 phase than on the C_{18} phase; however, in this case an additional effect consists in the alteration of the order of elution of some compounds. The low adsorption level on the C_8 phase could be the cause of the stronger retention than that on the C_{18} silica gel; this should not however result in the reversal of the elution order. The higher activity of the residual silanol groups on the C_8 sorbent compared to that on the C_{18} sorbent can neither explain the observed phenomenon since the elution order of sorbates in the methanol–water system is the same on both stationary phases. For this reason, Lavine *et al.*⁷⁴ have presumed that small pre-micellar aggregates of cetyltrimethylammonium bromide are formed inside the stationary phase and modify the retention of sorbates.

To explain the differences in selectivity observed in MLC, the interaction of sodium dodecyl sulfate and cetyltrimethyl- and dodecyltrimethylammonium bromides with Apex IC₁₈,⁸² Apex IC cyanopropyl and Apex IC₈⁸³ was studied using HPLC and ¹³C NMR. It was shown that the surfactant is adsorbed on the stationary phase and that this provides for a selective separation of isomeric vanillins. The use of sodium dodecyl sulfate makes it possible to achieve better separation of hydrophilic compounds because it forms a hydrophilic, negatively charged layer on the stationary phase surface. During adsorption of ammonium surfactants, the head groups are incorporated, at least partly, into the grafted phase owing to hydrophobic interactions of their methyl groups with the C_{18} radicals of the stationary phase.⁸² In the separation of a mixture of hydrophilic compounds with the aid of these cationic surfactants, the best results were obtained at high concentrations of the surfactant in the mobile phase, when the sorbate–micelle interactions are advantageous. The length of the hydrocarbon chain of the stationary phase is an important factor in the separation with the use of cetyltrimethyl- and dodecyltrimethylammonium bromide micelles: the behaviour of hydrophilic aromatic compounds on the C_8 and C_{18} phases is different.⁸³ It was noted⁸³ that when sodium dodecyl sulfate as well as cetyltrimethylammonium bromide are employed, the retention times of some ionogenic compounds are increased. This unusual phenomenon may be explained by strong interactions of the polar groups of the surfactant and the nitrile groups.

7. Effect of temperature

The effect of temperature is the least studied aspect of MLC. It is obvious from general speculations that the temperature should be higher than the Kraft point, which corresponds to the lower temperature limit for the existence of micelles (23 °C for cetyltrimethylammonium bromide⁷³). Researchers usually operate at higher temperatures (40–60 °C, most often at 40 °C) mainly because elevated temperatures enhance the chromatographic system efficiency and reduce the time of analysis.

The effect of temperature on the retention in MLC was investigated in thermodynamic terms.^{63,84} The retention of anthracene and its derivatives on C_{18} in a sodium dodecyl sulfate–1-propanol–phosphate buffer (pH 2.1) system was studied in the temperature range 303–353 K.⁸⁴ The results

obtained were interpreted using two models. There is no correlation between the enthalpies calculated in both models and the physicochemical properties of sorbate molecules. In the model based on the Van't Hoff equation without consideration of individual equilibria, the values of standard entropies correlate with the polarity of sorbate molecules.

Villanueva Camanas *et al.*⁴⁹ did not succeed in enhancing the efficiency of separation of some 6-mercaptopurine-based medicinal preparations by using sodium dodecyl sulfate and varying the temperature from 20 to 60 °C. They noted the influence of both organic modifiers (alcohols, acetonitrile) and temperature on the resolution owing to changes in selectivity; however, these parameters affect little the efficiency and their variation has insignificant practical application. As the studies devoted to a systematic investigation of the effect of temperature in MLC are very scarce, it is impossible to draw any generalising conclusions. It may only be said that it is advisable to use elevated temperatures in MLC for decreasing the viscosity of mobile phases. This increases the column efficiency and stabilises the operation of pumps the working pressures of which are restricted.

8. Effect of ionic strength

There are no separate studies concerning the investigation of the effect of ionic strength in MLC. Since the addition of salts leads to a lower CMC and, consequently, to an increase in the micelle concentration, the effect of ionic strength on selectivity may be described as the influence of the increasing concentration of micelles.

The selectivity of separation in micellar chromatography differs from that in conventional ion-exchange⁸⁵ and ion-pair chromatography. In MLC, after the column equilibration with 10^{-4} M cetyltrimethylammonium bromide solution, anions are eluted with 0.025 M NaCl solution in the following sequence: $\text{IO}_3^- < \text{NO}_3^- < \text{Br}^- < \text{NO}_3^- < \text{I}^-$ (see Ref. 30). The use of eluents containing high concentrations of an organic modifier (lower alcohols or acetonitrile) leads to degradation of micelles (in the presence of > 43.5% of methanol no micelles are formed at all⁸⁶), so that retention is controlled only by the extent of surfactant adsorption on the stationary phase, and the selectivity becomes the same as that in ion-exchange or ion-pair chromatography.

On the whole, it should be noted that studies of the effects of various factors on the selectivity in MLC should consider all three of the equilibria established in the system. In the first place, there is an interaction of sorbates with micelles, which is characterised by the association (binding) coefficient K_2 , and with the stationary phase characterised by the partition coefficient P_{SW} ; they have opposite effects on retention.

V. Retention and structure of sorbate molecules

In RP HPLC, three types of simulation of retention parameters (or their functions of parameters characterising specific features of the sorbate structure and influencing its chromatographic behaviour) are used, *viz.*, simple additive models, a retention–property correlation and a retention–structure correlation.¹ However, in ion-pair chromatography the complexity of the processes occurring prevents construction of models which describe the effect of structural characteristics of sorbates on retention. Nonetheless, there are indications¹ that the parameters of retention models may be related to the contributions from different structural fragments and to the Gantsch π -constants of hydrophobicity. It would seem that in MLC where interactions are more numerous than in RP HPLC and ion-pair chromatography, construction of such models is not feasible. However, the existence of a clear-cut dependence of solubilisation on hydrophobic and hydrophilic properties of sorbates has stimulated the attempts to apply correlations of the retention–property type, which relate the capacity factor and the partition coefficient in a 1-octanol–water system (P_{OW}).

Thus Khaledi and Breyer⁸⁷ have revealed that the values of k' correlate well with the $\log P_{\text{OW}}$ for 35 related compounds on the phenyl phase with a cationic surfactant; however, the dependence of $\log k'$ on $\log P_{\text{OW}}$ forms a plateau at high values of the partition coefficient, *i.e.*, for hydrophobic compounds. For aromatic compounds on the stationary C_8 and C_{18} phases, a better correlation was obtained for the dependence of $\log k'$ on $\log P_{\text{OW}}$, as in RP HPLC. The existence of a linear correlation $\log k' = f(\log P_{\text{OW}})$ was established for monosubstituted benzenes with sodium dodecyl sulfate, cetyltrimethylammonium bromide and Brij-35 as the mobile phases,⁸⁸ for a number of phenols and other monosubstituted benzenes with alcohol-modified mobile phases of sodium dodecyl sulfate and cetyltrimethylammonium bromide⁷⁶ and for a series of surfactants with mobile phases containing sodium dodecyl sulfate, cetyltrimethylammonium bromide and Brij-35.⁸⁹ A correlation between the $\log P_{\text{OW}}$ and the logarithms of the constant of sorbate association with the micelle was established.^{76,87,90} A linear correlation was found to exist between the $\log k'$ (the capacity factor in the absence of micelles) and $\log P_{\text{OW}}$.⁸⁷ The dependence of k' and $\log k'$ on $\log P_{\text{OW}}$ was studied by MLC for a series of benzene derivatives and surfactants on a stationary C_8 phase.⁹¹

Estimates of k' , k'_m (k' at zero micelle concentration) and P_{MW} were derived for 26 1,4-dihydropyridines, and it was shown that they correspond to the hydrophobicity scale.⁹² The best hydrophobicity scale is the $k' - \log P_{\text{OW}}$ correlation for the mobile phase of 0.031 M sodium dodecyl sulfate containing 3% of n-propanol; this phase is described by the equation $k' = 48/3 \log P_{\text{OW}} - 98.49$. The differences between the experimental and calculated values of $\log P_{\text{OW}}$ for 20 of the 26 compounds studied were found to be less than 3%.

A linear dependence was shown to exist between the free energy of transfer of a compound from the aqueous to the micellar phase in a water–octanol system for benzene and naphthalene derivatives in micellar¹⁸ and hybrid²⁰ eluents, as well as for substituted phenols.⁹³ The slope of the straight lines is virtually independent of the nature of the surfactant (sodium dodecyl sulfate, cetyltrimethylammonium bromide or Brij-35) or of the presence of an organic modifier.²⁰ This indicates that in all cases the reactions of sorbates with the micelles are based on hydrophobic interactions. For alkyl-substituted phenols, the value of the free energy of transfer of the aliphatic hydrocarbon groups is less negative for the sodium dodecyl sulfate micelles than in the octanol–water system, whereas for the phenols containing the OR, COR and COOR substituents the contribution to the hydrophobicity is larger in the presence of sodium dodecyl sulfate than in the octanol–water system.⁹³ These differences may be due to the fact that solubilisation of different sorbates can occur in the micelle at different sites which differ in dielectric constants, local microviscosity, steric factors and the occurrence of electrostatic interactions with the ionic head groups of surfactants for charged sorbates.

The second group of correlations relates retention to the structure of sorbates described with the aid of various descriptors,¹ the simplest of which is the number of the carbon atoms in the molecule (n_{C}). In the example of n-alkylbenzenes and alkylphenols in sodium dodecyl sulfate and cetyltrimethylammonium bromide-containing systems, including those with propanol added,¹⁹ it was shown that in contrast to RP HPLC where the dependence of $\log k'$ on n_{C} is linear, in MLC with both purely micellar and hybrid eluents only the dependence of k' on n_{C} is linear, whereas the dependence of $\log k'$ on n_{C} is better described by the quadratic function. Analogous dependences were derived in the studies of the retention of alkylbenzenes in the mobile phases containing Brij-22 or Brij-35.¹⁶ Alkylphenols in the micellar mobile phases of sodium dodecyl sulfate are an exception. For this group of compounds the dependence of $\log k'$ on n_{C} is linear, while the dependence of k' on n_{C} is quadratic, as in RP HPLC.¹⁹ For phenols and a hybrid sodium dodecyl sulfate mobile phase, the differences in k' and $\log k'$ are too small to allow one to

state with certainty which of the dependences is better approximated by the straight line. The cause of this phenomenon is not sufficiently clear. Khaledi *et al.*¹⁹ proposed two possible explanations. The first explanation is based on the difference in the location of various sorbates in (or on) the micelle since the heterogeneous nature of the micelles creates a unique situation where different sorbates in the same mobile phase have micro-environments differing in polarity. The second explanation relies on the model of interaction indices,^{94,95} according to which the dependence of $\log k'$ on the number of carbon atoms for aqueous-organic eluents is described by the equation

$$\log k' = (\log \gamma)n_C^2 + (\log \alpha)n_C + \log \beta, \quad (37)$$

where $\log \alpha$ and $\log \beta$ are constants and $\log \gamma$ is expressed by the Eqn (38)

$$\log k' \gamma = \frac{\Delta V_x \Delta I_x \Delta C_x C_M I_M}{2.3RT}, \quad (38)$$

where ΔV_x and ΔI_x are the changes in the sorbate volume and in the interaction index in a homologous series, ΔC_x and C_M are the proportionality constants for the sorbate and the mobile phase, I_M is the index of interaction for the mobile phase.

Usually the value of $\log \gamma$ for aqueous-organic eluents is so small that the first term of Eqn (37) may be neglected. It is probable that in MLC the product of $\Delta V_x \Delta I_x$ is somewhat larger for some homologues and this causes the departure of the dependence of $\log k'$ on n_C from linearity.

Nonetheless, Khaledi *et al.*¹⁹ have succeeded in revealing linear dependences of the logarithms of sorbate-micelle association (binding) constants (K_2) and of partition coefficients of sorbates between the extramolecular mobile phase and the stationary phase (P_{SW}) on n_C . Analysis of these dependences showed that the K_2 values for homologues are larger in the cetyltrimethylammonium bromide micelles than in the sodium dodecyl sulfate micelles, which points to a stronger interaction of sorbates with the cetyltrimethylammonium bromide micelles owing to the availability of hydrophobic environments. The slope of these straight lines is the measure of free energy calculated for the transfer of one methylene group from the bulk of solution into the micelle (dependence of K_2) or into the stationary phase (P_{SW}), and this slope is steeper for cetyltrimethylammonium bromide than for sodium dodecyl sulfate, which is indicative of the higher affinity of the methylene group of cetyltrimethylammonium bromide due to its larger hydrophobicity.

Hinze and Weber⁹⁶ proposed a more rigorous approach to the rationalisation of the non-linearity of the dependence of $\log k'$ on the number of the carbon atoms in the surfactant molecule in MLC in their paper entitled 'Why the relationship between the logarithm of k' and homologue number in micellar chromatography is not linear'. In RP HPLC, it is implied that each CH_2 increment in the chain of a homologue makes a constant contribution to the free energy of sorbate transfer between the mobile and stationary phases. In MLC, the retention of small-sized polar sorbates that are well soluble in water and poorly soluble in micelles is basically determined by the partition between the surfactant-modified stationary phase and the non-micellar mobile phase. In a homologous series, compounds become less water-soluble as their size increases, and in the extreme case of total insolubility in water the sorbates are partitioned between the chemically similar micellar phase and the surfactant-modified stationary phase. For this process, the free energy of one methylene group transfer from the mobile to the stationary phase (ΔG^m) is virtually equal to zero. As in MLC the ΔG^m value depends on the homologue size, the dependence of $\ln k'$ on the number of methylene groups in the sorbate (n^m) should not be linear.

$$\frac{1}{k'} = \left(\frac{V_m}{V_s} \right) \exp \left[\frac{\Delta G_{WS}^{fg} + n^m \Delta G_{WS}^m}{RT} \right] + \quad (39)$$

$$+ \left(\frac{V_x}{V_s} \right) \exp \left[\frac{\Delta G_{XS}^{fg} + n^m \Delta G_{XS}^m}{RT} \right]$$

where the subscripts 'X', 'W' and 'S' refer to the micellar, aqueous and stationary phases; V stands for the corresponding volumes of phases and the superscripts 'fg' and 'm' refer to the functional and methylene groups, respectively. The dependence of $\ln k'$ on n^m is described by the equation

$$\ln k' = -\ln[(1 - \Phi_x)\exp(a + n^m b) + \Phi_x \exp(c + n^m d)], \quad (40)$$

where $\Phi_x = V_x/V_m$ is the ratio of the volumes of micelles and stationary phase; a , b , c and d are constants. The parameters of a non-linear regression were calculated, the free energies of the methylene group transfer from the non-micellar part of the mobile phase (pure water or water containing 5 vol.% of alcohols) into the surfactant-modified stationary phase [parameter b , Eqn (40)] and the free energy of the methylene group transfer in the micelle-stationary phase system [parameter d , Eqn (40)] were estimated for alkylbenzenes with the use of sodium dodecyl sulfate-1-pentanol-water and Brij-35-water systems and also for methyl esters of fatty acids with the use of a sodium dodecyl sulfate-1-propanol-water system.

Recent years witnessed the appearance of more complex models which relate retention to the sorbate structure and which are based on the statistical analysis and the method of analysis of basic components.^{97,98} In the example of 17 surfactants with three different micellar mobile phases (sodium dodecyl sulfate, cetyltrimethylammonium bromide, Brij-35) it was shown that retention can be adequately described using only two of the nine descriptors: L/B (ratio of the maximum molecule length to its width) and one of the topological descriptors.⁹⁷ The contribution from the topological descriptors is most important in the case of cationic and anionic surfactants, whereas the electrostatic interactions are particularly substantial in the case of sodium dodecyl sulfate. Correlation equations of the types $\log k' = f(F, L/B, c)$ and $\log k' = f(n, L/B, c)$, where F is the correlation factor, c is the surfactant concentration in the micellar mobile phase, n is the number of π -electrons in the molecule, were derived. These equations are easier to use because the values of the corresponding descriptors can be calculated directly from the structural formulae of compounds. Analogous correlations can also be established for the partition coefficients P_{SM} , P_{SW} or P_{MW} since they can be calculated from experimental chromatographic data using Eqn (1) or (2).⁷⁶ For sodium dodecyl sulfate, correlations of the type $P_{SM} (P_{SW} \text{ or } P_{MW}) = f(L/B, F)$ were obtained; however, the regression is deteriorated in the sequence $P_{SM} > P_{MW} > P_{SW}$ because of the increased uncertainty of calculations.⁹⁷

In the hybrid mobile phases which contain sodium dodecyl sulfate with additions of methanol, 2-propanol or n-butanol the retention of unsubstituted PAH is described by the equation considering the size and shape of molecules.

$$\log k' = aF + bL/B + c, \quad (41)$$

where a , b and c are constants.⁹⁸

This model does not however describe methyl-substituted PAH. Therefore, new models were proposed which include electronic parameters allowing consideration of the distribution of electronic density in the molecule, *viz.*, dipole moments (DPMON) and the share of the non-polar unsubstituted surface area (NUSA/TSA) [Eqn (42)].

$$\log k' = aF + bL/B + c\text{DPMON} + d\text{NUSA/TSA} + e, \quad (42)$$

where a , b , c , d and e are constants. Equation (42) gives a satisfactory description of the retention of both unsubstituted and substituted surfactants upon addition of <20 vol.% of methanol or 2-propanol or <6 vol.% of n-butanol.

The influence of molecular structure on the constants of the sorbate-micelle and sorbate-stationary phase binding has been studied.^{99,100} The existence of a clear-cut linear dependence between the constants of the sorbate-micelle and sorbate-

stationary phase binding was demonstrated.¹⁰⁰ Fairly good quantitative dependences of the constants of sorbate–micelle and sorbate–stationary phase binding on solvatochromic properties were obtained.^{99, 100} The correlation between k' and solvatochromic parameters is better in the presence of tetradecyltrimethylammonium bromide micelles, whereas the correlation between $\log k'$ and solvatochromic properties is better in the presence of sodium dodecyl sulfate micelles; the addition of 7% of 2-propanol or 5% of butanol does not modify the strong correlations revealed for tetradecyltrimethylammonium bromide.⁹⁹ An important role in the retention of neutral sorbates is played by both the process of cavity formation and the hydrogen bonding. The examples considered above indicate that such models not only allow prediction of the retention of various sorbates but are also helpful for revealing interactions of sorbates with stationary and mobile phases.

Guermouche *et al.*¹⁰¹ studied theoretical aspects of the retention of 15 aromatic compounds in MLC using the zwitterion surfactant n-dodecyl 3-(*N,N*-dimethylamino)propane-1-sulfonate (DDDMAPS) and calculated the constants of equilibrium partition of sorbates using Eqn (1). Compared to the cationic and anionic surfactants in the DDDMAPS-containing mobile phases, the lowest values of K_{SW} and K_{MW} were obtained, which leads to larger capacity factors at a constant surfactant concentration. Sorbates are retained owing to hydrophobic interactions with the stationary phase and electrostatic interactions with the surfactant in the micelles as well as in the modified stationary phase. Molecular interactions were studied using the method of linear dependences of solvation energy.¹⁰¹ The sorbate size and basicity were shown to be the dominant factors affecting the retention. The dipolar environment in the zwitterionic DDDMAPS is larger and this influences the partition of sorbates: acidic sorbates are more easily bound to this surfactant.

A correlation between the retention and biological activity was established using models of the retention–property type. Breyer *et al.*¹⁰² revealed a clear-cut correlation between k' and biological activity, measured as $\log 1/c$, where c is the concentration required for a 50% inhibition of growth, for 26 *para*-substituted phenols. The advantage of this approach consists in that it uses a single parameter, *viz.*, retention in MLC, whereas normally three descriptors are used for estimating biological activity: $\log P_{OW}$, acid dissociation constant and resonance parameter. Owing to the unique properties of surfactant micelles in MLC, both hydrophobic and electronic interactions are combined in one parameter, *viz.*, k' . The nature and acidity of the stationary phase influence the correlation between k' and $\log 1/c$; the optimum system is cetyltrimethylammonium bromide supplemented with 10 vol.% of 2-propanol.

Escuder-Gilabert *et al.*¹⁰³ studied qualitative and quantitative correlations between the retention and the anesthetic strength, equianesthetic concentration, duration of action, toxicity and the half-life of anesthetics. Clear-cut correlations between k' and the anesthetic strength of compounds were established.

Deriving correct correlations requires reliable determination of the dead time (t_0) which is problematic in MLC. In MLC, the magnitude of t_0 is measured with respect to the introduction of water,^{93, 104} salt solutions (NaNO_3 ,^{25, 37} NaI and KI ^{11, 19}) and acetonitrile.⁶⁶

Torres Lapasio *et al.*¹⁰⁵ proposed four different criteria for determining the characteristic time at the beginning of chromatography (the time of the exit of the first peak, first perturbation) that may be called reference time.

1. Search for the first basic maximum or minimum.
2. Formation of groups reducing noises to a definite scale.
3. Formation of groups for scaling the slopes of the basal line noises.
4. First-derivative method consisting in the detection of an important change in the basal line slope upon the occurrence of a considerable perturbation. The best results are given by the noise-scaling criterion; in this case it is advisable to measure the

reference times upon addition of standard solutions or micellar solutions of sorbates. Determination of the reference time using a large number of different mobile phases has shown that it does not change noticeably as the mobile phase composition is modified.

VI. Analytical application of micellar liquid chromatography

The development of the theory of MLC was based on the studies of different organic compounds: non-ionogenic (substituted benzenes, phenols, naphthalenes, anthracenes, *etc.*) as well as ionogenic (amino acids and peptides), whereas practical uses of this method lie in the analysis of medicinal preparations (Table 1). Such an analytical application reflects several advantages of MLC: selectivity and capacity for simultaneous separation of ionic and non-ionic components of samples, direct introduction of biological samples without preliminary precipitation of proteins or extraction of drugs, as well as the possibility of fluorescence enhancement or stabilisation. Simplification of the sample preparation for the analysis of biological specimens is achieved owing to solubilisation of proteins on micellar aggregates since the protein–micelle aggregates have a large size and are not retained by the stationary phase. Low detection limits make it possible to detect specific compounds not only in pharmaceutical formulations but also in urine.

The possibility of enhancement of sensitivity of determination of some compounds in the presence of surfactants has been demonstrated. Thus the oxidation current of acetaminophen is increased in the presence of sodium dodecyl sulfate micelles.¹⁰⁸ An electrochemical detector with a cell of the 'reflecting wall of the three-electrode configuration' type with a carbon-fibre micro-electrode was designed for detecting acetaminophen. The compatibility of the separation by MLC with amperometric detection was first demonstrated by Khaleli and Dorsey;¹²⁶ dopamine was determined using a glassy-carbon electrode.¹²⁴

Steroids were determined in urine by the MLC method and detected using the terbium-sensitised fluorescence.¹⁰⁶ The micellar environment promotes an efficient Forster energy transition from donors (steroids) to acceptors [terbium(III) ions]. This method is highly sensitive and allows determination of as little as 100 pg of steroids in urine. This detection technique is appreciably more sensitive than the spectrophotometric detection,¹¹⁴ which is applicable only for the analysis of initial pharmaceutical preparations and is unsuitable for the analysis of biological samples.

The luminescence [sensitised by a terbium(III)–surfactant complex] in the inverted micelles in non-aqueous solutions (ethyl acetate or its mixture with hexane) was used for the detection of theophylline;¹²⁰ the presence of paraxanthin does not interfere with this determination due to the low efficiency of energy transfer to the lanthanide ion. This method minimises the fluorescence quenching induced by the use of inverted micelles in non-aqueous solvents.

Examples of the use of micellar mobile phases in the inorganic analysis are not numerous: separation of inorganic anions;^{30, 32, 85} cations of transition metals;^{9, 31} chelates;^{127–131} heteropolyacids;^{132, 133} different forms of arsenic,^{77, 134, 135} mercury,^{77, 135} selenium⁷⁷ and tin;^{77, 136} organic and inorganic compounds containing heavy metals.¹³⁷

Thus the separation of five anions on a column (250 × 5 mm) packed with ODS (5 μm) using 1.36×10^{-1} M aqueous cetyltrimethylammonium chloride as the eluent at a flow rate of 1.5 ml min^{-1} was effected within 10 min.⁸⁵ Detection was carried out at 205 nm. The order of elution: $\text{IO}_3^- < \text{NO}_2^- < \text{Br}^- < \text{NO}_3^- < \text{I}^-$ is analogous to the selectivity sequence for a typical, strongly basic anion exchange resin.

The use of micellar exclusion chromatography on a column packed with the Asahipak GC-310H sorbent, which is a polyvinyl alcohol gel, proved to be effective for the separation of both anions³⁰ and cations.³² In the separation of anions the elution order varies with the modification of hydrophobicity of the

Table 1. Determination of components of medicinal preparations by MLC using sodium dodecyl sulfate.

Components of medicinal preparations	Organic modifier	Detector	Detection limit	Object of analysis	Ref.
Steroids	acetonitrile	FL	100 pg	urine	106
Amiphenazole, amiloride, amphetamine, clostebol, ephedrine, phenylpropanolamine, methanediene, methoxyphenamine, nandrolone, spironolactone	—	SP	0.07–10.95 µg ml ⁻¹	"	107
Acetaminophen	n-propanol	EC	0.02 µg ml ⁻¹	"	108
Clenbuterol	n-butanol	SP	—	"	109
Diuretics	n-propanol	SP	1.7–2.9 µg ml ⁻¹	"	110
Caffeine, theophylline, theobromine	"	SP	0.36–1.23 µg ml ⁻¹	"	111
<i>N</i> -(1-Benzo[<i>b</i>]thien-2-yl)ethyl- <i>N</i> -hydroxyurea, its <i>N</i> -dehydroxylated metabolite	"	SP	0.08–0.1 µg ml ⁻¹	"	112
Sulfonamides	"	—	—	urine, milk	113
Amiloride, bendroflumethazide, chlorothalidone, spironolactone, triamterene	n-pentanol	—	—	pharmaceutical preparations	114
Diuretics	n-propanol	SP	0.029–0.55 µg ml ⁻¹	pills	115
Catecholamines	"	SP	2–16 µg ml ⁻¹	capsules, pills	48
Anabolic steroids	n-pentanol ^a	SP	6.4–860 ng ml ⁻¹	pills, suspension, gel, solution for injections	116
Proteinic amino acids	n-propanol	SP	(1.3–1.5) × 10 ⁻⁷ mol litre ⁻¹	pharmaceutical preparations	117
Diuretics	—	—	—	the same	118
β-Blockers (atenolol, metoprolol, oxyprenolol, diuretics (amiloride), bendroflumethazide, hydralazine	n-propanol	SP	—	pills, capsules	119
Theophylline	"	SP	6 µg ml ⁻¹	pills	120
6-Mercaptopurine, 6-thioguanidine	—	—	—	serum	121
4-Formylaminoantipyrine, 4-aminoantipyrine, 4-methylaminoantipyrine	n-pentanol	SP	10.54 µg ml ⁻¹ –17.0 ng ml ⁻¹	plasma	122
(<i>R</i>)- and (<i>S</i>)-Naproxenes	—	—	—	human liver microsomes	123
Dopamine	—	EC	—	—	124
Theophylline	ethyl acetate, hexane	FL	9 ng ml ⁻¹	—	125

Note: FL, fluorescent; SP, spectrophotometric; EC, electrochemical (amperometric) detectors, respectively; ^a microemulsion.

surfactant alkyl chain: with 0.06 or 0.01 M cetyltrimethylammonium chloride mobile phase, the anions are eluted in the sequence $\text{IO}_3^- < \text{I}^- < \text{Br}^- < \text{NO}_2^- < \text{NO}_3^-$, whereas in the presence of dodecyltrimethylammonium chloride this order is $\text{IO}_3^- < \text{Br}^- < \text{NO}_2^- < \text{I}^- < \text{NO}_3^-$ (see Ref. 30).

Using micellar exclusion chromatography, Okada²⁹ separated Pb(II), Co(II) and Cu(II) in 0.05 M sodium dodecyl sulfate containing 0.08 mol litre⁻¹ of NaCl (pH 4.0) and also a mixture of cations of rare-earth elements (Yb, Ho, Dy, Tb and Pr) and of transition metals [Cu(II), Pb(II), Zn(II), Ni(II), Co(II) and Mn(II)] in the gradient mode of elution with a mixture of 0.025 M sodium dodecyl sulfate and 0.08 M α-hydroxyisobutyric acid (pH 4.0) or with 0.025 M sodium dodecyl sulfate and 0.08 M tartaric acid (pH 4.3).³¹ Separation of 8 transition metal cations [Fe(III) < Cu(II) < Zn(II) < Ni(II) < Pb(II) < Co(II) < Cd(II) < Mn(II)] was performed in 20 min on a column with Inertsil ODS-2 with an aqueous mobile phase containing 0.0945 mol litre⁻¹ of sodium dodecyl sulfate and 0.0684 mol litre⁻¹ of tartaric acid (pH 4.02).²⁹

Miura *et al.*¹²⁸ determined the distribution constants of 2-(2-thiazolylazo)-4-methylphenol (TAMP) and 2-(2-thiazolylazo)-5-dimethylaminophenol (TAAP) in solutions of non-ionic surfactants [poly(oxyethylene)-4-nonylphenyl ether (PONPE), poly(oxyethylene)oleyl ester (POOE), Triton X-100, POL-10]; these constants were found to decrease as the length of the oxyethylene chain increased. Rapid elution of TAMP and TAAP is achieved using surfactants with shorter oxyethylene chains

because the reagents have the higher affinity to the micellar phase. The retention time is reduced as the number of oxyethylene units in PONPE and POOE decreases.

PONPE-20 was used for the separation of metal chelates with TAAP.^{127, 128} Of the nine chelates studied, only the V(V) chelate is eluted selectively, the peak of Fe(III) chelate overlaps with the peak of the solvent front, while the reagent itself and other complexes are strongly retained (and some of them are possibly degraded) in the column.¹²⁷ Probably, the use of hybrid eluents (supplemented with organic modifiers) would yield better results. Separation of Cu(II), Zn(II), Ni(II) and Co(II) takes 45 min using a mobile phase containing 0.006 mol litre⁻¹ of sodium dodecyl sulfate, 0.002 mol litre⁻¹ of 8-hydroxyquinoline-5-sulfonic acid and pH gradients of 3.5 → 3.9.¹³¹ Determination of aluminium with a detection limit of 1 ppb in the form of chelates in human serum with 8-hydroxyquinoline was performed on a column packed with CAPCELL PAK MF ph-1 with an eluent containing 20 mass % of acetonitrile, 0.01 M sodium dodecyl sulfate, 10⁻⁴ M EDTA, 0.01 M *N,N*-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid-based buffer (pH 7.0) with fluorescent detection (370–504 nm).¹³⁰ The contents of Ni(II), Co(II) and Cu(II) in metal alloys were determined using chelates with sodium diethyldithiocarbamate and the mobile phase containing 0.03 M cetyltrimethylammonium bromide, 10⁻⁴ M sodium diethyldithiocarbamate and 45% of 1-propanol (spectrophotometric detection).¹²⁹ The detec-

tion limits of Ni(II), Co(II) and Cu(II) were 68.1, 67.2 and 35.4 pg, respectively; the separation time did not exceed 6 min.

Compatibility of MLC with the mass-spectrometric determination with the use of induction plasma was demonstrated in the example of determination of arsenic using the cetyltrimethylammonium micelles.¹³⁵ In this case, the detection limits (90–300 pg) were comparable with that in ion-pair chromatography (0.4–1.2 ng cm⁻³ at a loop volume of 250 mm³ with detection by atomic-fluorescent spectrometry with preliminary generation of hydrides¹³⁸) but they were inferior to that in ion-exchange chromatography (20–91 pg¹³⁹). This may be due to the larger volumes of peaks and a complex composition of the mobile phase and, especially, to the influence of sodium ions from buffer solution which can suppress ionisation of arsenic.

A series of studies^{77, 135, 136} were devoted to the use of vesicles in MLC. If a micelle is a closed monolayer, then a vesicle is a closed bilayer. The cavity is filled with the substance which is contained in the environment.²² To be able to form vesicles the surfactant molecules should contain two (or more) hydrophobic hydrocarbon radicals with 16–18 carbon atoms. These requirements are met, for example, by didodecylmethylammonium bromide^{135, 136} and dihexadecyl phosphate.^{75, 136} These mobile phases can be used in combination with selective detection techniques, such as atomic-emission spectrometry with induction plasma (also after formation of hydrides), mass-spectrometry with induction plasma, atomic-absorption spectrometry of cold vapour and atomic-absorption spectrometry with electrothermal atomisation.

Interesting results were obtained in MLC of heteropolyanions:^{132, 133} a mixture of BW₁₂O₄₀⁵⁻, SiW₁₂O₄₀⁴⁻ and SiMo₁₂O₄₀⁴⁻ was separated within 10 min and a mixture of SiW₁₁FeO₃₉⁵⁻, BW₁₂O₄₀⁵⁻ and SiW₁₁O₃₉⁸⁻ within 7 min.

However, the results of the application of MLC in inorganic analysis, even though being interesting *per se*, are basically inferior to those achieved in ion-pair or ion-exchange chromatography.^{140–142}

VII. Comparison of the possibilities of ion-pair and micellar liquid chromatography

As the role of micelles is similar to that of organic modifiers owing to their ability to increase solubility of uncharged sorbates in water, MLC is usually compared to RP HPLC. Separation of uncharged and hydrophobic compounds, for which RP HPLC is widely used, is the field in which MLC is inferior as regards its efficiency, eluting strength and selectivity. The efficiency of columns in MLC is appreciably lower than that in RP HPLC and decreases as hydrophobicity of compounds increases. The micellar eluents are weak eluents; therefore, the retention times of hydrophobic sorbates are long. Selectivity is also low because of the similarity of processes which occur in the mobile and stationary phases,^{19, 66} although in a number of instances the reversal of the elution order is observed.^{143–145} All of these characteristics of the chromatographic system can be enhanced by the introduction of organic modifiers into the eluent; however, MLC will not all the same be competitive with RP HPLC in the separation of hydrophobic sorbates.

An advantage of the MLC method is the possibility of separating mixtures of ionic and non-ionic sorbates. Another method allowing solution of this problem is ion-pair chromatography. These methods have much in common: both use surfactants; electrostatic interactions play a substantial role (though if in ion-pair chromatography this role is crucial and determines retention, in MLC it is secondary), while organic modifiers regulate the eluting strength and selectivity of separation. Also, there are differences in principle between these two methods. Micellar solutions are considered in MLC as macroscopically homogeneous systems composed of two phases: the micelles and the bulk of aqueous solution. In the ion-pair chromatography, the mobile phases are homogeneous and consist solely of surfactant

monomers. Furthermore, the amount of surfactant adsorbed on the stationary phase increases with the concentration of the ion-pairing agent in the mobile phase. Descriptions of MLC by different authors are contradictory: some believe that the amount of adsorbed surfactant is almost constant after it exceeds CMC, while others argue that the surfactant adsorption remains substantial at concentrations several tens of times that of CMC.

Thorough comparison of the possibilities of both methods was carried out in the example of separation of amino acids and peptides.^{66, 146} The separation was performed using 2-propanol-modified sodium dodecyl sulfate-containing mobile phase. Investigation of the dependence of retention on the alcohol concentration showed that in the case of ion-pair chromatography the parameter of the solvent strength *S* correlates well with the logarithm of capacity factor in a purely aqueous phase ($\ln k'_0$). The selectivity of separation drops with the increasing content of the organic solvent in the mobile phase. Such dependences are also characteristic of RP HPLC. Totally different regularities were observed in MLC: variation of *S* proved to be reciprocal to changes in $\ln k'_0$, whereas the separation selectivity of most sorbate pairs increased as the content of the organic solvent in the mobile phase increased.

In MLC and ion-pair chromatography, the surfactant concentration has different effects on the retention of sorbates. In ion-pair chromatography the retention time of oppositely charged sorbates (at pH 2.5, the amino acids and peptides studied have a partial positive charge) increases with the concentration of the ion-pairing agent due to the larger amount of surfactant adsorbed on the stationary phase surface and forms a plateau upon saturation of the stationary phase. In MLC, the retention time is decreased as the total surfactant concentration in the system increases. In ion-pair chromatography there is no clear-cut dependence of selectivity on the ion-pair reagent concentration; though it is usually increased with the increase in concentration, particularly when sorbates differ in their charges. In MLC, the selectivity is as a rule enhanced as the micelle concentration increases. In ion-pair chromatography, the eluting strength of the mobile phase decreases as the ion-pairing agent concentration increases, whereas in MLC it increases with the concentration of micelles. Thus, the enhancement of selectivity and eluting strength occurs in parallel in MLC and antiparallel in ion-pair chromatography.

Many investigators noted better reproducibility of the retention characteristics in MLC compared to that in ion-pair chromatography. In the latter case, one often has to operate in the range where the retention is strongly dependent on the ion-pairing agent concentration; therefore, even minor changes in the mobile phase composition lead to a fairly appreciable variation of retention. Both methods were shown to have lower column efficiency compared to that in RP HPLC. Thus a new 25-cm long column packed with a C₁₈ sorbent had an efficiency of 14 000 theoretical plates in the elution with an acetonitrile–water mixture (25 : 75). In the presence of sodium dodecyl sulfate, its efficiency dropped to 5500 theoretical plates in both MLC and ion-pair chromatography. Nonetheless, the ion-pair chromatography has an advantage compared to MLC as regards the efficiency owing to the variation of the hydrophobic nature of the ion-pairing agent.

It should be noted in conclusion that MLC is an interesting method with the unique possibilities of selectivity variation; its theory has been well developed. The micellar liquid chromatography is an alternative to the RP HPLC method. Analytical chemists consider this method as the most useful in the analysis of biological specimens.

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Reactions of adamantanes in electrophilic media

I K Moiseev, N V Makarova, M N Zemtsova

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Abstract. Published data on the synthesis of adamantane derivatives bearing various functional groups (halogen, hydroxy, nitrate, amino, carboxy and others) are systematised and generalised. The bibliography includes 236 references.

I. Introduction

Synthesis, reactivity and application of adamantane derivatives have been considered in several monographs and reviews.^{1–4} These compounds are used both in the synthesis of pharmaceuticals^{5,6} and for the preparation of novel polymers.^{7,8} It was found that introduction of an adamantyl fragment into medical compounds enhances their biological activities owing to the higher fat-solubility.^{6,9} Some adamantane derivatives exhibit antiviral activities, *e.g.*, 1-aminoadamantane and 1-ethylaminoadamantane hydrochlorides, which are the active principles of antiviral Mydantan and Remantadinum manufactured by the pharmaceutical plant in Olaine, Latvia.

Nucleophilic substitution reactions of hydrogen are most widely used in the synthesis of adamantane derivatives. Nevertheless, no special consideration of the reactions of adamantane and its derivatives in electrophilic media has been given before even in the most comprehensive monographs.^{10,11}

The present review systematises and generalises published data on the synthesis of functionally substituted adamantanes using reactions in electrophilic media.

II. Substitution reactions in the adamantane series in electrophilic media

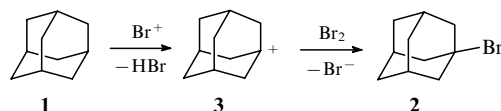
Hydride transfer reactions in organic chemistry are most comprehensively revealed in monographs.^{12,13} In these reactions, aluminium halides, BF₃, sulfuric acid, carbenium ions, protonated quinones and azobenzenes and some other compounds are commonly used as acceptors of the hydride ion.

The reactions of adamantane in electrophilic media should be considered as nucleophilic substitution at the saturated carbon atom.^{10,11} These reactions for adamantane and its derivatives can follow only the S_N1 mechanism, *i.e.*, via adamantyl cations, which then react with nucleophiles.^{14–22} The reaction rates are mostly controlled by electronic factors, *viz.*, electron-donating properties of substituents, which serve as ‘internal’ nucleophiles thus delocalising the positive charge on the central carbon atom, electron-withdrawing properties of the substituents in the leaving groups, which decrease the basicity of these groups and electrophilic properties of a medium.

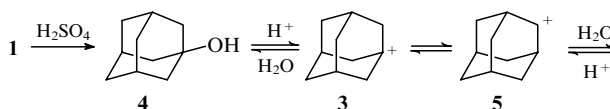
Only a few examples describing the nucleophilic substitution of hydrogen are known. These data mainly relate to the substitution of the hydride ion in polyhedranes (adamantane, proto- and homoadamantane, diamantane, bicyclo[3.3.1]nonane, *etc.*). The nucleophilic substitution of hydrogen in adamantane (**1**) has successfully been performed in electrophilic media (sulfuric acid, nitric acid, bromine), which, on the one hand, facilitated the hydride ion abstraction and, on the other hand, served as sources of nucleophilic species (HSO₄[–], ONO₂[–] and Br[–]).

Thus the bromination of adamantane (**1**) in liquid bromine occurs selectively at the bridgehead carbon atom yielding only monobromoadamantane **2**.^{14–16}

The reaction mechanism presumably involves the intermediate formation of the adamantyl cation **3**.¹⁶



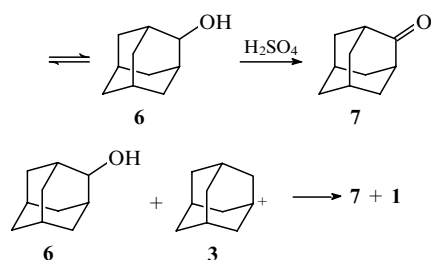
The reaction of adamantane (**1**) with sulfuric acid leads to adamantanone (**7**).^{17–19} The reaction scheme includes the oxidation of **1** with 96% sulfuric acid to 1-hydroxyadamantane (**4**), the generation of the adamantyl cation **3** and the 1,2-hydrogen shift resulting in an equilibrium between 1-hydroxyadamantane (**4**) and 2-hydroxyadamantane (**6**) and the oxidation of 2-hydroxyadamantane (**6**) to adamantanone (**7**). The latter can also be formed, along with adamantane **1**, due to the intermolecular transfer of the hydride ion from 2-hydroxyadamantane (**6**) to the cation **3**.



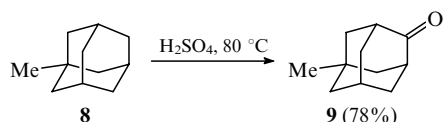
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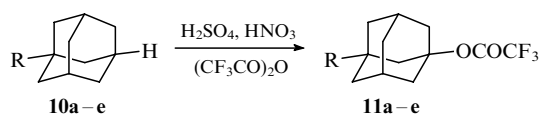
Uspekhi Khimii 68 (12) 1102–1121 (1999); translated by S V Chapyshev



The reaction of 1-methyladamantane (**8**) with 96% sulfuric acid at 80°C leads to a complex mixture of products in which 5-methyladamantan-2-one (**9**) is the major component.¹⁹

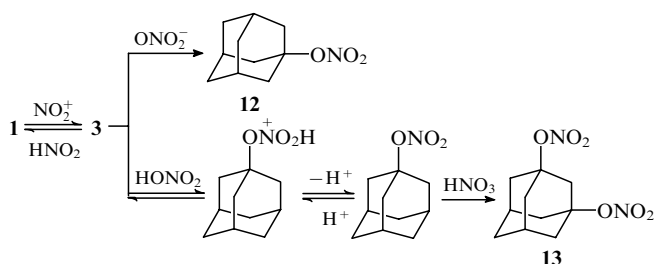
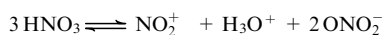


In systems containing a strong mineral acid (H_2SO_4 , HNO_3) and trifluoroacetic anhydride, the role of the hydride ion acceptor is probably played by the cations HSO_3^+ or NO_2^+ , which are generated *in situ* from the corresponding acids and weakly nucleophilic trifluoroacetic anhydride.²⁰ Thus the reactions of adamantane (**1**) and aryladamantanes **10a–e** in such systems yield the corresponding trifluoroacetoxy-substituted adamantanes **11a–e**.²⁰



R = 4- $\text{NO}_2\text{C}_6\text{H}_4$ (**a**), 4- $\text{MeSO}_2\text{C}_6\text{H}_4$ (**b**), 3- NO_2 -4- MeC_6H_3 (**c**), 4- BrC_6H_4 (**d**), 4- $\text{MeO}_2\text{CC}_6\text{H}_4$ (**e**).

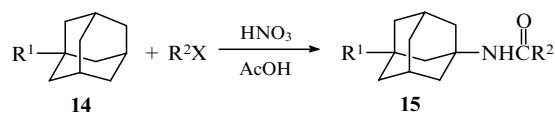
The reaction of adamantane (**1**) with concentrated nitric acid affords 1-adamantyl nitrate (**12**) and adamantane-1,3-diyl dinitrate (**13**).²¹



A mechanism of the formation of the nitrate **12** involving the stage of generation of the adamantyl cation **3** has been suggested^{22,23} based on studies of the behaviour of adamantane (**1**) in nitric acid and its mixtures with acetic acid.

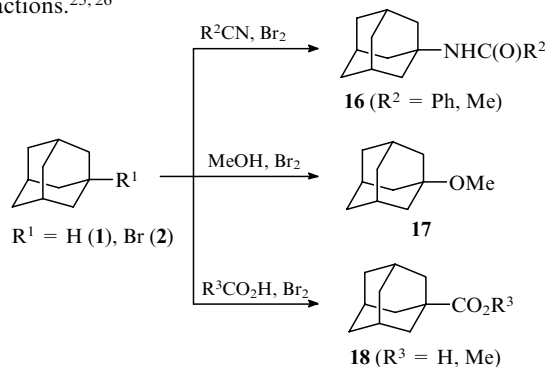
Exploration of the behaviour of adamantane (**1**) in electrophilic media made possible the development of the methods of synthesis of 1-bromoadamantane (**2**), 1-hydroxyadamantane (**4**) and nitrate **12**, which are convenient starting materials for the preparation of various functionally substituted adamantanes. It should be noted that the latter of these three compounds is the most readily available. The functionalisation of adamantane has been achieved using sulfuric and nitric acids²⁴ or bromine as electrophilic media.

The reactions of adamantane (**1**) and its derivatives **14** with nucleophiles such as urea, urethane or nitriles in concentrated nitric acid or in a mixture of HNO_3 and AcOH afford functionally substituted adamantanes **15**.²⁴

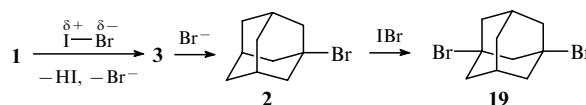


$\text{R}^1 = \text{H, Me, Et}$; $\text{X} = \text{NH}_2\text{CO}$; $\text{R}^2 = \text{NH}_2, \text{OEt}$;
 $\text{X} = \text{CN}$, $\text{R}^2 = (\text{CH}_2)_2\text{OMe}$.

It has been shown^{18,19} that functionalisation of adamantane and its derivatives can be performed in liquid bromine, which also functions as a Lewis acid. As an example, synthesis of compounds **16–18** using this method can be mentioned. By comparison with adamantane (**1**), bromoadamantane (**2**) reacts faster in these reactions.^{25,26}

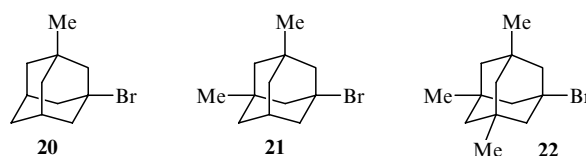


Yurchenko *et al.*^{27,28} have shown that adamantane (**1**) reacts with iodine monobromide in CCl_4 to give a mixture of 1-bromoadamantane (**2**) and 1,3-dibromoadamantane (**19**).



The authors believe that a dipole $\text{I}^{\delta+} - \text{Br}^{\delta-}$ with a partial positive charge on the iodine atom is responsible for the hydride ion abstraction from the adamantane molecule. Adamantyl cation **3** thus formed then reacts with the bromide anion. The dibromide **19** is formed from the bromide **2** according to the same mechanism.

UV-Spectral studies²⁹ showed that 1-bromoadamantane (**2**), 1-bromo-3-methyladamantane (**20**), 1-bromo-3,5-dimethyladamantane (**21**) and 1-bromo-3,5,7-trimethyladamantane (**22**) form molecular complexes with bromine, which have linear structures. Presumably, complexes of the π, σ -type with charge transfer from the lone pair of the bromine atom in bromoadamantanes to the molecule of Br_2 are realised in these cases. As a result, the polarisation of the C–Br bond is increased.



It is supposed³⁰ that the increase in the polarity of the C–Br bond in bromoadamantanes is associated with localisation of the positive charge in the centre of the adamantane cage rather than on the carbon atom of the C–Br bond. This is possible owing to the overlap of the inwardly directed, hybridised orbitals of the bridgehead carbon atoms in adamantanes. Complexation facilitates nucleophilic reactions at the carbon atom of 1-bromoadamantane (**2**). It has also been shown²² that the reactions that occur efficiently in liquid bromine, occur also in neutral solvents in the presence of molecular bromine, if its concentration is sufficient for the complexation.

The kinetics of the reactions of adamantane (**1**) and its derivatives and homologues with nitric acid in dichloromethane

Table 1. The rate constants for the reactions of adamantane derivatives with nitric acid in dichloromethane^a (Ref. 31).

Compound	Temperature /°C	Concentration /mol litre ⁻¹	10 ³ <i>k</i> _{eff} /s ⁻¹
 (1)	0	0.025	15.0±0.8
 Me (8)	0	0.025	8.7±0.4
 Me (23)	0	0.025	4.6±0.2
 Me (24)	0	0.025	1.78±0.09
	0	0.05	1.98±0.09
	10	0.05	4.2±0.1
	20	0.05	8.0±0.4
	30	0.05	1.21±0.05
 Me (25)	20	0.05	1.81±0.1
 CH ₂ CO ₂ Me (26)	20	0.05	41±2
 CO ₂ Me (27)	20	0.025	3.9±0.4
 ONO ₂ (12)	20	0.025	0.24±0.01
 C(NO ₂) ₃ (28)	20	0.025	0.041±0.002

^a Initial concentration of HNO₃ was 4 mol litre⁻¹.

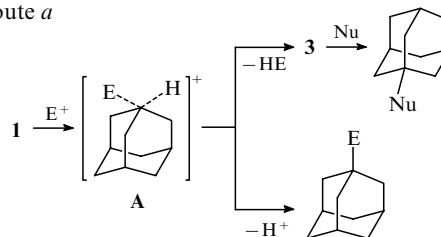
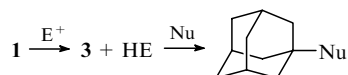
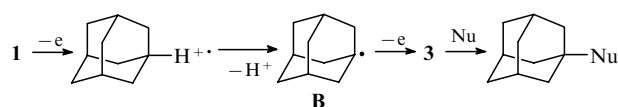
have been studied.³¹ Sequential methylation of the bridgehead positions of adamantane results in monotonic decrease in reactivity (Table 1), which is typical of the reactions involving the intermediacy of carbocations. The logarithms of the rate constants (*k*_{eff}) for these reactions calculated taking into account the statistical factor correlate fairly well (*r* = 0.993) with the logarithms of the rate constants for the solvolysis of the corresponding bromides (in 80% aqueous ethanol at 75 °C),³² which suggests that both types of reactions have similar mechanisms. Introduction of electron-withdrawing substituents into adamantane decreases the reactivities of its derivatives (Table 1). A correlation between the logarithms of the rate constants and the σ^* Taft constants is observed (*r* = 0.99, ρ^* = -0.77) for adamantanes substituted by the CH₂CO₂Me, CO₂Me, ONO₂ and C(NO₂)₃ groups. The sign of the reaction constant indicates that these substituents destabilise the positively charged intermediate species. The rather high absolute value of the ρ^* constant suggests that transition states in the reactions of adamantanes with nitric acid are highly polar.

The kinetic isotope effect for the reactions of 1,3,5-trimethyladamantane (24) and 7-deuterio-1,3,5-trimethyladamantane (25) is 4.4±0.3.³¹ This suggests that the dissociation of the C—H bond at the tertiary carbon atom is the rate-determining step. It is worth mentioning that the kinetic isotope effect for the reactions of adamantane (1) with nitronium salts is 1.86 (Ref. 33) and that for

the oxidation of isobutane with a mixture of H₂SO₄ and HNO₃ is 2 (Ref. 34).

The activation energy and entropy for the reaction of 1,3,5-trimethyladamantane (24) are equal to 43±7 kJ mol⁻¹ and 147±24 J mol⁻¹ K⁻¹, respectively.

Judging from these data, it is reasonable to assume that the reaction of adamantane (1) with nitric acid involves the intermediate formation of the adamantyl cation 3. The rate-determining step of this process is obviously the abstraction of the hydride ion from the tertiary carbon atom by an electrophile, which is most likely the nitronium ion. The adamantyl cation 3 thus formed is further stabilised by adding a nucleophile.³¹ The reactions of saturated hydrocarbons with sulfuric or nitric acids or their mixtures are well known. The mechanism of activation of the C—H bonds in adamantane or, in the other words, the mechanism of the hydride ion transfer is discussed in Refs 35–37. In adamantane and its homologues, this activation can be realised by three routes.

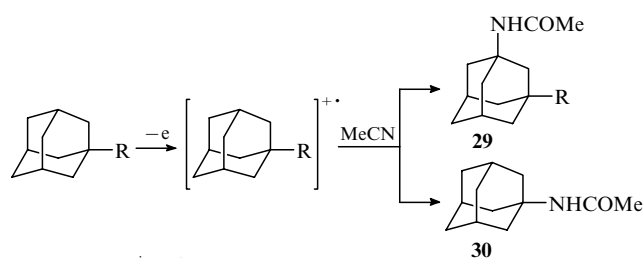
Route *a*Route *b*Route *c*

Of these three, no route can be ruled out from consideration, since each of them leads to the adamantyl cation 3. Route *a* implies realisation of a transition state **A** with a five-coordinate carbon atom. Such a transition state is used³⁵ to describe hydride ion transfer in the reactions of alkanes with carbocations in sulfuric acid or with nitronium salts. The nitration of alkanes according to Olah,³⁸ viz., with nitronium salts in a mixture of dichloromethane and sulfolane at 25 °C in the dark in the absence of moisture, giving rise to a mixture of nitroalkanes and nucleophilic substitution products also invokes the realisation of the transition state with a five-coordinate carbon atom. However, the question whether the transition state **A** is converted into the final products by proton abstraction or by the elimination of HNO₂ and subsequent reaction of the cation 3 with a nucleophile still remains open.

The route *b* has already been considered in detail for the reactions of adamantane (1) in such electrophilic media as liquid bromine, sulfuric and nitric acids. In these cases, the initially formed adamantyl cation 3 reacts further with HSO₄⁻, ONO₂⁻, Br⁻ or other nucleophilic species. The reactivity of adamantane in these electrophilic media decreases in the following order: H₂SO₄ > HNO₃ > Br₂.

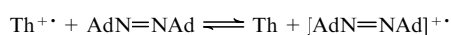
The reactions of adamantane (1) through a stage of single-electron transfer (route *c*) are also possible. However, this is considered in a limited number of publications (see, for example, Ref. 36).

The anodic oxidation of alkyladamantanes in dry acetonitrile yields 1-acetamido-3-alkyladamantane 29, while the anodic fragmentation of the same compounds leads to 1-acetamidoadamantane (30). The ratio of the reaction products depends on the nature of the alkyl substituents.³⁶

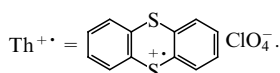
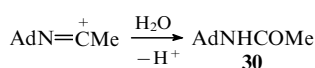
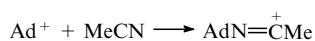
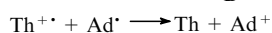
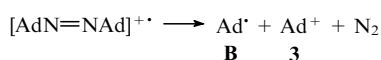


R = H, Et, Prⁱ, Bu^t.

Later, the decomposition of 1,1'-azoadamantane (**31**) into adamantyl radical **B** involving the stage of the formation of [AdN=NAd]⁺⁺ (Ad is 1-adamantyl) (route *c*) was described.³⁷ Thus the reaction of 1,1'-azoadamantane (**31**) with thianthreinium perchlorate in acetonitrile affords 1-acetamidoadamantane (**30**) in 90% yield.



31

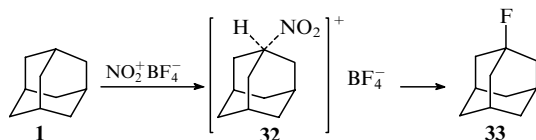


III. Halogenoadamantanes

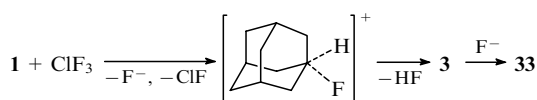
Halogenoadamantanes can be obtained from both adamantane itself and its derivatives bearing hydroxy, nitroxy and other nitrogen-containing functional groups or halogen atoms.

After the first reports^{14,15} on the synthesis of halogenoadamantanes from adamantane (**1**), several publications appeared in the literature, describing methods of introduction of fluorine, chlorine, bromine and iodine atoms into the adamantane molecule, which involve the intermediate formation of the adamantyl cation **3**. Using these methods, four halogen atoms can be introduced in the bridgehead positions of adamantane.

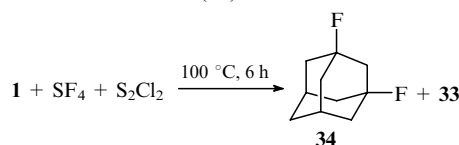
1-Fluoroadamantane (**33**) has been obtained by the reaction of adamantane (**1**) with a mixture of poly(hydrogen fluoride) and pyridine (30% Py, 70% HF).³⁹ The fluorination is carried out in the presence of nitronium tetrafluoroborate. The complex **32** with the five-coordinate carbon is assumed to be formed in the attack of the nitronium cation on adamantane, which then decomposes to give 1-fluoroadamantane (**33**).



1-Fluoroadamantane (**33**) can also be prepared by the reaction of adamantane (**1**) with xenon fluoride⁴⁰ or with ClF₃.⁴¹ In the latter case, 1,3-difluoro- and 1,3,5-trifluoro-adamantanes were formed together with the 1-fluoroadamantane (**33**). The reaction presumably involves the intermediacy of a complex with five-coordinate carbon and the adamantyl cation.⁴¹



Sulfur tetrafluoride reacts with adamantane in the presence of sulfur monochloride to give a mixture of 1-fluoro- (**33**) and 1,3-difluoro-adamantanes (**34**).⁴²

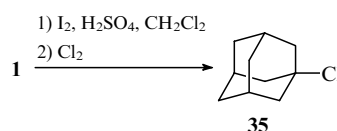


The fluorination of 1,3-dimethyladamantane (**23**) over CoF₃ affords a mixture of perfluorotrimethylbicyclo[3.3.1]nonane and perfluoro-1,3-dimethyladamantane (5%–10%).⁴³ The fluorination of 1,3-difluoro-5,7-dimethyladamantane, prepared by the reaction of 1,3-dihydroxy-5,7-dimethyladamantane with SF₄ (125 °C, 4 h), over CoF₃ also leads to a mixture of perfluorinated derivatives.⁴³

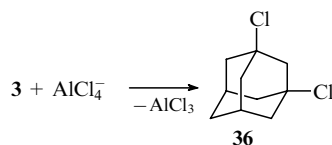
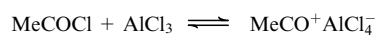
1-Fluoro- (**33**), 1,3-difluoro- (**34**), 1,3,5-trifluoro- and 1,3,5,7-tetrafluoro-adamantanes have been obtained by the action of sulfur tetrafluoride on adamantane (**1**).⁴⁴

Much more attention is paid to the problem of the adamantane chlorination. Molecular chlorine, organic and mineral acid chlorides, AlCl₃, FeCl₃ and others are used as chlorinating agents.

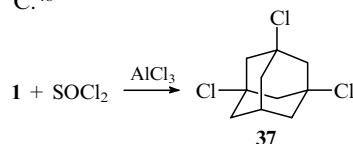
1-Chloroadamantane (**35**) can be obtained either by the treatment of adamantane (**1**) with a mixture of iodine and sulfuric acid in dichloromethane followed by passing of molecular chlorine through the reaction mixture⁴⁵ or by the reaction of adamantane (**1**) with molecular chlorine adsorbed on SiO₂.⁴⁶



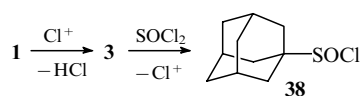
Acyl chlorides RCOCl (R = Me, Prⁿ, Prⁱ, Ph, cyclohexyl) in the presence of AlCl₃ are also rather efficient chlorinating agents. Thus the reaction of adamantane (**1**) with acetyl chloride yields 1,3-dichloroadamantane (**36**).⁴⁷



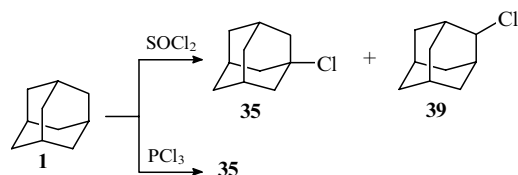
1,3,5-Trichloroadamantane (**37**) is obtained by the reaction of adamantane (**1**) with thionyl chloride in the presence of AlCl₃ at 75 °C.⁴⁸



In this reaction, adamantane sulfinyl chloride (**38**) is formed as the minor product probably due to the nucleophilic attack by the lone electron pair of the sulfur atom of thionyl chloride on the carbenium ion **3**.



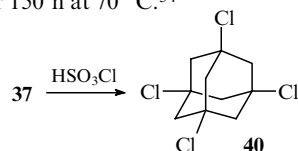
Adamantane (**1**) reacts with sulfonyl chloride in sulfolane at 60 °C to give 1-chloro- (**35**) and 2-chloro-adamantanes (**39**) in 97.5% and 2.5% yield, respectively.⁴⁹ 1-Chloroadamantane (**35**) is also obtained by the reaction of adamantane with phosphorus trichloride in trifluoroacetic acid.⁵⁰



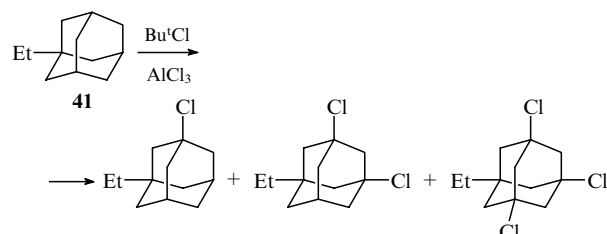
Unlike pure fluorosulfonic acid, which reacts with adamantane (**1**) to give 1-hydroxyadamantane (**4**),⁵¹ chlorosulfonic acid halogenates adamantane at -5°C [the ratio of reactants 1 : (8–10)] providing 1-chloroadamantane (**35**) in 60% yield.⁵²

Synthesis of 1-chloro-, 1,3-dichloro- and 1,3,5-trichloro-adamantanes by the reaction of adamantane (**1**) with chlorosulfonic acid has been described.⁵³ When the reaction mixture is kept below 5°C for less than 1 h, 1-chloroadamantane (**35**) is formed in 18.7% yield. 1,3-Dichloroadamantane (**36**) is obtained in 80.7% yield after 50–60 h, and 1,3,5-trichloroadamantane (**37**) is obtained in 70% yield after 140–240 h of the reaction. Either 1-chloro-3,5-dimethyl- or 1,3-dichloro-5,7-dimethyladamantane is formed in the chlorination of 1,3-dimethyladamantane (**23**) depending on the reaction conditions. 1,3,5-Trimethyladamantane (**24**) gives 1-chloro-3,5,7-trimethyladamantane.

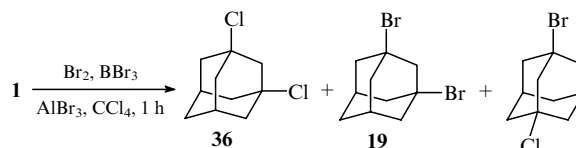
1,3,5,7-Tetrachloroadamantane (**40**) has been obtained by heating 1,3,5-trichloroadamantane (**37**) with chlorosulfonic acid for 150 h at 70°C .⁵⁴



Chlorination of adamantane (**1**) and its homologues can be accomplished with alkyl halides in the presence of Lewis acids. Thus the treatment of 1-ethyladamantane (**41**) with a mixture of *tert*-butyl bromide or *tert*-butyl chloride and AlCl_3 affords 1-chloro-3-ethyl-, 1,3-dichloro-5-ethyl- and 1,3,5-trichloro-7-ethyl-adamantanes.⁵⁵



A mixture of 1,3-dichloro- (**36**), 1,3-dibromo- (**19**) and 1-bromo-3-chloro-adamantanes was obtained by refluxing adamantane (**1**) in CCl_4 in the presence of boron tribromide and aluminium bromide.⁵⁶



A mixture of 1-chloro- (**35**) and 1,3-dichloro-adamantanes (**36**) was formed in the reaction of adamantane (**1**) with CCl_4 in the presence of AlCl_3 at 20°C .⁵⁷

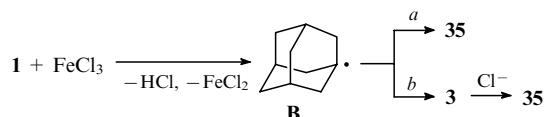
1,3,5,7-Tetrachloroadamantane (**40**) was prepared in 55% yield by refluxing adamantane (**1**) with AlCl_3 in CCl_4 .⁵⁸

The reaction of adamantane (**1**) with AlCl_3 in CCl_4 for 4 h at 20°C affords 1,3-dichloroadamantane (**41**) in 49% yield.⁵⁹

The effects of solvents and Lewis acids on the chlorination of adamantane (**1**) have been studied in detail.^{59,60} The yields and the ratio of 1-chloro- (**35**) and 2-chloro-adamantanes (**39**) obtained in these reactions in the presence of FeCl_3 or SbCl_5 are listed in Table 2. The yields of 1-chloroadamantane (**35**) are higher when SbCl_5 is used as a catalyst. The ratio of the isomers is influenced by the nature of the solvent and the Lewis acid.

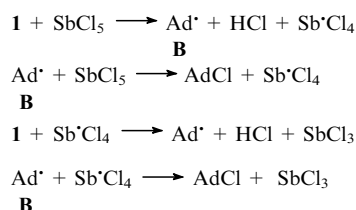
The mechanisms of the halogenation reactions of adamantane considered above are probably not purely ionic, since 2-chloro-adamantane (**39**) can be formed exclusively by the free-radical mechanism.

Two different mechanisms can be suggested for the reactions in the presence of FeCl_3 : the route *a* involving direct reaction of the radical **B** with FeCl_3 and providing 1-chloroadamantane (**35**) and the route *b* implying the intermediacy of the cation **3**.



(a) FeCl_3 ($-\text{FeCl}_2$); (b) FeCl_3 ($-\text{FeCl}_2$, $-\text{Cl}^-$).

The reaction of adamantane (**1**) with SbCl_5 can also be described by a scheme including a stage of the adamantyl radical **B** formation.



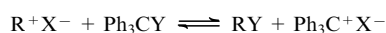
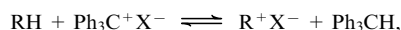
The chlorination of adamantane (**1**) in the presence of AlCl_3 and AgSbF_6 has been studied by Olah *et al.*⁶¹ A mixture of 1-chloro- (**35**) and 2-chloro-adamantanes (**39**) (in 63.2% and 2.9% yields, respectively) is formed when the ratio of the reactants Cl_2 : AlCl_3 : AdH is 1 : 0.1 : 1 (21 h, 25°C). If the ratio

Table 2. Chlorination of adamantane (**1**) in the presence of FeCl_3 and SbCl_5 .^{59,60}

Solvent	Temperature / $^{\circ}\text{C}$	FeCl_3			SbCl_5		
		Time / h	Total yield of 35 and 39 (%)	Ratio of 35 and 39	Time / h	Total yield of 35 and 39 (%)	Ratio of 35 and 39
CCl_4	78	6.5	4	11 : 1	3	7–9	(11–15) : 1
		54	64–72	(12–15) : 1	4	14–20	(13–15) : 1
		—	—	—	36	66–79	(11–16) : 1
CH_2Cl_2	40	7	2	20 : 1	0.5	24	31 : 1
		10	4	28 : 1	1	40–42	(35–39) : 1
		—	—	—	3	68–79	(36–42) : 1
CH_2Cl_2 , CCl_4	48	2.5	3	42 : 1	2	52	22 : 1
		4.5	3–6	(27–42) : 1	5	75	21 : 1
		7	8–9	(23–30) : 1	6.5	76	22 : 1

$\text{Cl}_2:\text{AgSbF}_6:\text{AdH}$ is 5:1:10 (21 h, -15.5°C), the yields of 1-chloro- (**35**) and 2-chloro-adamantanes (**39**) are 62.4% and 1.2%, respectively. In addition, 1-hydroxyadamantane (**4**) is formed in 36.3% yield. On the other hand, the ratio of 1-chloroadamantane (**35**) to 2-chloroadamantane (**39**) in photochemical chlorination was 1:(0.6–2.1).⁶²

It is known that triphenylmethyl cation is an effective acceptor of the hydride ion (*i.e.*, this serves as a 'soft' organic acid in terms of the HSAB principle). Using this cation, it is possible to generate carbenium ions from hydrocarbons and functionalise them by the reactions with appropriate nucleophiles. Triphenylmethyl cation can be used in such reactions as a catalyst. In this case, triphenylmethane derivatives serve as the sources of nucleophiles which react with the newly formed carbenium ions and also regenerate the triphenylmethyl cations.



X^- is a weakly nucleophilic anion.

This type of functionalisation has been studied for various hydrocarbons, including adamantane.⁶³



$\text{Y} = \text{OH}, \text{Cl}, \text{OMe}, \text{O}(\text{CH}_2)_2\text{OAc}.$

The reaction was carried out in a mixture of CH_2Cl_2 and MeNO_2 at 70°C using $\text{Ph}_3\text{COSO}_2\text{CF}_3$ (0.05 mol per mol of AdH) as a precursor of triphenylmethyl cation. The results obtained are listed in Table 3.

Table 3. Functionalisation of adamantane (**1**) by triphenylmethane derivatives.⁶³

Y	Ratio $\text{Ph}_3\text{CY}:$ $:\text{AdH}$	Time /h	Yields (%) ^a			
			AdY	Ph_3CH	AdOH (4)	AdH (1)
OH	1:1	14	59(57)	80		40
Cl	1:1	9	78(40)		0	10
OMe	1.25:1	2.5	31(20)	87	12	20
$\text{AcO}(\text{CH}_2)_2\text{O}$	1.25:1	3.5	50(40) ^b	71	15	10

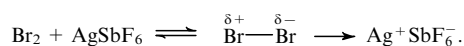
^a Determined by GLC, the isolated yields are given in parentheses; ^b after deacylation.

As can be seen from the Table 3, such functional groups as Cl and OH are readily introduced into adamantane and these exchange reactions can find synthetic application. The yields of the ethers are substantially lower, probably because of competitive disproportionation of trityl ethers.

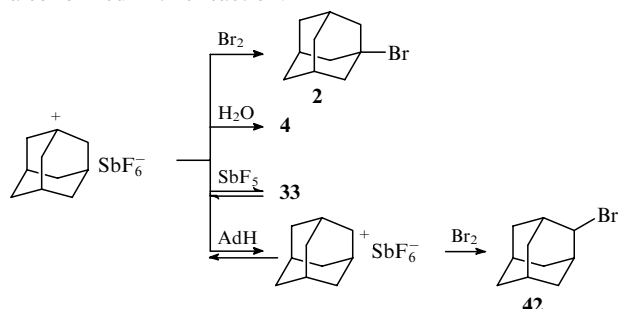
Several studies have been devoted to the preparation of bromoadamantanes. As has been mentioned above, 1-bromo-2-adamantane (**2**) was synthesised in 78% yield by the reaction of adamantane (**1**) with bromine in the presence of AlCl_3 .¹⁵

The synthesis of the bromide **2** by the oxidative bromination of adamantane (**1**) with the stoichiometric amount of bromine or an alkali metal bromide in trifluoroacetic acid in the presence of nitrogen-containing oxidants such as alkali nitrates or nitrites or NO_2 has been proposed as an alternative. This affords 1-bromo-2-adamantane (**2**) in quantitative yield.⁶⁴

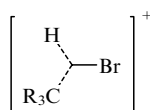
Anhydrous AgSbF_6 in CH_2Cl_2 catalyses the bromination of adamantane. At -45.5°C , 1-bromo-2-adamantane (**2**) is obtained in 54.1% yield.⁶⁵ A strongly polarised complex of Br_2 with AgSbF_6 is supposed to be the brominating species in this reaction.⁶⁵



1-Hydroxy- (**4**), 2-bromo- (**42**) and 1-fluoro-adamantanes (**33**) are also formed in this reaction.



A two-electron three-centre transition state of the carbenium type is believed⁶⁵ to be realised in this reaction.



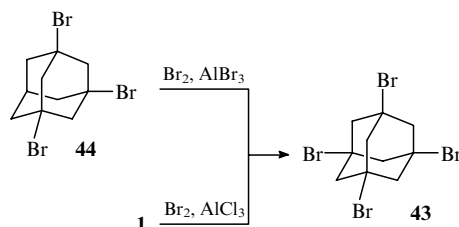
Synthesis of 1,3-dibromo-2-adamantane (**19**) by the reaction of adamantane (**1**) with bromine in the presence of AlBr_3 (78% yield) or in the absence of a catalyst in autoclave at 150°C for 22 h (12.4% yield) has been described.^{15, 66–70}

A detailed study⁶⁶ of the reaction of adamantane (**1**) with bromine in the presence of a mixture of AlBr_3 and BBr_3 has been performed. It was shown that the composition of the reaction products depends on the ratio of the catalysts used. Later, 1,3-dibromo-2-adamantane (**19**) was obtained in 97% yield by the bromination of adamantane (**1**) in the presence of Fe and small amount of water.⁶⁸

The reaction of adamantane (**1**) with bromine in the presence of Fe in Freon-113 (1,1,2-trichloro-1,2,2-trifluoroethane) or in hexafluorobenzene affords dibromide **19** in 97.3% yield and of 99% purity.⁶⁹ A complex mixture of products comprising 1,3,5-trichloro- (**37**, 27.3%), 1-bromo-3,5-dichloro- (16.6%), 1,3-dibromo-5-chloro- (27.4%), 1,3,5-tribromo- (12.0%), 1-bromo-3,5,7-trichloro- (10.8%) and 1,3-dibromo-5,7-dichloro-adamantanes (5%) were obtained in the presence of AlCl_3 .⁶⁹

The treatment of adamantane (**1**) with bromine at 100°C under 27.2 atm also yields 1,3-dibromo-2-adamantane.⁷⁰

1,3,5,7-Tetrabromo-2-adamantane (**43**) has been obtained in 75% yield by heating 1,3,5-tribromo-2-adamantane (**44**) with bromine and AlBr_3 in an autoclave at 150°C for 2 h.¹⁶



Synthesis of 1,3,5,7-tetrabromo-2-adamantane (**43**) by bromination of adamantane (**1**) has also been performed under relatively mild reaction conditions (an equimolar amount of AlCl_3 , 30 min at 20°C and then 3 h at 60°C).⁷¹

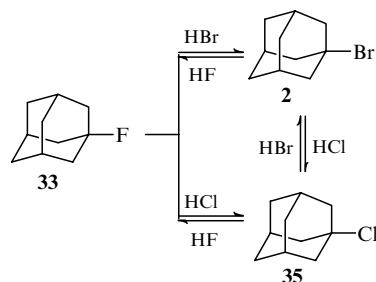
1,3,5-Tribromo-2-adamantane (**44**) has been synthesised⁷² from adamantane (**1**) under the conditions used earlier¹⁵ for the preparation of 1,3-dibromo-2-adamantane (**19**).

1,3-Dibromo- (**19**) and 1,3,5,7-tetrabromo-adamantanes (**43**) have been prepared from salts of the corresponding acids by the Hunsdiecker reaction.^{73, 74}

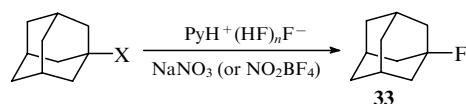
Interestingly, 1,3,5,7-tetrabromoadamantane (**43**) has also been synthesised by the reaction of 2-chloroadamantane (**39**) with bromine in the presence of the equivalent amount of AlBr_3 .⁷⁵ No product containing the chlorine and bromine atoms together in the same molecule was detected in this reaction.

The methods for direct iodination of adamantane (**1**) are unknown. Iodoadamantanes can be obtained by a substitutive iodination of chloroadamantanes or hydroxyadamantanes. These methods are considered below.

Halogenated adamantanes can also be synthesised from adamantanes bearing other functional groups. A possibility for halogen exchange in halogenoadamantanes upon their treatment with appropriate hydrogen halides has been demonstrated.^{76,77}

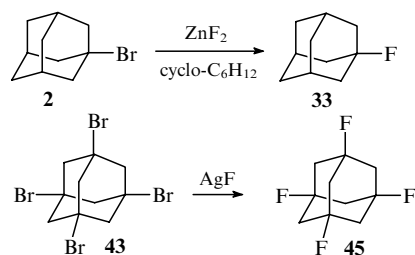


1-Fluoroadamantane (**33**) has been obtained by the treatment of 1-chloro-, 1-bromo- or 1-iodoadamantane with a mixture of poly(hydrogen fluoride) and pyridine in the presence of nitronium tetrafluoroborate or sodium nitrate.⁷⁸

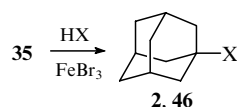


$\text{X} = \text{Cl}, \text{Br}, \text{I}$.

1-Fluoro- (**33**), 1,3-difluoro- (**34**) and 1,3,5,7-tetrafluoroadamantanes (**45**) have also been synthesised by the reactions of the corresponding bromides **2** and **43** with ZnF_2 or AgF .⁷⁹



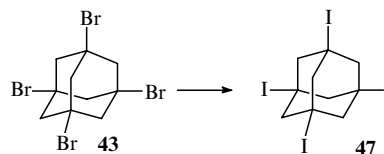
1-Bromo- (**2**) and 1-iodo- (**46**) adamantanes have been obtained by the reaction of 1-chloroadamantane (**35**) with gaseous HBr or HI in CCl_4 or CH_2Cl_2 in the presence of FeBr_3 .⁸⁰ The latter was prepared *in situ* from $\text{Fe}(\text{CO})_5$ and Br_2 .



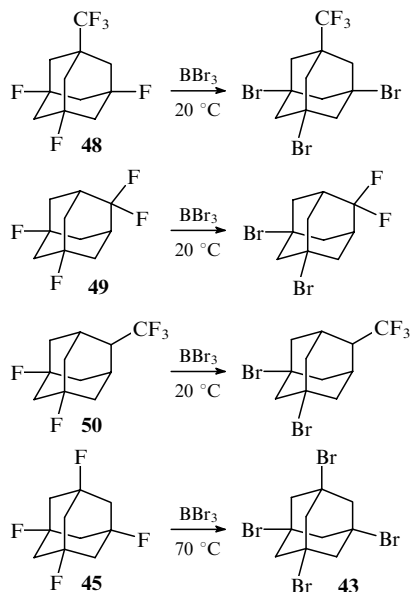
$\text{X} = \text{Br}$ (**2**), I (**46**).

A similar procedure has been proposed⁸¹ to exchange the bridgehead halogen atoms in bromo- and iodoadamantanes. The method is based on the generation *in situ* of an aluminium halide catalyst by the reaction of an excess of aluminium with bromine in a halogenated solvent. The results obtained are summarised in Table 4. In CH_2I_2 , exchange of bromine by iodine in 1-bromo- (**2**) and 1,3,5,7-tetrabromo- (**43**) adamantane occurs at room temperature in several minutes and is accompanied by the formation of adamantane (30%). Using this method, 1,3,5,7-tetraiodo- (**47**) adamantane was obtained in 83% yield.

1,3,5,7-Tetraiodo- (**47**) adamantane is formed from 1,3,5,7-tetrabromo- (**43**) in 75% yield.⁸²



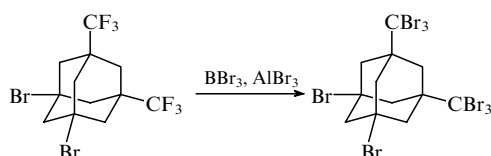
The replacement of the fluorine atoms in 1,3,5-trifluoro-7-trifluoromethyl- (**48**), 2,2,5,7-tetrafluoro- (**49**), 2-trifluoromethyl-5,7-difluoro- (**50**) and 1,3,5,7-tetrafluoroadamantane (**45**) by the bromine atoms under the action of BBr_3 has been studied.⁸³ The exothermic reactions of compounds **48**, **49** and **50** with BBr_3 begin at room temperature, whereas the exchange of the fluorine atoms in 1,3,5,7-tetrafluoroadamantane (**45**) by the bromine atoms requires heating.



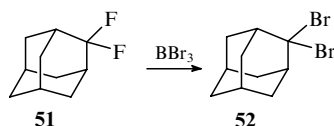
Only the bridgehead fluorine atoms were found to be exchangeable. The trifluoromethyl groups are completely inert towards the action of neat BBr_3 . However, the addition of a catalytic amount of AlBr_3 allows the exchange of the fluorine atoms in the trifluoromethyl groups by bromine. The reactions were carried out with a great excess of BBr_3 , which serves simultaneously as a reagent and as a solvent.⁸⁴

Table 4. Reaction conditions and yields of halogenoadamantanes.⁸¹

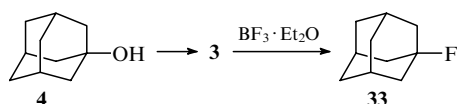
Substrate	Solvent	Temperature /°C	Time /min	Product	Yield (%)
1-Bromo- (2)	CH_2I_2	20	0.5	1-Iodo- (46)	47
	CHCl_3	65	1.5	1-Chloro- (35)	89
1,3,5,7-Tetrabromo- (43)	CH_2I_2	80	15	1,3,5,7-Tetraiodo- (47)	83
	CHCl_3	20	1200	1,3,5,7-Tetrachloro- (40)	88



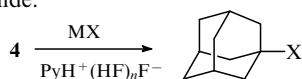
As reported by Cuddy *et al.*,⁸⁵ 2,2-dibromoadamantane (**52**) isomerises in the presence of AlBr_3 . However, this dibromide can be obtained by the reaction of 2,2-difluoroadamantane (**51**) with BBr_3 . No isomerisation of the reaction product was also observed in the reaction of 2,2,5,7-tetrafluoroadamantane with BBr_3 .⁸⁶



1-Hydroxyadamantane (**4**) or its nitrate **12** are widely used as starting compounds in the synthesis of halogenoadamantanes. Thus 1-fluoroadamantane (**33**) was obtained by the reaction of 1-hydroxyadamantane (**4**) with boron trifluoride diethyl etherate.^{87–89}

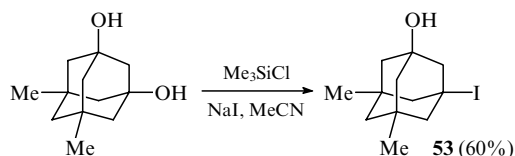


By analogy with the halogen substitution, pyridinium poly(hydrogen fluoride) was employed for the replacement of the adamantane hydroxy group by the fluorine atom.^{90,91} 1-Fluoro- and 2-fluoro-adamantanes are formed from the corresponding alcohols in virtually quantitative yields. For the preparation of adamantanes with other halogen atoms, this reagent is used in combination with the appropriate metal or ammonium halide.



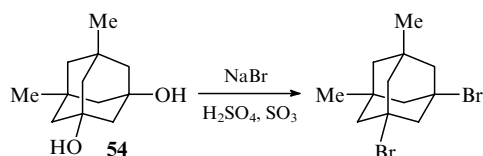
$\text{M} = \text{Na}, \text{K}, \text{NH}_4$; $\text{X} = \text{Cl}, \text{Br}, \text{I}$.

A convenient procedure for the replacement of the hydroxy group by iodine is the use of a mixture of Me_3SiCl and NaI .⁹² For example, 1-iodo- (46, yield 80%) and 1-hydroxy-3-iodo-5,7-dimethyl-adamantanes (**53**) have been prepared by this procedure. In the latter case, only one hydroxy group can be substituted even with an excess of the halogenating reagent.

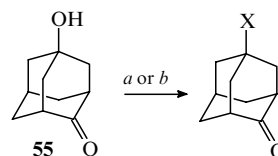


The replacement of the hydroxy group in compound **4** by a halogen can be performed by the reactions with halogens, alkali metal halides or hydrohalic acids in sulfuric acid. Thus 1-bromoadamantane derivatives have been obtained by the reactions of 1-hydroxyadamantane (**4**) and its derivatives with bromine in sulfuric acid.^{93,94}

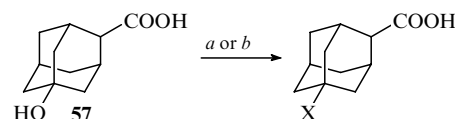
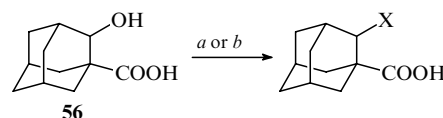
1,3-Dibromo-5,7-dimethyladamantane has been prepared by the reaction of 1,3-dihydroxy-5,7-dimethyladamantane (**54**) with bromine in oleum.^{95–97}



The hydroxy groups in the hydroxy ketone **55** and hydroxy carboxylic acids **56** and **57** have successfully been replaced by halogens.^{98–101}



(a) HBr , $\text{X} = \text{Br}$ (83%); (b) SOCl_2 , $\text{X} = \text{Cl}$ (90%).



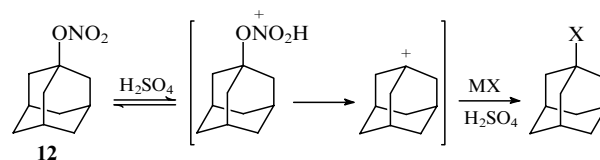
(a) PBr_5 , $\text{X} = \text{Br}$; (b) $\text{KI}, \text{H}_3\text{PO}_4$; $\text{X} = \text{I}$.

The replacement of the hydroxy group in 2-hydroxyadamantane-1-carboxylic acid (**56**) by halogens presumably follows the $\text{S}_{\text{N}}2$ mechanism.

1,3-Diiodoadamantane has been obtained by the reaction of 1,3-dihydroxyadamantane with hydroiodic acid.¹⁰²

Yet another method for the introduction of the halogen atoms into adamantanes is the reactions of adamantyl nitrates with hydrohalic acids or their salts in sulfuric acid.

Thus the nitrate groups in 1-adamantyl nitrate (**12**) and adamantane-1,3-diyl dinitrate (**13**) have successfully been replaced by the chlorine or bromine atoms using the reaction of these adamantanes with potassium (sodium) chloride or bromide in 98% sulfuric acid.¹⁰³



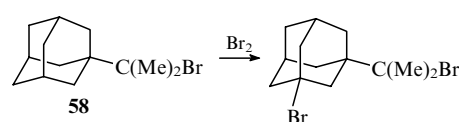
$\text{M} = \text{Na}, \text{K}$; $\text{X} = \text{Cl}, \text{Br}$.

1-Bromo-(2),¹⁰⁴ 1,3-dichloro- (**36**) and 1,3-dibromo-adamantanes (**19**)¹⁰⁵ were obtained in a similar manner.

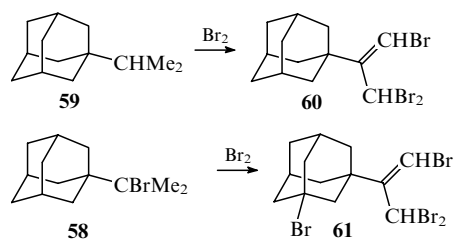
Under the action of halogenating agents on adamantanes bearing Alk , Ph , CO_2H , CF_3 , $\text{C}(\text{NO}_2)_3$, NO_2 , NH_2 and other groups either the adamantane hydrogen atom in the 3-position or the substituent is replaced depending on the nature of the substituent.

No problem arises in the bromination of 1-bromo-3-methyl-,¹⁰⁶ 1-methyl- (**8**),^{107,108} 1-ethyl-,¹⁰⁹ 1-*tert*-butyl-,¹¹⁰ 1,3-dimethyl- (**23**),¹⁰⁸ 1,3,5-trimethyl- (**24**)¹¹¹ and 1-ethyl-3-methyl-adamantanes with bromine.¹⁰⁶ The yields of the corresponding bromoadamantanes are almost quantitative.

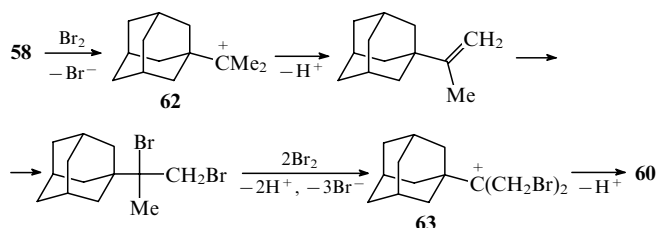
The bromination of 2-(1-adamantyl)-2-bromopropane (**58**) is worth a more detailed consideration, since the structure of the product obtained in this reaction has not initially been established. It was supposed that 2-(3-bromo-1-adamantyl)-2-bromopropane is formed in the bromination of compound **58** with bromine at 70–80 °C for 2 h.¹¹²



However, further studies^{113, 114} have shown that it was the side chain that underwent bromination of 1-isopropyladamantane (**59**) yielding 2-(1-adamantyl)-1,3,3-tribromoprop-1-ene (**60**), and compound **58** is brominated to give tetrabromo-substituted derivative **61**.



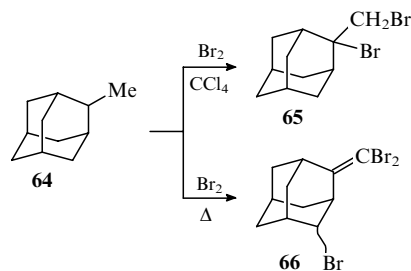
Analogous products were obtained in the bromination of 1-isopropyl-3,5,7-trimethyladamantane and 2-bromo-2-(3,5,7-trimethyl-1-adamantyl)propane.¹¹³ A mechanism involving the intermediate formation of cations **62**, **63** and the tribromide **60** has been proposed¹¹³ to account for the reaction of 2-(1-adamantyl)-2-bromopropane (**58**) with bromine.



Judging from the ratio of the rate constants for solvolysis of 2-(1-adamantyl)-2-bromopropane (**58**) and 1-bromo-3-isopropyladamantane ($10^4:1$), an assumption was made¹¹² that the rates of bromination of the side chain and nucleus in 1-isopropyladamantane (**59**) should also differ by four orders of magnitude. However, since only the nucleus of 1-isopropyladamantane is brominated in the reaction, a complex reaction scheme including several rearrangements of carbenium ions was proposed to account for this contradiction.

In fact, solvolysis of bromides and bromination involving the saturated carbon atom occur most likely by different mechanisms.¹¹³ The rate-determining stage in the solvolysis is the formation of a carbenium ion, whereas the rate of the bromination is determined by a stage which precedes the ionisation, *e.g.*, the formation of a complex $R^+ - H - Br^+ - Br^-$. The energy of such a complex is lower if the adamantane nucleus rather than side chain takes part in the complex formation.

The reaction of 2-methyladamantane (**64**) with a 10% solution of bromine in CCl_4 leads to 2-bromo-2-bromomethyladamantane (**65**), while a mixture of *exo*- and *endo*-2-bromo-4-(dibromomethylidene)adamantanes (**66**) is formed upon refluxing 2-methyladamantane (**64**) with bromine for 4–5 h. A scheme of the formation of compound **66** has been proposed.¹¹⁵



A mixture of 1-bromo-2-methyl-, 1-bromo-4-methyl- and 1-bromo-3-methyl-adamantanes was formed upon treatment of 2-methyladamantane with bromine.¹¹⁶

Table 5. The rate constants for the solvolysis of alkylbromoadamantanes in 80% ethanol.

Compound	$10^5 k$ /s ⁻¹	k_{rel}	$\Delta H^\ddagger$ /kcal mol ⁻¹	$\Delta S^\ddagger$ /cal mol ⁻¹ deg ⁻¹
1-Bromoadamantane (2)	8.76 (22.5)	1.00 (1.0)	23.1 (23.63)	-10.1 (-9.6) ^a
1-Bromo-3-methyl- adamantane (20)	6.05 (15.9)	0.69 (0.7)	23.6 (24.36)	-9.6 (-8.1) ^a
1-bromo-3-ethyl- adamantane	8.42 (22.5)	0.96 (1.0)	23.3 (24.5)	-9.4 (-7.0) ^a
1-Bromo-3-isopropyl- adamantane	11.9 (32.1)	1.36 (1.4)	24.5 (24.0)	-5.4 (-7.8) ^a
1-Bromo-3,5-dimethyl- adamantane (21)	4.12	0.47	24.5	-7.4
1-Bromo-3,5,7-tri- methyladamantane (22)	(6.93)	0.31 (0.31)	—	—

Note. According to the data in Ref. 117 (70 °C). Data from Ref. 109 (Et_3N , 75 °C) are given in parentheses.

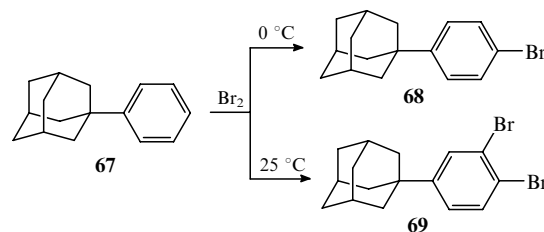
^a $\Delta S^\ddagger$ values at 60 °C.

The effect of the nature and number of alkyl substituents on the stability of the adamantyl cations can be evaluated by an analysis of the rate constants for the solvolysis of the corresponding alkylbromoadamantanes (Table 5).¹¹⁷

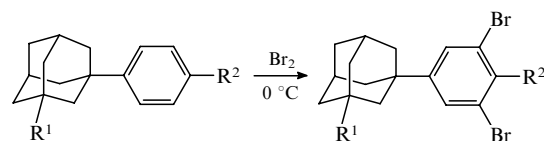
As expected, the more the number of methyl groups in 1-bromoadamantane, the lower the rate of solvolysis. However, this is increased in the series 3-methyl-, 3-ethyl- and 3-isopropyl-substituted 1-bromoadamantanes (6.05×10^{-5} , 8.42×10^{-5} and 11.9×10^{-5} , respectively).

Both the aromatic ring and the adamantane nucleus are expected to be susceptible in the bromination of aryladamantanes.

1-Phenyladamantane (**67**) reacts with bromine under reflux to give a mixture of products from which no individual compound was isolated;¹¹⁸ however, 1-(4-bromophenyl)adamantane (**68**) was obtained at 0 °C, and 1-(3,4-dibromophenyl)adamantane (**69**) as the product of substitution of two hydrogen atoms in the aromatic ring was prepared at 25 °C.¹¹⁹

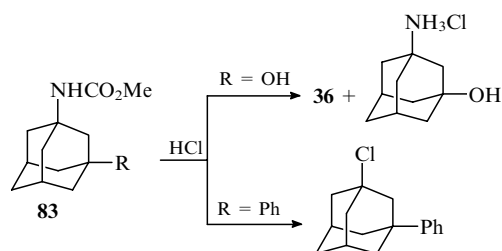


The introduction of the carboxy group into position 3 of the adamantane nucleus in 1-phenyladamantane does not affect the character of the phenyl ring substitution. On the other hand, if electron-donating substituents are present on the phenyl ring, the corresponding dibromides are formed even at 0 °C.¹¹⁹



$R^1 = H, CO_2H$; $R^2 = OMe, OH, Me$.

The bromination of 4-(1-adamantyl)acetanilide (**70**) with bromine in acetic acid leads to 4-(1-adamantyl)-2-bromoacetanilide (**71**).¹²⁰



Treatment of 1-nitroadamantane with bromine in the presence of an equimolar amount of AlBr_3 was shown¹³¹ to afford 1,3-dibromoadamantane (**19**) in 26%–30% yield.

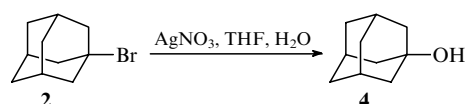
A method for the preparation of phosphorus-containing adamantanes by the reactions of hydroxy- and nitroso-substituted adamantanes with phosphorus trichloride or acid chlorides of trivalent phosphorus has been developed.^{132–134}

From the data presented above one can conclude that the introduction of the halogen atoms into adamantanes can be performed by various halogenating agents, *viz.*, halogens, hydrogen halides, thionyl chloride, chlorosulfonic acid, alkali metal halides in sulfuric acid, a mixture of nitronium tetrafluoroborate with pyridinium poly(hydrogen fluoride), *etc.* The choice of the reagent is dictated by the nature of leaving group. The $\text{NO}_2\text{BF}_4\text{--PyH}^+(\text{HF})_n\text{F}^-$ system is the most versatile reagent, which can be employed for the replacement of the hydrogen and halogen atoms and hydroxy groups in adamantanes by fluorine atoms. From the practical standpoint, the most convenient method for the introduction of a halogen into adamantanes consists in the treatment of hydroxy- and nitroso-adamantanes with hydrohalic acids or their salts in concentrated sulfuric acid.

IV. Synthesis of hydroxyadamantanes and their nitrates

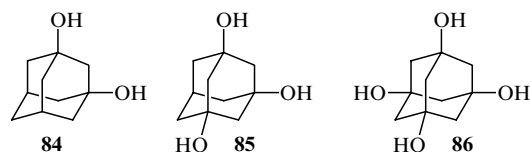
Adamantane (**1**) and 1-bromoadamantane (**2**) are most widely used as starting compounds in the synthesis of hydroxyadamantanes and their nitrates.

Preparation of adamantane-1-ol (**4**) by the hydrolysis of 1-bromoadamantane (**2**) was described for the first time by Landa *et al.*¹⁴ This compound was also obtained by the reaction of 1-bromoadamantane (**2**) with silver nitrate in aqueous THF.¹⁵



The reactions of 1-bromoadamantane (**2**) with silver nitrate in different solvents (benzene, phenol, dichloromethane, diethyl ether) was studied; it was shown that 1-adamantyl nitrate is formed in quantitative yield if the reaction is carried out in ether.¹³⁵

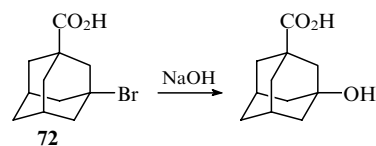
Since the increase in the number of bromine atoms in adamantanes makes them more resistant to hydrolysis, 1,3-dihydroxy- (**84**), 1,3,5-trihydroxy- (**85**) and 1,3,5,7-tetrahydroxyadamantanes (**86**, 84% yield) were obtained by the reaction of the corresponding bromides with Ag_2SO_4 in concentrated sulfuric acid.^{136, 137}



Hydrolysis of 1,3-dibromoadamantane (**19**) in an autoclave at 190–200 °C in alkaline, neutral and acidic media affords 1,3-dihydroxyadamantane (**84**) in quantitative yield.¹³⁸ When the reaction is carried out at lower temperature, 1-bromo-3-hydroxy-

adamantane could be isolated. 1-Hydroxy-3-methyladamantane was obtained from 1-bromo-3-methyladamantane (**20**).¹⁰⁹

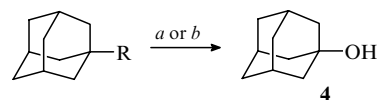
3-Bromoadamantane-1-carboxylic acid (**72**) undergoes the replacement of the bromine atom by the hydroxy group in 3 M aqueous alkali.¹²²



The rate constants for the hydrolysis of 1-bromoadamantane (**2**), 3-bromoadamantane-1-carboxylic acid (**72**) and 1,3-dibromoadamantane (**19**) (100 °C, 74% aqueous dioxane) were found¹¹⁸ to be equal to 7.98×10^{-4} , 1.3×10^{-5} and $2.4 \times 10^{-6} \text{ s}^{-1}$, respectively.

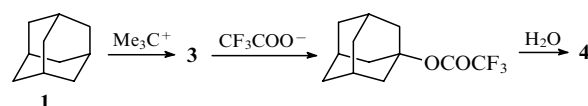
Hydroxyadamantanes were also prepared by the reactions of adamantane and its derivatives with sulfuric, nitric, fluorosulfonic and trifluoroacetic acids.

Treatment of adamantane (**1**) with a mixture of Br_2 and nitric acid affords 1-hydroxyadamantane (**4**).¹³⁹ This compound was also obtained by the action of 69% nitric acid on 1-bromoadamantane (**2**).¹⁴⁰



(a) HNO_3 , Br_2 , $\text{R} = \text{H}$; (b) HNO_3 , $\text{R} = \text{Br}$.

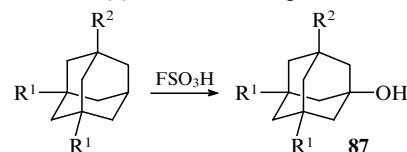
A one-step method for the preparation of adamantane-1-ol (**4**) from adamantane (**1**) by the reaction with a mixture of trifluoroacetic acid and Bu^tOH (55 °C, 12 h, the ratio $\text{AdH}:\text{Bu}^t\text{OH}:\text{CF}_3\text{CO}_2\text{H}$ is 1:2.5:17) in dichloromethane was proposed.^{141, 142} A reaction scheme including the intermediate formation of the adamantyl cation **3** was suggested.



The use of the system trifluoroacetic acid–56% nitric acid made possible the preparation of 1-aryl-3-hydroxyadamantanes by the replacement of hydrogen in aryladamantanes. In the case of reactive aryl substituents, the oxidation is accompanied by the nitration of the aromatic ring.²⁰ The reaction conditions and the yields of the corresponding alcohols are listed in Table 6.

Treatment of adamantane with 100% nitric acid affords 1-hydroxyadamantane-4-one in 77% yield.⁹⁸

Hydroxyadamantanes **87** were obtained by the reactions of adamantane (**1**) and its homologues with fluorosulfonic acid.⁵¹

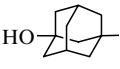
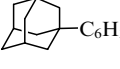
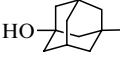
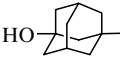
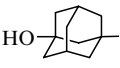
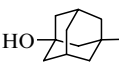
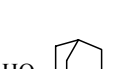


$\text{R}^1 = \text{R}^2 = \text{H}$; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$; $\text{R}^1 = \text{R}^2 = \text{Me}$.

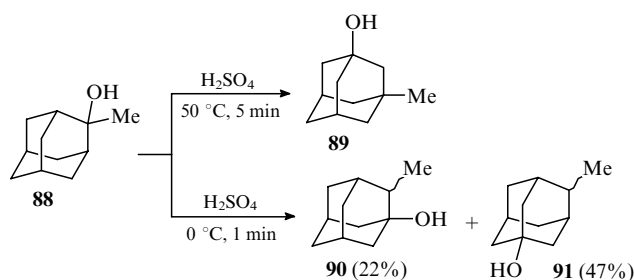
1-Hydroxyadamantane (**4**) is a reaction product of adamantane (**1**) with the system bis(trimethylsilyl) peroxide–trifluoromethanesulfonic acid.¹⁴³

Adamantanes with the hydroxy group at the bridgehead carbon atom can be obtained by the isomerisation of 2-alkyl-2-hydroxyadamantanes on treating them with concentrated sulfuric acid. Thus 2-hydroxy-2-methyladamantane (**88**) is converted into tertiary alcohols **89–91** (a mixture of *Z*- and *E*-isomers) under the action of 96% H_2SO_4 .¹⁴⁴ The composition of the reaction products depends on the temperature and time of the reactions.

Table 6. Synthesis of hydroxyadamantanes.²⁰

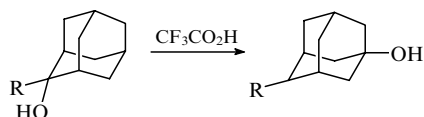
Substrate ^a	<i>t</i> /h	Products	Yield (%)
AdC ₆ H ₄ Me-4 (2.4 : 1)	2	HO-  -C ₆ H ₃ Me-4-NO ₂ -3	20
		 -C ₆ H ₃ Me-4-NO ₂ -3	62
AdC ₆ H ₃ Me ₂ -3,4 (3.6 : 1)	3	HO-  -C ₆ H ₂ Me ₂ -3,4-NO ₂ -5	26
AdC ₆ H ₄ NO ₂ -4 (2.4 : 1)	2	HO-  -C ₆ H ₄ NO ₂ -4	60
AdC ₆ H ₄ Br-4 (1.2 : 1)	2	HO-  -C ₆ H ₄ Br-4	32
AdC ₆ H ₃ Me-4-NO ₂ -3 (3.6 : 1)	3	HO-  -C ₆ H ₃ Me-4-NO ₂ -3	58
AdC ₆ H ₄ CO ₂ H-4 (1.2 : 1)	2	HO-  -C ₆ H ₄ CO ₂ H-4	11

^a The ratio HNO₃ : substrate is given in parentheses.



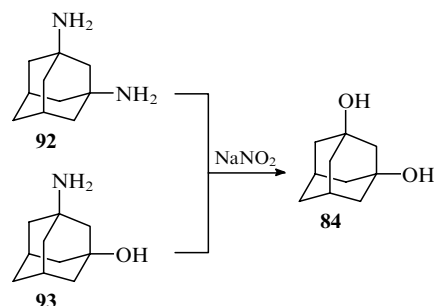
At 25 °C, 2-hydroxy-2-methyladamantane (**88**) gives a mixture of alcohols **90** and **91**, while at 45 °C (10 min), 1-hydroxy-3-methyladamantane (**89**) is the major reaction product.¹⁹

In trifluoroacetic acid, 2-hydroxy-2-*R*-adamantanes isomerise into *Z*- and *E*-isomers of 1-hydroxy-4-*R*-adamantanes.¹⁴⁵



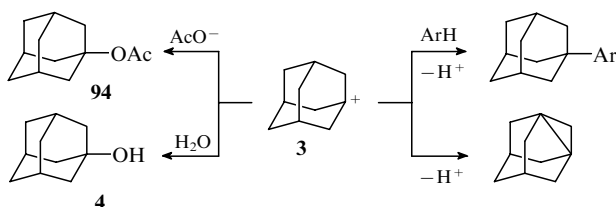
Thus the isomerisation of 2-hydroxy-2-methyladamantane (**88**) leads to a 1:1 mixture of *Z*- and *E*-isomers of 1-hydroxy-4-methyladamantane in 90% overall yield.

The well-known method for the preparation of alcohols such as deamination of amines is also used in the synthesis of hydroxyadamantanes.^{146–151} Thus the deamination of 1,3-diaminoadamantane (**92**) and 1-amino-3-hydroxyadamantane (**93**) by the action of NaNO₂ in acetic acid was shown to result in the formation of 1,3-dihydroxyadamantane **84**.¹⁴⁶



Besides the expected 1-hydroxyadamantane (**4**), adamantane (**1**) was identified as the reaction product in the deamination of 1-aminoadamantane (**80**).¹⁴⁹

The deamination of 1-aminoadamantane (**80**), including that in the presence of benzene and anisole, has been studied in detail.¹⁵⁰ It was expected that the adamantyl cation **3** would alkylate the arenes, react with external nucleophiles or rearrange.

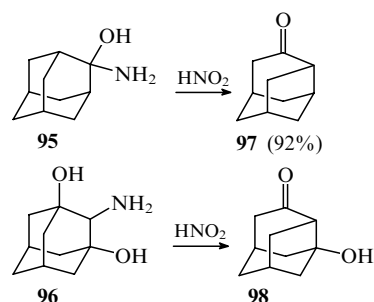


However, no aryladamantane was found among the reaction products when the deamination was carried out in the presence of benzene or anisole (Table 7).¹⁴⁸

Table 7. Deamination of 1-aminoadamantane (**80**).¹⁴⁸

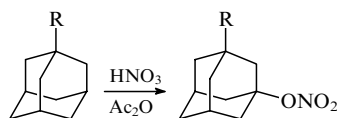
Reagent	Reaction conditions		Yield (%)	
	Solvent	<i>T</i> /°C	4	94
NaNO ₂	AcOH, H ₂ O	85	97.0±1.0	3.0±1.0
NaNO ₂	HCl, H ₂ O	85	100	
<i>n</i> -C ₅ H ₁₁ ONO	AcOH, PhH	refluxing	40.0±0.5	59.0±0.5
<i>n</i> -C ₅ H ₁₁ ONO	AcOH, PhOMe	the same	100	

The deamination of 2-amino-2-hydroxy- (**95**) and 2-amino-1,3-dihydroxy-adamantanes (**96**) is accompanied by a carbon skeleton rearrangement leading to the formation of tricyclic ketones **97** and **98**.¹⁵¹



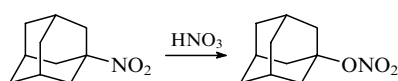
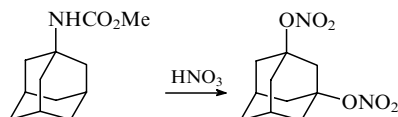
Hydroxyadamantanes are also synthesised from the corresponding nitrates, which, as was mentioned above, are prepared by the treatment of adamantanes with nitric acid.²¹ Later, the reactions of substituted adamantanes with nitric acid in acetic anhydride was studied.¹⁵² In these reactions, 1-chloro- (**35**) and 1-bromo-adamantanes (**2**) produce nitrate **12** due to the replacement of the halogens. As regards adamantane-1-carboxylic acid

(73), 1-(trinitromethyl)adamantane (28) and the nitrate 12, they undergo the replacement of the hydrogen atom in the 3-position.



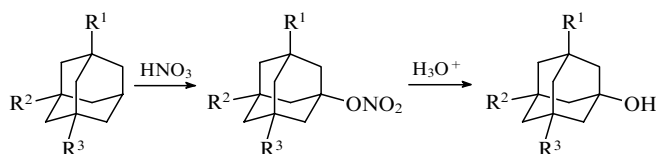
R = CO₂H, C(NO₃)₃, ONO₂.

Adamantanes with nitrogen-containing functional groups like NHCO₂Me and NO₂ react with nitric acid through the replacement of these groups by the nitrate group.



Upon treatment with a mixture of nitric acid and acetic anhydride, urethanes give nitrourethanes and 1-aminoadamantane (80) gives 1-nitroxy-3-nitroadamantane.¹⁵²

A method for the preparation of alkyladamantanols by the hydrolysis of the corresponding nitrates in 25%–30% nitric acid has been described.¹⁵³



R¹ = Me: R² = R³ = H; R² = Me, R³ = H; R² = R³ = Me;
R¹ = Et, R² = R³ = H.

The preparation of hydroxyadamantanes from their nitrates is the most convenient method, taking into account its simplicity and availability of the starting materials. Using this method, 1-hydroxyadamantane (4), 1,3-dihydroxyadamantane (84), 3-hydroxyadamantane-1-carboxylic acid and many other compounds have been synthesised.

Later, this method was extended to 2-substituted adamantanes.^{154–156}

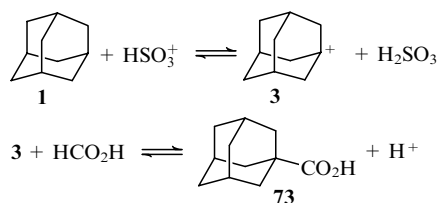
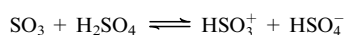
V. Synthesis of adamantanecarboxylic acids

The Koch–Haaf reaction is widely used in the synthesis of carboxylic acids of the adamantane series. Adamantane (1), 1-bromoadamantane (2), 1-hydroxyadamantane (4) and its nitrate 12 are used as starting compounds.

Adamantane-1-carboxylic acid (73) was obtained by the reaction of 1-bromo- (2) or 1-hydroxyadamantane (4) with formic acid in sulfuric acid^{15, 157} or of adamantane (1) with formic and sulfuric acids in the presence of *tert*-butyl alcohol.^{158, 159}

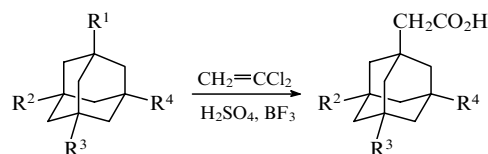
As was shown by Langhals *et al.*,¹⁶⁰ the maximum yield (84%) of adamantane-1-carboxylic acid (73) was achieved when the ratio AdOH (4):HCOOH:H₂SO₄ was 1:1:24. The yield is decreased in a deficiency of formic acid.

Adamantane-1-carboxylic acid (73) was also obtained from adamantane (1) in 20% oleum.^{161, 162} The reaction is assumed¹⁶¹ to involve the intermediate formation of the adamantyl cation 3.



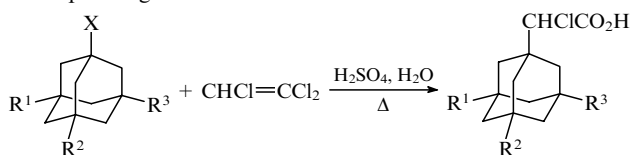
To synthesise adamantanecarboxylic acids from adamantane, the latter is made to react with CO in sulfuric acid or in oleum (autoclave, 90–160 °C).^{163, 164} This provides a mixture of adamantane-1-carboxylic acid (73) and adamantane-1,3-dicarboxylic acid in the ratio of 1:6.

(1-Adamantyl)acetic acid is synthesised from 1-bromo- (2) or 1-hydroxyadamantanes (4) and dichloroethylene in 80%–100% H₂SO₄ in the presence of BF₃ at 0–15 °C.¹⁶⁵ The preparation of adamantylacetic acids from functionally substituted adamantanes and adamantane homologues has also been described.¹⁶⁶



R¹ = Br, OH, OAc; R², R³, R⁴ = H, Me.

The reactions of adamantane and its derivatives with trichloroethylene in the presence of 90% sulfuric acid yield the corresponding α-chloroacetic acids.¹⁶⁷

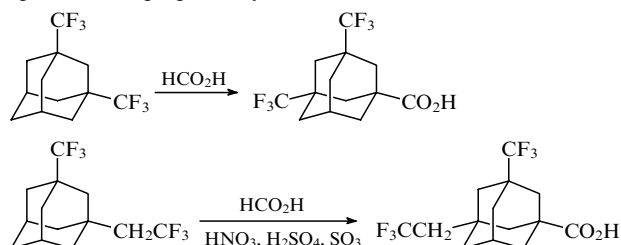


X = H, Br, OAc; R¹, R² = H, Me; R³ = H, Br, CH₂CO₂H.

3-Alkyladamantane-1-carboxylic acids are obtained from alkyladamantanes in sulfuric acid in the presence of *tert*-butyl alcohol and 95% formic acid.

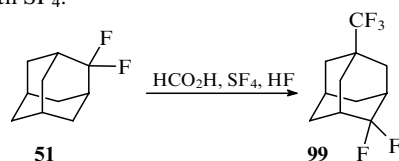
Using this approach, 3-methyl-, 3,5-dimethyl- and 3,5,7-trimethyladamantane-1-carboxylic acids have been synthesised in 72%, 49.8% and 38.5% yields, respectively.¹¹¹ Also, the synthesis of 3-methyl-,¹⁰⁶ 3-methyl-5-ethyl- and 3-bromomethyladamantane-1-carboxylic acids¹⁰⁷ as well as of 3-carboxymethyl-1-adamantyl-, 3-carboxymethyl-5-methyl-1-adamantyl- and 3-carboxymethyl-5,7-dimethyl-1-adamantylacetic acids¹²⁶ has been described. Adamantane-2-carboxylic acid was synthesised from 2-hydroxyadamantane (6).^{168, 169}

Adamantanecarboxylic acids bearing the trifluoromethyl groups were also prepared by the Koch reaction.¹⁷⁰

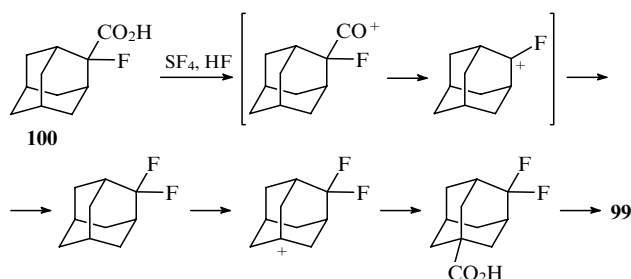


The reactivities of the trifluoromethyl- and trifluoroethyl-substituted adamantanes were shown¹⁷¹ to be lower than those of non-fluorinated adamantanes due to the more difficult hydride ion abstraction from the former with the generation of the corresponding carbenium cations. Therefore, the preparation of 3-fluoromethyladamantane-1-carboxylic acid from 1-trifluoromethyladamantane required that the reaction of the latter with CO was carried out in a mixture of nitric and sulfuric acids.¹⁷¹

Treatment of adamantane (**1**) or 2,2-difluoroadamantane (**51**) with a mixture of formic acid, SF₄ and HF in dichloromethane yielded trifluoromethyl-containing adamantanes (e.g., compound **99**) rather than the corresponding carboxylic acids. These are formed as the result of reactions of intermediate carboxylic acids with SF₄.¹⁴⁷



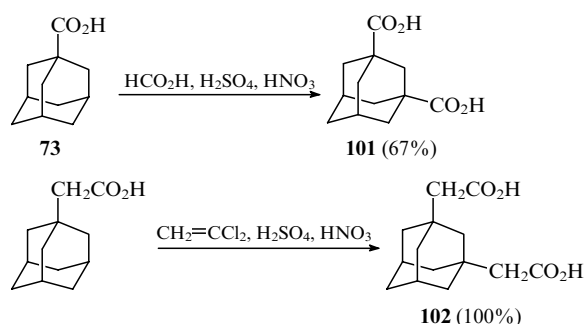
Studies of the reaction of 2-fluoroadamantane-2-carboxylic acid (**100**) with SF₄ and HF were undertaken to clarify the mechanism of these transformations.¹⁴⁸ This reaction afforded 4,4-difluoro-1-trifluoromethyladamantane (**99**), thus supporting the reaction scheme proposed earlier.¹⁴⁷



Dicarboxylic acids of the adamantane series were also synthesised by the Koch–Haaf reaction. Thus adamantane-1,3-dicarboxylic acid was obtained from 1,3-dibromoadamantane (**19**) or 3-bromoadamantane-1-carboxylic acid (**72**).^{16, 122}

A two-step synthesis of adamantane-1,3-dicarboxylic acid and (3-carboxymethyl-1-adamantyl)acetic acid from adamantane (**1**) or the corresponding monocarboxylic acids has been proposed.^{172–175}

Adamantane-1,3-dicarboxylic acid (**101**) or (3-carboxymethyl-1-adamantyl)acetic acid (**102**) can be prepared from the corresponding monocarboxylic acids. In these cases, the reactions are carried out in a mixture of nitric and sulfuric acids with formic acid or CO and dichloroethylene as the carboxylating reagents for the former and the latter, respectively.¹⁷³

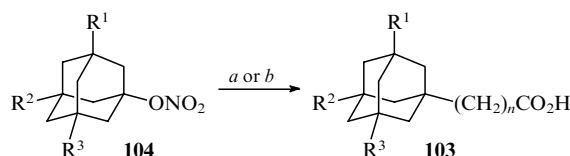


Using regression analysis, it was established that the best yields of the acids **101** (94%) and **102** (66%) starting from adamantane (**1**) are achieved with a mixture of nitric and sulfuric acids in 60% oleum.¹⁷⁴

Dicarboxylic acids of the adamantane series, like the acid **102**, are of interest as starting materials in the synthesis of polyamides and polyesters.^{176–178}

Adamantanecarboxylic acids can be prepared from the corresponding nitrates. Thus adamantane-1-carboxylic acid (**73**) has been obtained in 94% yield from 1-adamantyl nitrate (**12**) and formic acid in sulfuric acid.^{104, 179}

The preparation of carboxylic acids **103** from aryl- and alkyl-substituted adamantyl nitrates **104** has been described.^{180–182}



R¹, R², R³ = H, Alk, Ar;

(a) HCO₂H, H₂SO₄ (*d* = 1.84 g cm^{−3}), *n* = 0;

(b) CH₂=CCl₂, H₂SO₄, *n* = 1.

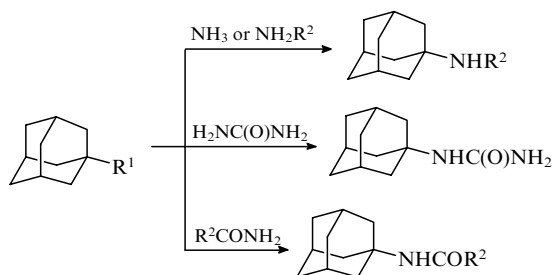
Using this approach, the corresponding dicarboxylic acids have been obtained from nitrates of 3-hydroxyadamantane-1-carboxylic and (3-hydroxy-1-adamantyl)acetic acids, however, more concentrated sulfuric acid was required in this case.¹⁸³

A mixture of 1-formyladamantane and ethyladamantane-1-carboxylate results from the formylation of adamantane in CH₂Br₂ in an atmosphere of CO in the presence of superacid systems as catalysts.¹⁸⁴

VI. Aminoadamantanes

The great interest in the synthesis of amino-substituted adamantanes is caused first of all by the discovery that 1-aminoadamantane hydrochloride (**80**) is active against influenza virus.

Amines of the adamantane series are obtained by the reactions of 1-bromoadamantane (**2**), 1-hydroxyadamantane (**4**) or 1-adamantyl nitrates with ammonia, amines, amides or nitriles of carboxylic acids, urea, *etc.*



R¹ = Hal, OH, ONO₂; R² = H, Alk, Ar.

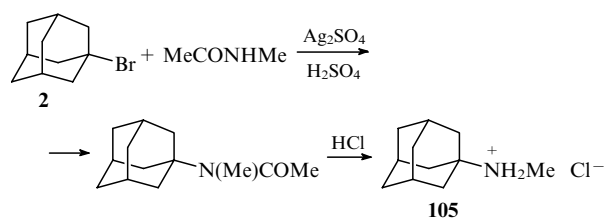
Oleum, concentrated H₂SO₄ or HNO₃ are used as an electrophilic medium. *N*-Adamantylamides are converted into the corresponding amines by alkaline or acid hydrolysis. 1-Aminoadamantane is synthesised from 1-bromoadamantane (**2**) under the action of ammonia at 200 °C for 6 h.¹⁸⁵

The preparation of compounds of the general formula AdNR¹R² [R¹, R² = H, Ph, Alk(C₁–C₁₂), AlkO, cyclo-Alk, HetAr, *etc.*] has been described.¹⁸⁶ Thus 1-dodecylaminoadamantane was obtained by the reaction of 1-bromoadamantane (**2**) with dodecylamine for 8 h.

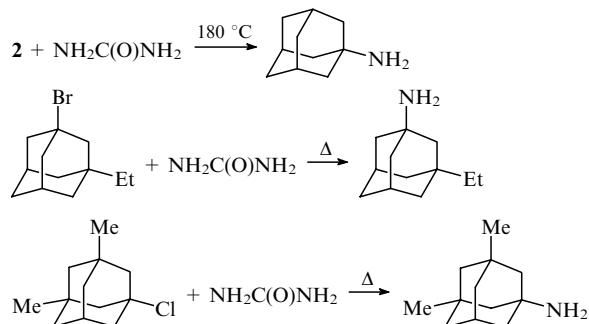
1-Aminoadamantane can be synthesised under fairly mild conditions with the use of amides, e.g., formamide. The reaction of 1-bromoadamantane (**2**) with formamide is carried out in concentrated H₂SO₄.^{187, 188} *N*-(1-Adamantyl)formamide thus formed is converted into 1-aminoadamantane under the action of 10% NaOH or 20% HCl. This method served as the basis for the manufacture of 1-aminoadamantane hydrochloride (**80**) (Amantadine, Mydantan and Symmetrel).¹⁸⁹

The reactions of 1-hydroxyadamantane with alkylamides in trifluoroacetic acid have been proposed for the preparation of *N*-[1-(1-adamantanyl)alkyl]amides.¹⁹⁰

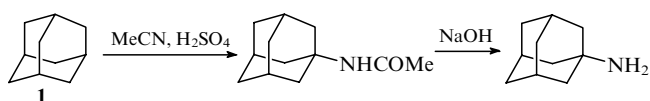
N-Alkyl-1-aminoadamantanes, including 1-methylaminoadamantane hydrochloride (**105**), were obtained from the bromide **2** and *N*-alkylacetamides.¹⁹¹ In these reactions, silver sulfate was used as an electrophilic catalyst.



The synthesis of aminoadamantanes by the reactions of urea or its alkyl derivatives with 1-halogenoadamantanes has been described in some patents.^{192–194} As a rule, the reactions are carried out at high temperature.

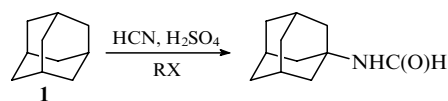


Stetter *et al.*¹⁹⁵ were the first to have studied the reactions of 1-bromo- (**2**) and 1-hydroxyadamantane (**4**) with acetonitrile in the presence of acid catalysts (the Ritter reaction). 1-Acetamidoadamantane was obtained by these reactions in 61% yield. Diethylene glycol was used as a medium for the alkaline hydrolysis of 1-acylaminoadamantane.¹⁹⁶



The reaction of hydrocyanic acid with adamantane (**1**) in sulfuric acid in the presence of a hydride ion acceptor leads to 1-formamidoadamantane. The influence of the reaction conditions on the yield of this product has been studied by Haaf.¹⁹⁷

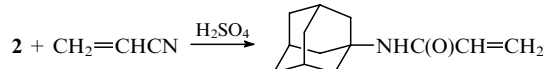
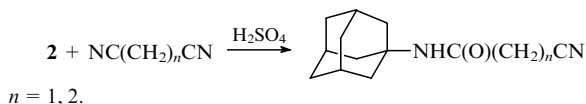
The reaction is carried out at 21–26 °C in an excess of 96%–100% H₂SO₄ using the molar ratio adamantane:acceptor:HCN = 0.1:0.4:1.7.



R	X	Solvent	Time /h	Yield (%)
Bu ^t	OH	n-hexane	1.5	78
EtCHMe	OH	the same	2.0	75
Bu ^t	OH	cyclohexane	1.0	60
Bu ^t	Cl	CCl ₄	1.5	42

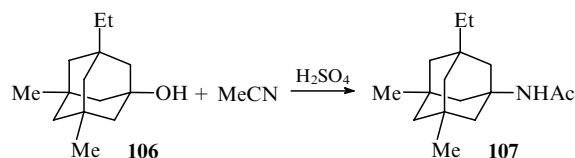
In the reaction of adamantane with acetonitrile under similar conditions, 1-acetamidoadamantane was obtained in 36% yield.¹⁹⁷

Nitriles of not only aliphatic monocarboxylic acids, but also of saturated dicarboxylic acids (maleic, adipic) and unsaturated monocarboxylic acids, *e.g.*, acrylic, have been used in the reactions with 1-bromoadamantane (**2**).¹⁹⁸

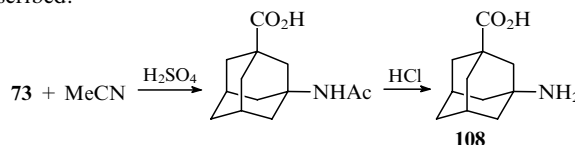


Adamantyl cation can be generated in the Ritter reaction using NOPF₆.¹⁹⁹ The reactions of 1-bromoadamantane (**2**) with acetonitrile and propionitrile in the presence of NOPF₆ and subsequent hydrolysis resulted in *N*-adamantylamides.

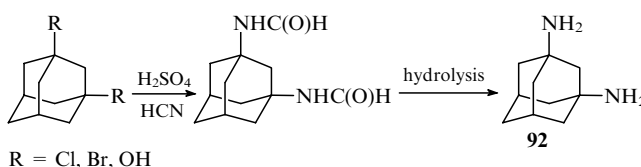
Alcohols react nicely with acetonitrile in the presence of H₂SO₄. Thus 3-ethyl-1-hydroxy-5,7-dimethyladamantane in the reaction with acetonitrile in sulfuric acid gives the corresponding acetamide **107**.²⁰⁰



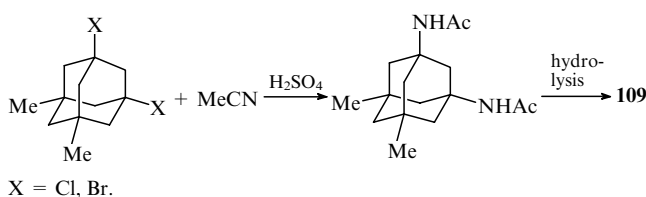
The preparation of 3-aminoadamantane-1-carboxylic acid (**108**) from adamantane-1-carboxylic acid (**73**) has been described.²⁰¹



Diamines are of particular importance for the chemistry of polymers. Methods for the synthesis of diaminoadamantanes have been reported in several patents.^{102, 202, 203} Thus 1,3-diaminoadamantane (**92**) was prepared by the ammonolysis of 1,3-diiodoadamantane. The reaction is carried out at 260 °C under a pressure above 1000 atm.¹⁰² 1,3-Diaminoadamantane (**92**) is also synthesised by the reactions of hydrocyanic acid with 1,3-dichloro-, 1,3-dibromo- or 1,3-dihydroxy-adamantanes in sulfuric acid.²⁰²

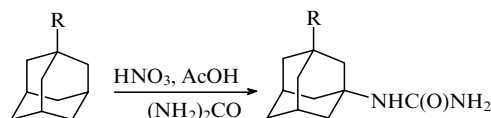


Diaminodimethyladamantane (**109**) is obtained by the reactions of 1,3-dichloro- and 1,3-dibromo-5,7-dimethyl-adamantanes with acetonitrile.²⁰³



Nitrates of the corresponding alcohols can also be used as starting compounds in the synthesis of aminoadamantanes. Thus 1-acetamidoadamantane is formed in the reaction of 1-adamantyl nitrate (**12**) with acetonitrile.²⁰⁴

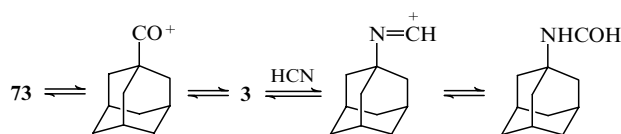
It was later shown that adamantane (**1**) and its homologues can be functionalised with urea in a mixture of acetic acid and HNO₃.²⁰⁵ The isolation of only the *N*-alkylation products of urea provides evidence in favour of the intermediacy of carbocations.



R = H, Me, Et.

Carboxylic acids can also serve as starting compounds in the synthesis of the corresponding aminoadamantanes.²⁰⁶ Thus adamantane-1-carboxylic acid (**73**) in 100% sulfuric acid produces the adamantyl cation (**3**), which then reacts with HCN or RCN

providing *N*-adamantylformamide or *N*-adamantylacetamide in 56% and 51% yields, respectively.



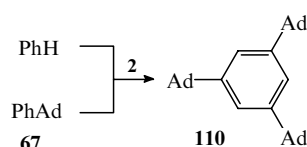
VII. Aryladamantanes

Halogenoadamantanes, adamantanol and their *O*-nitrates are used for the alkylation of aromatic compounds with adamantane.

The reaction of bromoadamantane (**2**) with benzene has been used by Stetter *et al.*¹⁵ to prepare phenyladamantane (**67**). The synthesis of some other adamantane-substituted aromatic compounds was also described.^{207, 208}

Either adamantane with several phenyl groups or benzene bearing up to three adamantyl substituents are formed in the reaction of 1-bromoadamantane (**2**) with benzene in the presence of Lewis acids, depending on the ratio of the reactants.^{209, 210}

1,3,5-Triadamantylbenzene (**110**) has been synthesised by the reaction of benzene or 1-phenyladamantane (**67**) with 1-bromoadamantane (**2**) in liquid SO₂ in the presence of AlCl₃.²¹⁰ A small amount of *p*-diadamantylbenzene was also isolated.



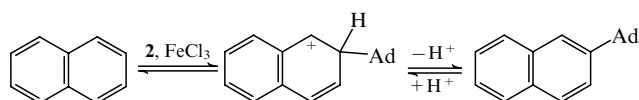
1,3,5-Triphenyladamantane and 1,3,5,7-tetraphenyladamantane have been synthesised by the reaction of 1-bromoadamantane (**2**) with benzene in the presence of *tert*-butyl bromide and a catalytic amount of AlCl₃.²⁰⁹

It was shown²¹¹ that the reaction of 1-bromoadamantane (**2**) with toluene in the presence of water resulted only in 4-(1-adamantyl)toluene, while a mixture of 4-(1-adamantyl)toluene and 3-(1-adamantyl)toluene was obtained in the presence of ZnCl₂ or FeCl₃.

1-Bromoadamantane (**2**) reacts also with naphthalene, 2-methylnaphthalene, biphenyl, anthracene, phenanthrene and fluorene to give the corresponding substituted adamantanes.²¹²

The reactions of naphthalene and its derivatives with 1-bromoadamantane (**2**) were the subject of several studies.^{213–219}

Thus the reaction of 1-bromoadamantane (**2**) with naphthalene in the presence of FeCl₃ at 60–140 °C leads to 2-(1-adamantyl)naphthalene. The second molecule of adamantane is introduced either in the 6- or 7-position.²¹⁵

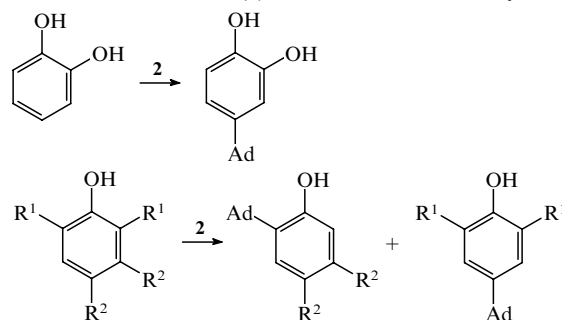


According to Stewart–Breigleb models of 1- and 2-adamantyl naphthalene, the molecule of the former is much more sterically hindered due to the spatial interaction of the hydrogen at the C(2) atom of the adamantane fragment and the H(8) atom of naphthalene.

Attempts to obtain 2-(1-adamantyl)naphthalene by the isomerisation of 1-(1-adamantyl)naphthalene were unsuccessful. 2-(1-Adamantyl)naphthalene has been synthesised by the reaction of 1-hydroxyadamantane (**4**) with naphthalene in the presence of phosphoric anhydride.²¹⁶ *N*-Acetyl-1-aminonaphthalene is alkylated under these conditions with hydroxyadamantane to give the corresponding 4-adamantyl-1-aminonaphthalene.²¹⁶

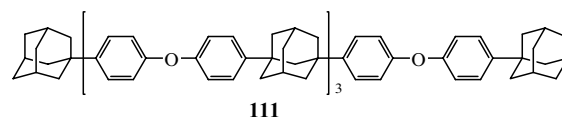
Phenol, anisole, catechol, 2,6- and 3,4-dimethylphenols, *o*-, *m*- and *p*-cresols, diphenyl ether and others were also reacted with 1-bromoadamantane (**2**).^{220–227}

Thus phenol, 2,6- and 3,4-dimethylphenols and catechol react with 1-bromoadamantane (**2**) in the absence of a catalyst.²²²

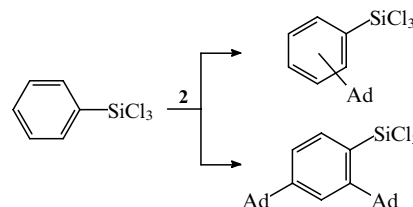


R¹, R² = Me; R¹ = H, Me.

2,6-Di(*tert*-butyl)phenol and 2-methoxyphenol react with 1-bromoadamantane (**2**) at 130–140 °C to form 4-adamantylphenols. The alkylation of *m*-aminophenol with 1-bromoadamantane (**2**) leads to adamantane-substituted *m*-aminophenol.²²³ 4,4'-Diadamantyl diphenyl ether is formed upon heating of 1-bromoadamantane (**2**) with diphenyl ether in carbon disulfide in the presence of aluminium chloride. In the presence of zinc chloride and at elevated temperature, the oligomer **111** becomes the major product.^{207, 223}

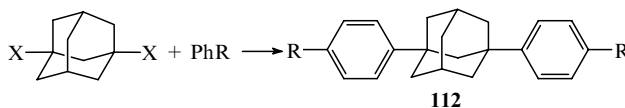


The possibility of alkylation of phenylchlorosilanes with 1-bromoadamantane (**2**) has been demonstrated.²²⁸



It should be noted that the reaction of 1-bromoadamantane (**2**) with methyl(phenyl)dichlorosilane results in a mixture of mono- and polyadamantylbenzenes.²²⁸

1,3-Dichloro- and 1,3-dibromo-adamantanes react with aryl(alkyl)chlorosilanes at 160–200 °C in the presence of ZnCl₂ to give 1,3-di(alkylchlorosilylalkyl)phenyladamantanes **112**.²²⁹ 1-(Alkylchlorosilylalkyl)phenyladamantanes are also formed in appreciable yields.

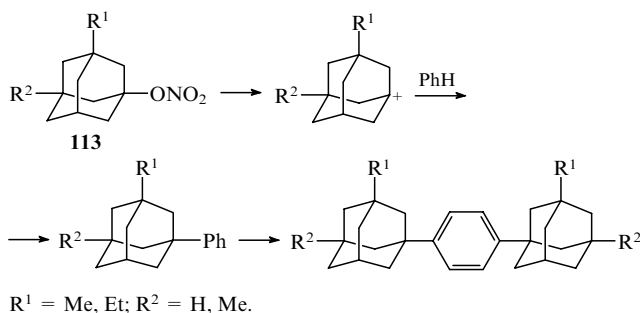


X = Cl, Br; R = CH₂SiMe₃, C₂H₄SiMe₃, C₂H₄SiMeCl₂, C₂H₄SiCl₃, CH₂SiMe₂Cl, CH₂SiCHCl₂, CH₂SiCl₃.

1,3-Dibromoadamantane was found to be more reactive than its 1,3-dichloro-analogue and aryl(alkyl)chlorosilanes can be arranged according to their reactivity in the following order: PhCH₂SiMe₃ > PhC₂H₄SiMe₃ > PhC₂H₄SiMeCl₂ > PhC₂H₄SiCl₃ > PhCH₂SiCH₂Cl > PhCH₂SiMeCl₂ > PhCH₂SiCl₃.

Mono- (**12**) and dinitrate **13** were also used as the alkylating reagents. The nitrate **12** readily reacts with benzene, toluene, ethylbenzene, *p*- and *m*-xylenes and anisole yielding the corresponding mono- and di-substituted adamantanes.²³⁰ The preparation of 1,3-diaryladamantanes from the dinitrate **13** was also described.²³⁰

The nitrates **113** were used in the synthesis of diadamantyl-substituted arenes.¹⁸⁰

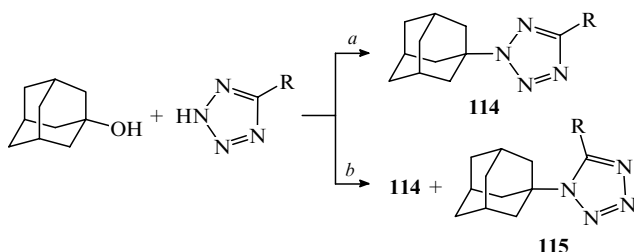


Reactions of 1-adamantyl nitrate (**12**) with such heterocyclic compounds as thiophene, 2-nitrothiophene, thiophene-2-carboxylic acid, furan and 2-furoic acid have been described.²³¹ The alkylation was carried out in concentrated sulfuric acid at -5°C ; the corresponding 1-hetaryladamantanes were obtained in 40%–60% yields.

Data concerning the relative reactivities of 1-bromoadamantane (**2**), 1-hydroxyadamantane (**4**) and its nitrate **12** in the reaction with isopropylbenzene have been reported.²³² The highest yield of *p*-adamantylisopropylbenzene was obtained from adamantyl nitrate.

In recent years, an efficient procedure for the introduction of the adamantyl substituent into the aromatic ring of crown ethers by their direct alkylation with hydroxyadamantane in the presence of boron trifluoride diethyl etherate as a catalyst has been developed.²³³

1-Hydroxyadamantane (**4**) has been used as an alkylating reagent for 1,2,4-triazoles and 5-R-tetrazoles.^{234–236} Its reactions with tetrazoles in 85% sulfuric acid gave the corresponding 2-(1-adamantyl)tetrazoles **114**, while a mixture of 2-(1-adamantyl)tetrazoles **114** and 1-(1-adamantyl)tetrazoles **115** was formed in 94% sulfuric acid.



(a) 85% H_2SO_4 ; (b) 94% H_2SO_4 .

The studies of the reactions of adamantanes in electrophilic media have expanded the general concept of the mechanism of C–H bond activation and made it possible to develop preparative methods for the synthesis of halogen-, hydroxy- and nitroxy-substituted adamantanes. The latter are of particular interest as starting materials. Among the methods of adamantane functionalisation, the reactions with urethanes, amides and nitriles in nitric acid or its mixtures with AcOH or Ac_2O are worth especial attention. Some of these reactions have formed the basis for technological processes in the manufacture of pharmaceuticals Remantadinum and Mydantan.

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Non-isothermal regimes and chemical control of branching-chain processes

V V Azatyan

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Abstract. Non-isothermal modes of branching-chain reactions are analysed. Characteristic features of these reactions caused by the simultaneous action of the reaction chain avalanche and self-heating are considered in terms of concepts of the modern theory. New data are presented indicating that chain branching is the predominant factor in gas combustion processes not only at very low pressures, as it was assumed earlier, but also at atmospheric and higher pressures. The specific character of the temperature dependence of the rate of chain reactions and data dealing with the discovery of a special chain combustion mode, chain thermal explosion, are considered. The efficiency of chemical control of chain combustion in any mode including explosion, flame propagation and its transition to detonation by virtue of highly efficient non-corrosive inhibitors is demonstrated. The bibliography includes 135 references.

I. Introduction

The significance of the discovery of branching-chain processes (BCP) and chain combustion^{1–3} for the development of chemistry is well known. A special place in the variety of the kinetic features of this frequently encountered class of reaction belongs to the combustion mode, which differs fundamentally from the 'purely thermal' combustion both in phenomenological features and the factors determining this mode. In recent years, it was shown that the branching-chain mechanism (BCM) predominates in most gas combustion processes not only at very low pressures, as had been considered until recently, but also at atmospheric pressure and at higher pressures. Combustion in air of virtually any hydrogen-containing compound (including hydrocarbon fuel), inorganic gaseous hydrides, and many pyrophoric compounds containing

no hydrogen follows a BCM. Branching-chain decomposition of, for example, nitrogen trichloride is known.³

Until recently, the theory of BCP has considered only isothermal chain combustion processes which take place at pressures factors of tens or hundreds lower than atmospheric pressure, mainly in the vicinity of the first ignition limit (P_1) (Fig. 1). Under isothermal conditions, no self-heating or convection is involved; therefore, chemical mechanisms play the crucial role. Thus, this approach proved fruitful in identification of the chemical factors and elucidation of their role in chain combustion. However, chain combustion processes at pressures markedly higher than P_1 are exothermic and proceed at high rates; hence, they are accompanied by a substantial increase in the temperature of the reaction mixture. The combined influence of two fundamentally different factors, the avalanche multiplication of the intermediate active species and self-heating, both accelerating the process, determines the specific character of virtually all features of branching-chain combustion, which differ fundamentally from those of 'purely thermal' combustion caused by self-heating and heat transfer. Unlike the theory of BCP, the scope of combustion

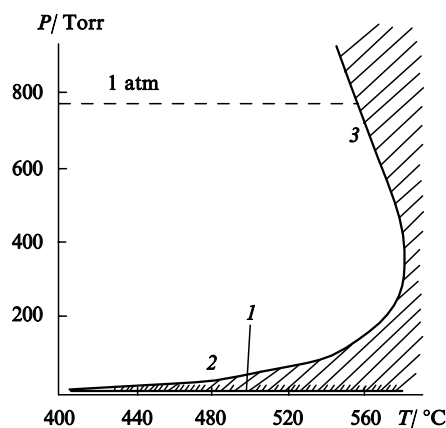


Figure 1. Region of self-ignition of a stoichiometric mixture of H_2 with O_2 in a reactor 7.4 cm in diameter with the surface coated with KCl.^{3,6} (1), (2) and (3) are the first, second and third ignition limits, respectively.

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theory has actually been limited until recently to the latter type of combustion, this chemical process being represented as a simple one-step or, rarely, two-step reaction. Only quite recently was systematic investigation into the specific features of non-isothermal BCP started.

This review covers the regularities of BCP under non-isothermal conditions, brought about by self-heating of the reacting gas, and the role of chain mechanism over a wide range of pressures including the pressure region important for practical purposes. The data presented bring to light the governing role of chain mechanism under atmospheric and higher pressures in any mode of gas combustion; they demonstrate the specific pattern of the temperature variation of the BCP rate, disclose the chain thermal explosion mode and reveal the important role of BCM in the origination of detonation. Efficient methods and means for the chemical control of ignition, developed combustion, explosion and deflagration-to-detonation transition are described. New aspects of the relevant sections of the combustion theory and chemical kinetics are considered.

II. The main differences between thermal and chain ignition

Ignition and developing combustion are progressively self-accelerated chemical reactions. The kinetics of these reactions are characterised by not only increasing rates but also increasing accelerations (see, for example, Refs 3–5):

$$\frac{dW}{dt} > 0, \quad \frac{d^2W}{dt^2} > 0, \quad (1)$$

where W is the reaction rate and t is time.

Among other factors, ignition and combustion are governed by the positive feedback between the reaction rate and self-heating. Thermal ignition, caused by this factor alone, occurs if the rate of heat evolution (q_+) prevails over the rate of heat removal (q_-) and if the increase in the heat evolution rate upon rise of the temperature is more pronounced than the increase in the heat removal rate, *i.e.* the following conditions should be satisfied simultaneously:^{3–5}

$$q_+ \geq q_-, \quad (2)$$

$$\frac{dq_+}{dT} \geq \frac{dq_-}{dT}, \quad (3)$$

where

$$q_+ = WQ, \quad (4)$$

Q is the heat of the reaction,

$$q_- = \frac{\alpha S(T - T_0)}{V}, \quad (5)$$

α is the heat removal coefficient, S and V are the surface area and the volume of the reaction chamber, respectively, and $(T - T_0)$ is the difference between the temperatures of the reaction mixture and the reactor walls.^{3–6} The equality signs in relations (2) and (3) refer to the critical condition of thermal ignition.

In the theory of combustion, a chemical process is usually represented as a simple reaction, the rate of which depends on the temperature according to the Arrhenius law. Since the reaction rate (and hence, the rate of heat evolution), unlike the rate of heat removal, increase non-linearly with temperature, inequality (3) starts to be fulfilled, in addition to relation (2), after a definite temperature has been attained during heating. Therefore, accumulation of thermal energy in the reaction system becomes progressive, which results in an accelerated rise in temperature. Correspondingly, the chemical process becomes progressively self-accelerated, *i.e.* thermal ignition takes place.

Branching-chain ignition, unlike the thermal one, is caused by avalanche-like multiplication of active intermediate products — free atoms, radicals and, in some cases, excited species — upon

fast reactions with the starting reactants and with one another.^{1–8} This type of multiplication takes place if the rate of generation of active species, chain carriers (CC), is greater than the rate of their decay. The rate of BCP is

$$W = -\frac{d[B]}{dt} = w_0 + k_b n[B], \quad (6)$$

where $[B]$ and n are the concentrations of the starting reactant and the CC, respectively, w_0 is the rate of chain initiation, *i.e.* the rate of appearance of CC in reactions involving only the starting molecules, and k_b is the effective rate constant for chain branching (the rate-determining step of the process).^{1,3,8}

The change in the CC concentration is described by the equation

$$\frac{dn}{dt} = w_0 + (f - g)n, \quad (7)$$

where f and g are the branching and chain termination rates for unit concentration of CC (specific rates with respect to CC), equal to

$$f = 2k_b[B], \quad (8)$$

$$g = k_{het} + k_{hom}[B][M] \quad (9)$$

(k_{het} and k_{hom} are the effective rate constants for the heterogeneous and termolecular termination, respectively, and $[M]$ is the concentration of the gas mixture).^{1–3} The difference $(f - g)$ is often denoted by φ .

It follows from Eqn (6) that at initial stages of the process, when the decrease in the concentration of the starting compounds is still insignificant but the w_0 value can already be neglected, the following relations hold:

$$W \sim n,$$

$$\frac{dW}{dt} \sim \frac{dn}{dt},$$

$$\frac{d^2W}{dt^2} \sim \frac{d^2n}{dt^2} \quad (10)$$

because the relative change in the concentration $[B]$ is much smaller than the relative change in n .

It is obvious that for $f > g$, the concentration of CC increases with time with progressive self-acceleration, *i.e.*

$$\frac{d^2n}{dt^2} > 0. \quad (11)$$

The same follows from Eqn (7). Correspondingly, the rate of variation of the concentrations of the starting compounds in their reactions with active intermediate species, *i.e.* the rate of the process as a whole, increases progressively. This is indicated by relation (10) provided that inequality (11) holds. The attainment of a high reaction rate over a short period of time as a result of progressive self-acceleration is ignition. Thus, chain self-acceleration is caused by the positive feedback between the reaction rate and the CC concentration [see Eqns (6) and (7)]. Self-acceleration passes to the chain ignition mode in the case where multiplication of active intermediate species becomes avalanche-like because the multiplication rate exceeds the decay rate. Self-heating is not necessary for chain ignition. During progressive self-acceleration, high reaction rates can be attained; being exothermic, the reaction is accompanied by substantial light and heat evolution when the reactant concentrations are sizeable. This is a consequence of chain ignition alone.

It can be seen from Eqn (7) that, when $f < g$, the process occurs from the very beginning in a qualitatively different kinetic mode in which the increase in n (and, hence, in W) is retarded

$$\frac{d^2n}{dt^2} < 0.$$

In this mode, as the concentration of CC approaches the steady state value

$$n_{st} = \frac{w_0}{g - f}$$

the right-hand side of Eqn (7) and, correspondingly, dn/dt diminish and approach zero, which implies a complete cessation of increase in n and W . Since the rate of reaction between valence-saturated compounds w_0 is very low, it follows from the last-mentioned expression that under conditions where chain termination substantially prevails over chain branching (*i.e.* the g value noticeably exceeds f), the steady-state values of n and W are also extremely low.

Thus, the relation

$$f \geq g \quad (12)$$

is the condition for chain ignition. The equality sign determines the critical condition for transition from the steady-state mode, in which the reaction rate is extremely low, to the chain ignition and combustion mode.

For initial stages, when the variation of the f and g values during an isothermal reaction can yet be neglected, integration of Eqn (7) gives ^{1,3,7}

$$W = \frac{w_0}{f - g} \{ [\exp(f - g)t] - 1 \}. \quad (13)$$

It can be seen from this expression [see also Eqn (7)] that at $f > g$, the rate of the process increases with progressive self-acceleration, whereas at $f < g$, the increase in the reaction rate becomes less pronounced until a steady-state rate is attained.

It is noteworthy that, to consider the f and g values invariant with time, it is not enough to assume the process to be isothermal and neglect only the consumption of the initial compounds, as has been done until recently (see below). Heterogeneous propagation of reaction chains is not taken into account in Eqn (13) either.⁹

Since f and g depend on the initial reactant concentrations, temperature and the reactor geometry in different ways, the ratio of these parameters is governed by the reaction conditions. It has been found ^{1-3,6} that the specific patterns of the dependence of f and g on $[B]$ and $[M]$ and on the temperature stipulate the existence of two limiting pressures of ignition, which are both much lower than atmospheric pressure. For most combustible gases, these limiting values coalesce as the temperature diminishes, thus forming an ignition peninsula ^{1-3,6-9} (see Fig. 1).

If the chains branch upon reactions of CC not only with the initial molecules but also with one another (non-linear branching), the ignition condition can be written as follows:

$$f \geq g - 2(w_0 k_+)^{1/2}, \quad (14)$$

where k_+ is the effective rate constant for non-linear branching.³ When there is no external source of atoms or radicals, the second term in the right-hand part of the equation is much smaller than the first one and the ignition is actually determined by relation (12). Therefore, expression (12) is used in this paper, although the discussion equally refers to expression (14).

If the quadratic chain termination (*e.g.*, recombination of the CC) is taken into account in addition to the linear chain termination, characterised by the parameter g , the rate of variation of n in the one-center consideration can be written as

$$\frac{dn}{dt} = w_0 + (f - g)n - k_- n^2, \quad (15)$$

where k_- is the rate constant for the quadratic termination.

The solutions of Eqn (7) at $f > g$ are unstable (Lyapunov instability), while the solutions of non-linear equation (15) are stable at any ratio of f to g (when $f > g$, the stability is non-asymptotic). Proceeding from this fact, some researchers (see, for example Refs 10–15) who, unlike some other authors,¹⁻⁹ define ignition as a kinetic mode described by only unstable solutions of equations, concluded that chain self-ignition requires self-heating, allowing for which accounts for the instability of the solutions.

Thus they disclaimed one of the most important statements of the BCP theory, *viz.* the assumption that self-heating is not obligatory for chain self-ignition to occur. According to this view, it was proposed to elucidate the ignition conditions resorting to analysis of the character of solutions of the set of kinetic equations together with the heat balance equation and regarding the ignition limit as the condition of coalescence of stable and unstable singular points (bifurcation) on the concentration–temperature phase plane. However, this definition of ignition and this approach to the determination of its limit do not correspond to the essence of this phenomenon and, therefore, contradict experimental data. Experiments show that chain ignition is possible even when the reaction system is monotonically cooled provided that inequality (12) holds. This can be illustrated in relation to a model BCP — combustion of H_2 with O_2 above the first ignition limit.¹⁶ When the pressure is low (~ 0.1 Torr) and only slightly exceeds P_1 (by 5%–8%), burning lasts for 10–15 s after an induction period. In addition to the monotonic decrease in the pressure, caused by the reduction of the number of gas moles in the reaction, the specially arranged monotonic decrease in the temperature immediately after admission of the mixture in the reactor can also be observed during this period. Ignition was detected as the appearance of chemiluminescence after the induction period and the progressive acceleration of the consumption of the reactants.

It has been shown ¹⁷⁻¹⁹ that equations such as (15) (or, in a more general case, a set of equations with negative quadratic terms corresponding to the concentrations of CC), although all of their solutions are stable, describe two qualitatively different isothermal modes of BCP: progressive self-acceleration ($d^2W/dt^2 > 0$) up to high rates, *i.e.* ignition, and the extremely slow reaction with establishment of a steady-state rate ($d^2W/dt^2 < 0$). It was also demonstrated that transition from one isothermal mode to the other following variation of the initial conditions has a critical character and is determined by the equality

$$f = g \quad (16)$$

both with and without allowance for the quadratic termination. If the rate constants appearing in f and g are known, the critical conditions of ignition, for example, the first and second limits calculated from expression (16) taking account of (8) and (9), coincide with the experimental values (*e.g.*, see Refs 3, 8, 20–23). This confirms once again the statement that self-heating is not a necessary condition for chain ignition.

Thus, when the notion of ignition is defined correctly, kinetic equations permit one to describe its origin without self-heating. Strict mathematical analysis of differential equations of ignition and combustion in terms of the above definition of this phenomenon as a kinetic mode characterised by progressive self-acceleration has been carried out.^{24,25} The quantitative theory of the first and second ignition limits underlie precision methods for determination of rate constants.^{20,23,26-32} When reactions (most of all, bimolecular) of CC with one another and heterogeneous development of reaction chains are taken into account, the theory also describes quantitatively the kinetics of isothermal chain combustion near the first limit, isothermal critical phenomena within the ignition region, and hystereses of various kinetic characteristics over a broad pressure region.^{9,33-36}

Azatyán³⁷ has considered the difference between thermal and chain self-acceleration from the molecular-kinetic viewpoint, *i.e.* in terms of the mechanism assuming an increase in the number of species able to overcome the energy barrier to the reaction during the process (Fig. 2). The values marked on the abscissa axis are activation energies for the reactions of the initial molecules with each other (E_1) and with active intermediate species (E_2). The areas under the Boltzmann curves of the distribution of species over energy, to the right of E_1 and E_2 correspond to the number of the initial molecules whose energy exceeds the energy needed for them to enter into the reactions. As the temperature increases, the distribution curve shifts to the right (see Fig. 2); thus, the number

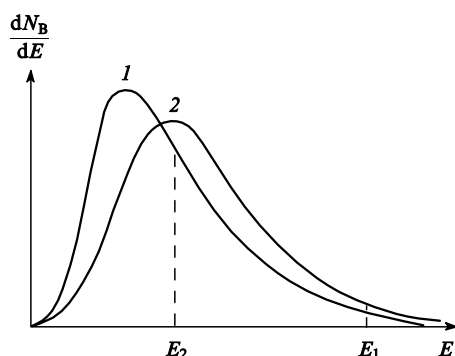


Figure 2. Equilibrium energy distribution of the initial molecules at temperatures T_1 (1) and T_2 (2) ($T_1 < T_2$); E_1 and E_2 are the activation energies of reactions of the initial molecules with one another and with chain carriers, respectively.

of molecules of the initial compound able to overcome the energy barriers E_1 and E_2 increases. In the case of BCP, the number of species able to overcome the energy barrier and enter into the reaction increases even if no rise in temperature occurs in the reaction mixture (the distribution function does not shift towards higher energies). This is due to multiplication of free atoms and radicals in their reactions with the starting compounds, which require overcoming the barrier E_2 , which is much lower than E_1 . The area under the distribution curve on the right of E_2 (the fraction of initial molecules capable of reacting with free atoms and radicals) is quite large even at relatively low temperatures. Since reactions of atoms and radicals with the initial molecules not only give final products but also result in regeneration and multiplication of these atoms and molecules, the process self-accelerates even without self-heating. If $f > g$, progressive self-acceleration is observed, *i.e.* ignition takes place. Thus, chain ignition and combustion are due to chemical factors; they differ fundamentally from the self-heating factors and can alone ensure the progress of the reaction in this mode.

In the chain combustion accompanied by self-heating, the distribution curve also shifts towards higher temperatures; therefore, the number of species capable of reacting increases due not only to the chain avalanche but also to an additional increase in the number of reactive substances (both intermediate and initial), caused by the rise in temperature. This enhances additionally the chain avalanche. The specific features of combustion caused by the joint effect of the chain avalanche and self-heating are considered in Sections V and VIII. When the initial concentrations of reactants increase above the region of the first limit, self-heating which accompanies chain combustion becomes more and more pronounced, its influence on chain combustion being largely determined by the specific character of energy liberation during these processes.

Thus, the phenomena of chain and thermal ignition are caused by fundamentally different factors; the processes determining the critical conditions for their origination and the mechanisms of self-acceleration are also dissimilar. Self-heating is not a necessary condition for chain ignition.

III. Specific features of the energetics of branching-chain processes

In simple exothermic reactions, the energy equal to the difference between the chemical energies of the initial and final components is converted only to the kinetic energy of particles, *i.e.* it is liberated as heat. On the contrary, the greater part of the energy evolved during the developing BCP combustion is converted into chemical energy of active intermediates. This is a crucial factor determining the kinetic features of BCP.

Table 1. Energy characteristics of the elementary reactions of a chain cycle.

Number of step	Reaction	ΔH /kJ mol ⁻¹	E /kJ mol ⁻¹
I	$\text{H} + \text{O}_2 = \text{OH} + \text{O}$	66.9	69.9
II	$\text{OH} + \text{H}_2 = \text{H}_2\text{O} + \text{H}$	-60.7	21.5
III	$\text{O} + \text{H}_2 = \text{OH} + \text{H}$	8.4	43.5
II	$\text{OH} + \text{H}_2 = \text{H}_2\text{O} + \text{H}$	-60.7	21.5
A	$2\text{H}_2 + \text{O}_2 + \text{H}_2 = 2\text{H}_2\text{O} + 2\text{H}$	-46.1	

Let us consider the liberation of energy in a developing chain combustion over one chain cycle[†] for the model reaction of H_2 with O_2 using a procedure similar to that used in a previous study.³ In this particular case, a chain cycle consists of the elementary reactions presented in Table 1; the Table also presents the respective changes in the enthalpy (ΔH) and the activation energies (E). The ΔH values were calculated from thermochemical data;³⁸ the E values correspond to the recommendations given in the literature.^{39,40}

It can be seen that each chain cycle yields two additional chain carriers, free hydrogen atoms, in addition to two molecules of the final product. If the overall reaction



followed a molecular pathway, it would give off 477.8 kJ mol⁻¹ of heat. Meanwhile, the real process A, which follows a BCM, affords only 46.1 kJ mol⁻¹ per branching-chain cycle, *i.e.* less than 10% of the heat of the overall process B.

As noted above, in conventional exothermic reactions, the difference between the chemical energies of the starting compounds and the reaction products is converted almost entirely into heat (to within a very small fraction of energy dissipated as radiation). Conversely, in a developing branching-chain combustion process, a substantial portion of the difference between the energies of the initial and final components is spent for the formation of free atoms and radicals, *i.e.* it is accumulated in the system as chemical energy of unpaired spins. This type of energy is the most rational for self-acceleration of the process not only due to the very high chemical reactivity of species with a free valence but also because they can be regenerated in reactions with the initial valence-saturated reagents. Indeed, the fraction of heat evolved during combustion and used to increase the number of the initial molecules able to overcome the energy barrier to a molecular reaction is extremely low because the activation energy is high. The rest of the thermal energy is dissipated or wasted in heating the final products. Meanwhile, the reactions of CC characterised by low energy barriers involve a much greater percentage of the initial molecules; in addition the free-valence energy (in the form of high reactivity) is actually transferred as a baton to the newly formed atoms and radicals and even provides for their multiplication. Only when the content of the initial reactants in the gas mixture decreases and the final stage of combustion, in which recombination becomes more significant, is approached, does energy evolve as heat. Of course, at the initial stages of the process when the content of reactants is still high, chain carriers also recombine partially, simultaneously with their participation in chain propagation (see Table 1, steps I–III). The role of chain termination by the route representing back reaction with respect to step I is especially significant in the combustion of hydrogen-containing compounds even at low pressures.⁹

The percentage of energy evolved in the chain termination, which ensures self-heating of the reaction mixture, depends on the rate of heterogeneous recombination, the heat of which is

[†] A chain cycle is the repeating set of several elementary reactions of CC including the CC regeneration.^{3,8,31}

extracted by the reactor walls. For example, at very low pressures (near the first limit), chain termination is heterogeneous, the energy evolved being almost entirely absorbed by the reactor walls. In the above example of energy evolution in a chain cycle, only the indicated $\sim 10\%$ of the energy of overall process B is evolved in the bulk of the gas phase. At low pressures, virtually all the heat evolved is extracted by the reactor walls through conductive heat transfer, because the duration of combustion is hundreds or thousands times longer than the characteristic time of heat removal. This accounts for the fact that virtually no self-heating is observed near the first limit.

The numbers of free atoms and radicals diminish upon recombination; nevertheless, the concentrations of these species in the area of branching-chain combustion are many orders of magnitudes higher than the thermodynamically equilibrium values and even than those concentrations which would exist without chain branching. This is confirmed by direct measurements of concentrations of atoms and radicals during chain combustion processes of various types (see, for example, Refs 41–47).

The overall reaction A of a chain cycle shows that only one third of the consumed dihydrogen is converted into atomic hydrogen. The rest of dihydrogen is used in the formation of H_2O . It is due to this fact that the free energy (G) decreases to a degree which permits accumulation of atomic hydrogen (and other CC), bringing about a local increase in G . The overall change in the free energy G is negative; therefore, combustion proceeds spontaneously. In view of the foregoing, it becomes clear that the statements that half the dihydrogen in an oxygen–hydrogen flame is converted into atomic hydrogen, which can be found in the literature (see, for example, Ref. 48), are at variance with the thermodynamic prohibition; indeed, realisation of this process would require absorption of a large amount of heat ($\Delta H \approx 200$ kJ per mole of O_2) and a nearly equal increase in the free energy (the entropy change is insignificant in this case). This means that such a process cannot occur spontaneously. It is also obvious that the number of free hydrogen atoms cannot exceed the number of H_2O molecules formed, even if they did not recombine at all (this can also be seen from the final stoichiometry of the chain cycle). Therefore, concentrations of hydrogen atoms (such as those presented in Fig. 136 in a monograph⁴¹) much greater than the total concentration of H_2O in the flames of stoichiometric (or enriched in the combustible component) H_2 – O_2 mixtures are impracticable.

Since the concentrations of excited species in branching-chain combustion are much higher than the equilibrium values, the radiation of such flame is much more intense than that in a non-chain combustion. In some processes, chain branching involves species in not only vibrationally^{49–55} but also electronically^{53, 54} excited states. The inverted population of energy levels corresponding to a branching-chain mechanism is used in chemical lasers.^{56–58}

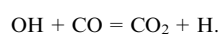
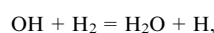
Thus, high concentrations and high reactivity of reactive intermediate species as well as their ability to be regenerated and multiplied in reactions with the initial compounds determine the advantage of the BCM over a non-chain mechanism. This advantage is realised not only at low pressures.

It has been noted in studies,^{59, 60} devoted to the elucidation of the mutual influence of chain branching and self-heating, that, when $f > g$, the W , dn/dt and dW/dt values are related to n through positive feedback [see also Eqns (7) and (10)]. The branching rate constant (k_b), which is related to the kinetic coefficient f [see Eqn (8)], increases with temperature according to the Arrhenius law. The temperature dependence of g is much weaker than that for f . Moreover, as noted above, in the case of termolecular chain termination, g decreases with increase in temperature. Therefore, an increase in temperature sharply increases the difference $f - g$, which appears in Eqn (7) as a positive factor in n ; thus, the positive feedback of n with dn/dt , W , and dW/dt values is enhanced. The progressive growth of W

and dW/dt brings about a similar progressive increase in the rate of heat evolution (q_+) and a rise in temperature. Thus, self-heating intensifies the chain avalanche and the process acceleration, and the enhancing chain avalanche, in turn, accelerates self-heating. This non-additive combined action of chain branching and self-heating accounts for the specific character of non-isothermal BCP including the specific temperature dependence of the chain combustion rate.

IV. Temperature dependence of the specific rate of branching-chain processes

The kinetic features of a BCP have been considered in substantially fewer studies than the first and second ignition limits. The temperature dependence of the BCP rate has received even less attention. On the basis of experimental data referring to very low pressures, it has been found⁴¹ that the rates of combustion of H_2 and CO in oxygen are proportional to the rates of the steps



Relying on this fact, it was claimed that temperature variations of these and some other branching-chain processes ‘should evidently obey the Arrhenius law’. In another study,⁵⁵ this statement has been extended and it has been suggested that the rates of the rate-determining step and the chain process as a whole follow identical patterns of temperature variation. The fact that the chain propagation reactions (including the rate-determining step) constitute a branching chain is, however, ignored. This means that the temperature dependence of the reaction rate is determined not only by the temperature dependences of the rate constants of these steps themselves but, to a larger extent, by the temperature variation of the concentrations of chain carriers. Therefore, attempts to describe the temperature variation of the BCP rate by an Arrhenius function give different activation energies for the same chain process (depending on the process conditions);^{61–66} in addition, the resulting values are usually very high (in some cases, > 600 – 700 kJ mol^{−1}). This is not only much greater than the activation energy values typical of reactions involving free atoms or radicals but also exceeds the activation energies of reactions of the initial valence-saturated molecules with one another and even the energies needed to cleave the bonds in these molecules. Obviously, these ‘activation energies’ do not correspond to the real energy barriers to the reactions and only point to the fact that the temperature variation of the specific rate of a BCP deviates crucially from the Arrhenius law. This also follows from the unnaturally great magnitudes of ‘pre-exponential factors’ for the rate constants (see, for example, Refs 61, 65).

Vedenev *et al.*,¹⁵ who considered the role of self-heating in the ignition of H_2 and O_2 , transformed the exponential quantity of the Arrhenius function for the rate constant using the known⁵ ‘exponential quantity expansion’ technique. Subsequently, the resulting new function was expanded into the Taylor series with respect to the temperature, the series being restricted to the linear term. Meanwhile, the nonlinear character of the temperature dependence of the reaction rate is the most important feature of combustion; when it is neglected, the notion of combustion itself loses its meaning (see, for example, Ref. 5).

The temperature dependence of the BCP rate has been presented^{1, 7, 41} by the following expression:

$$W = \frac{A \exp(-E/RT)}{1 - B \exp(-E_1/RT)}, \quad (17)$$

where A and B are temperature-independent factors and E and E_1 are effective activation energies. However, this formula is inapplicable to a real process. Indeed, if $B \exp(-E_1/RT) > 1$, then $W < 0$, which has no physical meaning. In addition, at a particular finite temperature corresponding to the equality

$$B \exp\left(-\frac{E_1}{RT}\right) = 1,$$

the rate of the process becomes infinitely great, even at the beginning of the reaction, which has no physical meaning either.

The drawbacks of Eqn (17) are due to the fact that it has been derived using the following formula for the length of branching reaction chains (v_b):^{1,3,7}

$$v_b = \frac{\alpha}{\beta - \delta}, \quad (18)$$

where α , β and δ are the probabilities of chain propagation, termination and branching, equal to the ratio of the effective rate of the corresponding step to the sum of the rates of all these steps.

When deriving Eqn (17), Semenov^{1,7} substituted the v_b value expressed by Eqn (18) into the known relation

$$W = w_0 v, \quad (19)$$

where v is the chain length, and also took into account the temperature dependence of the rate constants included in the α , β and δ values.

However, we have shown⁵⁹ that Eqn (18), which has been used also in other studies,^{41,65,67} does not correspond to the real process. For example, for $\delta > \beta$, *i.e.* under conditions corresponding to ignition and combustion, it gives inevitably a negative value for the chain length. The $\beta - \delta$ difference, appearing in the expression for the flame propagation rate, has resulted (when $\delta > \beta$) in imaginary values for this rate.⁶⁷

In our study,⁵⁹ a fundamentally different expression for v_b has been proposed

$$v_b = \frac{(\alpha/\beta)[(\alpha\delta h/\beta)^m - 1]}{\alpha\delta h/\beta - 1}. \quad (20)$$

Here h is the average number of new branches for one branching step,

$$m = k_b[B]\alpha_1\delta t, \quad (21)$$

where α_1 is the probability that at least two of the active sites formed in the multiplication step enter into chain continuation reactions.

Unlike expression (18), Eqn (20) affords real, positive values of the chain length for any ratio of the branching and termination probabilities. This equation also shows that v_b (the length of the growing chain) increases with time, the kinetics of this increase being dependent on the ratio of probabilities of the reaction chain branching and termination, which is consistent with the essence of this phenomenon. Under conditions where the inequality $\alpha\delta h > \beta$ holds, the increase in v_b and, according to Eqn (19), also the increase in W proceed with progressive acceleration up to fairly high values. However, when $\alpha\delta h < \beta$, the increase in the v_b and W values slows down until steady-state values are attained. The critical point for the transition from one kinetic mode to the other is determined by the equality:

$$h\alpha\delta = \beta. \quad (22)$$

It can be seen from Eqn (21) that the exponential quantity m includes the k_b value, which is an Arrhenius function of temperature. Therefore, in the combustion mode, *i.e.* for $\alpha\delta h > \beta$, the temperature dependences of v_b and W_b contain a positive Boltzmann factor in the exponential quantity (the double exponent law) and, thus, they differ fundamentally from the Arrhenius law.

When deriving the analytical expression for the variation of the BCP rate as a function of temperature,⁵⁹ we took into account the fact that the contribution of w_0 to the rate of variation of CC concentrations in a propagating combustion process is insignificant, except for the very early steps of the process. This provides grounds for neglecting the w_0 value in Eqns (6) and (7) for the time

$t > t_0 \approx 2.5/\varphi$. Integration of the equation obtained in this way from Eqn (7)

$$\frac{dn}{dt} = (f - g)n, \quad (23)$$

with allowance for the f value [see Eqn (8)] and for the temperature dependence of k_b , gave the following expression for the temperature variation of the concentration of chain carriers:⁵⁹

$$n = n_0 \exp\left\{\int_{t_0}^t \left[f_0 \exp\left(-\frac{E_b}{RT}\right) - g\right] dt\right\}. \quad (24)$$

Here n_0 is the concentration of chain carriers at t_0 , E_b is the activation energy of branching, $f_0 = 2k_b^0[B]_0$, where k_b^0 is the pre-exponential factor for the constant k_b , $[B]_0$ is the initial concentration of the reactant B participating in the chain branching step.

By substituting this expression into the rate equation

$$W = k_b n_0, \quad (25)$$

we obtain the temperature dependence of the specific rate⁵⁹

$$\frac{W}{[B]_0} = k_b n_0 \left\{ \exp \int_{t_0}^t \left[f_0 \exp\left(-\frac{E_b}{RT}\right) - g \right] dt \right\}. \quad (26)$$

The rate constants for chain termination vary with temperature to an appreciably lesser extent than the rate constant for branching; therefore, the temperature dependence of the rate of the process is mainly determined by the first term in the square brackets.

Thus, when the difference $\varphi = f - g$ is positive, *i.e.* in the chain combustion mode, the increase in the specific rate of BCP with temperature is due not only to the increase in k_b but also (to a greater extent) to the substantial increase in the n value, the temperature dependence of which [see Eqns (24) and (26)] contains this rate constant and its Boltzmann factor in the positive exponential quantity.

This type of dependence was verified experimentally in relation to a model BCP, namely combustion of H_2 with O_2 near the first ignition limit.⁶⁰ The reaction was carried out at several temperatures, which were maintained in each experiment using a thermostat. The high-speed recording of pressure, chemiluminescence and temperature were carried out. Due to the low pressures of the mixture, exceeding only slightly the pressure of the first ignition limit P_1 , to heterogeneous chain termination, which ensured removal of the energy of recombination, and to the high rate of conductive heat removal, the process was virtually isothermal at each specified temperature. The time taken to reach the maximum reaction rate counted from the end of the induction period was 0.36–0.5 s, which is thousands of times longer than the time of heat removal. The degrees of conversion considered were relatively low; hence, the consumption of O_2 could be neglected without substantial error, *i.e.* the subintegral function in expression (26) could be considered to be constant. Thus, as applied to the given reaction, Eqn (26) can be represented in the form

$$\frac{W}{[O_2]_0} = k_1[H]_0 \exp\left\{\left[2k_1^0[O_2]_0 \exp\left(-\frac{E_1}{RT}\right) - k_{het}\right](t - t_0)\right\}. \quad (27)$$

In this expression, E_1 is the activation energy of the rate-determining step (branching), equal to 69.9 kJ mol⁻¹, and k_{het} is the rate constant for heterogeneous decay of H atoms, which is known^{3,8} to be equal to $2k_1[O_2]_1$, where $[O_2]_1$ is the O_2 concentration at the first ignition limit. This expression was used to determine the ratios of the rates of the virtually isothermal chain combustion at various temperatures. Table 2 presents the results obtained experimentally and by calculations using Eqn (27). The third column contains the value for the increase in the reaction rate calculated in accordance with the Arrhenius law using the same activation energy for the branching step.

Table 2. Ratios of the reaction rates at the temperatures 773 and 768 K.

$t - t_0 / s$	Experiment	Calculation by formula (27)	Calculation by the Arrhenius law
0.06	1.60	1.45	—
0.08	1.70	1.62	1.07
0.10	1.62	1.75	—

Since self-heating of the mixture in these experiments is rather weak and remains almost constant, it can be neglected when considering the ratio of the rates with an even smaller error. It can be seen from Table 2 that the experimental reaction rate increment caused by the rise in temperature is in agreement with that calculated from Eqn (27) and exceeds substantially the value expected relying on the Arrhenius law. Slight increase with time of the value presented in the third column is due to the fact that consumption of O_2 was not taken into account.

The unusually sharp temperature dependence of the branching-chain combustion rate ('the double exponent law') is brought about by the positive feedback relationship between the n value and dn/dt , W and dW/dt , considered above, which results in a non-additive combined effect of the chain avalanche and self-heating on the process rate. The double exponential law determines the enhanced sensitivity of the rate of a chain reaction to temperature variations; in particular, this facilitates fulfillment of condition (3). Yet another important feature of the temperature dependence of the BCP rate is that it varies exponentially as a function of the difference between the branching and chain termination specific rates ($f - g$). Therefore, both the reaction rate itself and its temperature dependence are highly sensitive to reactant concentrations and other parameters of the reaction system.

Equation (20) also indicates that, when the inequality $\alpha\delta h < \beta$ holds, the chain length reaches the steady-state value

$$v_b = \frac{\alpha}{\beta(1 - h\alpha\delta/\beta)}.$$

In accordance with equality (16), the process rate also reaches a steady-state value under these conditions, the self-acceleration of the reaction diminishing from the very beginning. Substitution of the v_b value from the last equality into Eqn (19), with allowance for the temperature dependences of the rates of the steps determining the α , β and δ values, gives an expression similar to (17), which refers only to a very slow steady-state reaction without ignition.

Thus, the BCP rate follows different temperature variation patterns, depending on whether the reaction occurs in the combustion mode or in the very slow mode without progressive self-acceleration.

The pattern of the temperature variation of the BCP rate identified in the study of Azatyan⁵⁹ provides an interpretation for the unusually high effective activation energies, different for the same reaction depending on the experimental conditions, found in the studies noted above. In fact, any continuous function, including that for the temperature dependence of the reaction rate, can be represented approximately, in some narrow range of the argument, in the form

$$W(T) = b \exp\left(-\frac{a}{RT}\right),$$

where a and b are coefficients which are constant over the temperature range considered and play the roles of activation energy and preexponential factor, respectively.

By taking the logarithm of both parts of this expression with allowance for the condition of contact between the specified and approximated functions and by differentiation with respect to T , we obtain

$$a = RT_0^2 \left[\frac{d \ln W(T)}{dT} \right]_{T_0}, \quad (28)$$

$$b = W(T_0) \exp \left\{ T_0 \left[\frac{d \ln W(T)}{dT} \right]_{T_0} \right\}, \quad (29)$$

where T_0 is the center of the temperature range considered. The rate of BCP depends sharply on the temperature [see expression (26)]; therefore, if this dependence is represented by the Arrhenius form, the derivative appearing in square brackets in expression (28), and, hence, the effective activation energy prove to be abnormally high. Since f and g , present under the first exponent in relation (26), depend on the process conditions in different manners [see Eqns (8) and (9)], the effective activation energy of this BCP should change appreciably upon variation of the reaction conditions. This is confirmed by all the experimental data. When the temperature variation of the BCP rate is described using an Arrhenius function, the 'pre-exponential factor' b found from Eqn (29) becomes too great and has no physical meaning.

V. The governing role of the branching-chain mechanism in the ignition and combustion of gases under atmospheric and higher pressures

The theory of BCP was based only on experimental data obtained under isothermal conditions because virtually all experimental studies on the kinetics of chain combustion have been performed at very low pressures in the absence of self-heating. It is clear that characteristic features of an isothermal process cannot be extended to non-isothermal conditions; therefore, the theory developed resorting to experimental data which refers only to isothermal regimes should be actually regarded as a theory of isothermal chain processes. Elucidation of the role of chain branching and avalanche multiplication of active intermediate species in the phenomenology of the process over a broad range of pressures (including atmospheric and higher pressures) presents considerable interest both for the theory of chemical kinetics and combustion and for the solution of applied problems related to the control of combustion modes.

It has been considered until recently that the BCM plays a crucial role only in combustion at very low pressures, tens or hundreds times lower than atmospheric pressure (see, for example, a number of publications^{3-7, 41, 55, 68-76}). Interpretation of the nature of the third combustion limit is an important point in the formation of these views. The pressure of this limit (P_3) for, for example, H_2-O_2 mixtures, lies in the range of > 40 kPa (which includes atmospheric pressure) and increases with a decrease in the temperature^{3, 6} (see also Fig. 1). According to the generally accepted views, ignition in the region of P_3 is a non-chain process brought about only by self-heating, which accompanies the reaction (see, for example, several publications^{3-7, 13, 41, 48, 55, 69-82}). An important role of a chain mechanism has been recognised only for very low pressures located in the ignition peninsula, closer to the first ignition limit (region I in Fig. 1).

The statement that the reaction in the region of P_3 is a thermally induced non-chain process has been substantiated by the facts that ignition at this (and higher) pressures is accompanied by great self-heating of the reaction mixture and by explosion and that the P_3 values for a hydrogen-air mixture calculated from the critical condition of thermal explosion^{5, 82} are in good agreement with the results of experimental measurements reported in other publications.^{83, 84} For instance, it has been stated in a monograph³ (p. 436) that 'the excellent agreement between the calculations and experiments indicates unambiguously that the third limit for mixtures of hydrogen with oxygen has a thermal nature.' Similar statements can be found in some other studies.^{4, 5, 41, 55}

The interpretation of the third ignition limit as a non-chain phenomenon is equivalent to the assertion that ignition and combustion of gases under atmospheric and higher pressures are induced only by self-heating. Indeed, since the third limit includes these pressures, the factors determining ignition and combustion play a crucial role at any pressure in the region of P_3 and above. In addition, since propagation of, for example, a laminar flame occurs as layer-by-layer ignition following the heat transfer from the burning area to a neighbouring layer of the mixture which has not yet reacted, the view of non-chain 'purely thermal' character of ignition at pressures near P_3 is equivalent to the statement that the flame propagates through a non-chain process.

Oxidation of hydrogen is usually regarded as a model BCP, because the main steps of its mechanism and a number of kinetic features are common to processes of this type. Many regularities of other branching-chain reactions and combustion processes are interpreted by proceeding from the views on the H_2 oxidation. This also refers to the view that the role of BCM at atmospheric and higher pressures and at high temperatures is insignificant. For instance, it is claimed in a monograph⁷⁰ (p. 52) that 'Branching-chain reactions are not so frequently encountered; moreover, for combustion temperatures above 1000°C, which exist even in the flames of dilute hydrogen–oxygen mixtures, thermal self-acceleration exceeds markedly the acceleration related to the branching-chain propagation. The latter is apparently the only mechanism of acceleration in some cool flames, for example, in CS_2 – O_2 cool flames. This self-acceleration mechanism seems to predominate also in the cool flames of hydrocarbons and other organic compounds. However, self-acceleration in so-called hot flames, *i.e.* those normally dealt with in practice, occurs by a thermal rather than chain mechanism.' Below it is also written that 'an increase in the temperature in a reacting system induces thermal explosion at pressures below those for which the condition of chain explosion is met ...' (p. 182).

Actually, this has been the generally accepted opinion. Even nowadays, only the two lower limits are usually considered to be the limits of chain ignition; plots for only these limits are usually included in the graphical depiction of chain combustion regions.^{3–7, 48, 58, 74–81, 85, 86} Branching-chain chemical processes are considered as a class of reactions, which although interesting, occur only in the exotic region of very low pressures and relatively low temperatures.

Characteristic features of combustion at higher pressures have been interpreted taking self-heating as the only reason for self-acceleration of the process (see, for example, studies^{3–7, 68–82, 87, 88}). Meanwhile, some specific features of combustion at atmospheric pressure point to a very important role of a chain mechanism. One of these features is the effect of small admixtures of propane on the ignition of carbon monoxide in air under atmospheric pressure; these admixtures can either promote or inhibit the reaction depending on the amount added (Fig. 3).⁸⁹ The important role of BCM in the combustion of gases is also indicated by the results of studies on the mutual effect of chain avalanche and self-heating and on the temperature dependence of the BCP rate, which refer not only to low but also to atmospheric and higher pressures.^{37, 59, 60} The contribution of a chain mechanism has been taken into account in the interpretation of ignition delay at near-atmospheric pressures⁹⁰ and in the numerical solution of equations related to combustion.^{91–93} However, as has been correctly noted,^{92, 94} combustion has been usually represented as a one- or two-step reaction, the temperature dependence of the reaction rate being written as an Arrhenius function (see, for example, Refs 95–98). Even when the steps that can compose reaction chains were taken into account in the numerical modelling of combustion, they were still inserted in the reaction mechanism together with a large number of other (including insignificant) steps. The relative roles of the chain and thermal factors either have not been considered at all or, in those cases where pressure exceeded the second ignition limit, ignition

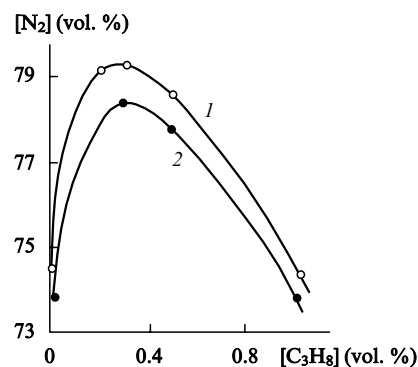


Figure 3. Ignitability of a $CO + O_2$ mixture in N_2 vs. the content of propane at 0.1 MPa and 293 K; (1) in the presence of 0.11% of water vapour, (2) the mixture was dried with dry ice.

and combustion have been considered to be non-chain processes.^{72–76, 99–102} Although Zel'dovich *et al.*⁴ admits that most combustion processes follow chain mechanisms, he still considers these processes, as other researchers, only from the viewpoint of thermal combustion and uses the corresponding equations.

Our analysis^{103, 104} shows that the views according to which the BCM is restricted to the region of very low pressures are faulty. The substantial increase in the temperature and the appearance of thermal explosion are often regarded as evidence supporting the 'purely thermal' character of the third ignition and combustion limit under these conditions. However, any process, irrespective of its type and chemical mechanism, is able to switch to the thermal explosion mode provided that the conditions expressed by Eqns (2) and (3) are fulfilled.¹⁰³ This is equally true for chain processes. A specific feature of BCP is the fact that, owing to chain avalanche, reactions can proceed in the combustion mode even in those cases where conditions (2) and (3) do not hold. When these conditions are fulfilled, chain combustion passes into a mode in which the chain avalanche is accompanied by thermal avalanche. Moreover, in the case of BCM, transition to the thermal avalanche mode should occur in broader ranges of initial conditions and kinetic parameters than in the case of non-chain reactions. Indeed, if condition (12) holds and the reaction proceeds in the chain combustion mode, the rate of heat evolution reaches great values even at relatively low temperatures and low concentrations of the reactants. This facilitates fulfillment of the self-heating condition [see relation (2)]. In addition, the exceptionally sharp, non-Arrhenius temperature variation of the rate of chain combustion [see function (26)] makes easier the fulfillment of the second necessary condition for the generation of chain avalanche, relation (3). Therefore, as indicated by experimental data reported in the literature,¹⁰⁵ branching-chain combustion can readily switch to a mode involving a thermal avalanche (chain-thermal explosion) even when the reactant concentrations and temperatures are so low that thermal explosion is impossible and, hence, it is not observed in non-chain processes (see below).

Thus, substantial self-heating and thermal explosion do not give occasion for rejecting the important role of chain mechanism in ignition and combustion at atmospheric and higher pressures: these phenomena are also peculiar to branching-chain reactions. The agreement between the calculated and experimental temperatures of the third ignition limit is not a convincing argument either. These calculations were performed⁸² using the expression obtained for the critical condition of thermal explosion

$$\frac{QEr^2W}{RT_0^2\lambda} = \delta_{cr}, \quad (30)$$

where r is the radius of the reactor, λ is the heat conduction coefficient of the gas mixture, δ_{cr} is a dimensionless critical parameter; for example, for a cylindrical reactor it is equal to two.¹⁰⁶ The empirical formula for the rate constant for H_2 oxidation, obtained previously⁶¹ using the data related to pressures approaching P_3 ,

$$w = kP_{H_2}^2 P_{H_2O}, \quad (31)$$

(where P_{H_2} and P_{H_2O} are the partial pressures of hydrogen and the water vapour formed, respectively, and k is an empirical rate constant) was substituted into the above expression.

The temperatures of the ignition limit at atmospheric pressure found from expression (30) were consistent with the results of measurements^{83,84} carried out in reactors with various diameters. This provided grounds to conclude that BCM does not play any role in the ignition at the third limit and that combustion at these or higher pressures is brought about only by accelerating self-heating.^{3-5,41,55} In other publications,³⁻⁵ it has been assumed that a chain process is possible at the third limit over a KCl surface but only as an exception.

In our study,¹⁰³ we attracted attention to the fact that, since expression (30) was derived without any restrictions regarding the type of reaction or its chemical mechanism, it is also applicable to BCM. Therefore, the agreement between the results of calculations by Eqn (30) and experimental results can be considered equally reasonably to be an indication of a branching-chain reaction mechanism. It was also noted that Eqn (31) used in these calculations is empirical; it has been selected in accordance with the observed kinetics of the overall process. Therefore, the fact that Eqn (31) holds cannot serve as evidence supporting a molecular (rather than chain) mechanism either. Thus, the consistency of experimental data with the results of calculations according to Eqn (30), valid for reactions of any type, does not provide grounds for rejecting an important role of chain avalanche in combustion in the region of high pressures.

It is also noteworthy that, in addition to the experimental data mentioned above,^{83,84} which agree with the calculations,⁸² some other data which differ markedly from the calculated results are also known (see, for example, Refs 62, 63, 65). Since Eqn (30) was derived for reactions of any type, discrepancy between the data found from this equation and those obtained experimentally may point to inconsistency of some calculation variables with the experimental conditions; however, in some cases, this discrepancy can imply an inadequate description of the phenomenon by kinetic equations. For example, it is stated in a study¹⁰¹ devoted to the numerical simulation of hydrogen combustion that the calculation carried out with the assumption of a constant temperature does not attest to the possibility of sharp transition from the slow process mode to the ignition mode in the vicinity of the third ignition limit. According to this calculation, the reaction rate only increases smoothly following an increase in the initial pressure of the mixture, *i.e.*, the process does not proceed by a chain mechanism. This result, however, cannot be regarded as evidence for the 'purely thermal' character of the real ignition limit because the calculations were based on kinetic equations the order of which does not correspond to the real reaction course. More precisely, the equations in the study cited were set up under the assumption that the rate constants for the heterogeneous decay of active intermediate species (including HO_2 radicals) were proportional to the heterogeneous recombination coefficients, *i.e.*, it was assumed that the rate of heterogeneous chain termination is limited by the probability of adsorption of CC upon collisions with the surface (the kinetic control of heterogeneous chain termination) even at pressures of the third ignition limit. Meanwhile, by using known coefficients of the heterogeneous decay of the H and O atoms and OH and HO_2 radicals even on inert surfaces and the diffusion coefficients for these species and by comparing the rates of their decay in the kinetic and diffusion regimes, one can easily make certain that heterogeneous chain termination reactions at high pressures are mainly limited by the

diffusion rate rather than by the probability of adsorption upon collision with the surface. For example, the coefficients for the heterogeneous decay of CC reported in the study in question¹⁰¹ are matched by chain termination rate constants that are several times greater than those observed with the rate-determining role of diffusion and calculated by the known formula³

$$k_D = \frac{39D}{d^2}, \quad (32)$$

where D is the diffusion coefficient of an active intermediate species, d is the reactor diameter, and the numerical factor with D allows for the spherical shape of the reactor.

Thus, the slowest (rate-determining) step in the capture of active species by the surface under conditions used in the study cited¹⁰¹ is diffusion rather than the attachment of the species to the surface. Since the diffusion coefficient (and, hence, the rate 'constant' k_D) is inversely proportional to pressure, the order of kinetic equations with respect to the gas concentration should be three rather than two. Therefore, if the rate-determining role of diffusion is taken into account even when self-heating is neglected, solution of the set of kinetic equations in a particular temperature range indicates that, in addition to the two critical pressures (P_1 , P_2), there exists the third critical pressure (P_3) of chain self-ignition, which is much higher than P_1 and P_2 . When the initial pressure reaches each of these limits, the slow, steady-state reaction mode sharply switches to fast, progressive self-acceleration, *i.e.* ignition. When self-heating is not taken into account, the pressure P_3 becomes somewhat overestimated compared to the experimental value. This is due to the fact that at these high pressures, slight self-heating which accompanies the reaction in the slow mode facilitates somewhat the fulfillment of the condition of chain ignition; due to the slight increase in the temperature, chain branching starts to prevail over chain termination at lower pressures than it would occur without self-heating. An analytical expression indicating the presence of three self-ignition limits without self-heating has been obtained and verified by numerical solution of a set of equations.¹⁰⁷

In order to find whether ignition, combustion and explosion at high pressures are brought about by the avalanche-like progressive self-heating alone or they are due, most of all, to chain branching, one should consider a feature of the process peculiar to only one of these two accelerating factors, either self-heating or chain avalanche. As specific features exhibited near atmospheric pressure or at higher pressures, we have chosen¹⁰³ the dependence of the process kinetics and the P_3 value on the chemical properties of the reactor surface and the influence of minor admixtures on the ignition and flame propagation including its transition to detonation.

Experimental data demonstrating the dependence of the P_3 value and the process kinetics on the material of the reactor surface are known. For example, it has been shown^{4,29} that P_3 above a KCl surface is markedly higher than those above quartz and glass surfaces. Numerous data (see, for example several studies^{6,29,62,63}) indicate that the process kinetics at the third-limit pressures depend on the chemical properties of the reactor walls. Hysteresis phenomenon is known, which means, for example, that the kinetic behaviour of the reaction system in a particular experiment depends on what reaction has been carried out in the preceding experiment prior to evacuation of the reactor.^{6,62,108-111} However, these data have not been taken into account in considering the role of chain mechanism in the ignition and combustion near atmospheric pressure. Meanwhile, if the process were 'purely thermal', neither the reaction kinetics nor P_3 would depend on the material or, particularly, on the 'previous history' of the surface. This dependence is exactly a characteristic of radical and chain reactions. It is an integral feature of the third ignition limit and of the reaction kinetics observed when the reactants contact with a solid surface. It is also noteworthy that the results of calculations without allowance for heterogeneous chain propagation and chemical modification of

the surface cannot correspond to the process characteristics observed experimentally even though a large number of reactions are included in the process scheme and self-heating is taken into account. For example, the results of the calculation of the temperature dependence of the first ignition limit reported in a study¹⁰¹ do not correspond to the experimental data presented in the same publication because heterogeneous chain propagation is not taken into account. In some studies devoted to the numerical solution of sets of equations for the third limit, heterogeneous reactions are completely neglected (see, for example, Refs 112, 113).

The chain mechanism of the process at atmospheric pressure is also indicated unambiguously by the data on the influence of admixtures of some compounds on the ignition of various combustible gases; in some cases, the dependence of the efficiency of an admixture on its amount has an extremum (see Fig. 3).⁸⁹ Yet another example is the decrease in the upper concentration limit of hydrogen ignition in air at atmospheric pressure from 75% to 55% in the presence of 1.5% of dibromotetrafluoroethane.¹⁰³

Until recently, the influence of additives on ignition has been explained in applied studies either by dilution of the mixture and by the change in its thermal characteristics (increase in the heat capacity, acceleration of heat removal) or regarded as being equivalent to ionisation or chain termination without giving preference to either of these reasons (see, for example, Refs 114–117). However, small amounts of additives (0.3%–1.5%) cannot dilute a mixture, change heat capacity or decrease self-heating to a noticeable extent.

It is obvious that a theory in which self-heating is considered to be the only reason for the generation and progress of combustion cannot account for the pronounced influence of small admixtures of chemical substances on these processes at near atmospheric and higher pressures. It does not explain either the dependence of the efficiency of an admixture on its chemical properties or the above-mentioned extremum character of the effect of propane in concentrations of about tenths of percent. It is notable that the substantial effect of small admixtures on ignition and combustion, which, as can be seen from the given examples, is manifested, in particular, at atmospheric pressure, is actually ignored in the studies on the theory of combustion, in which various aspects of combustion, ignition and explosion are considered in detail. In some recent publications, the dissimilar influence of various admixtures on combustion has been taken into account by introducing empirical coefficients.¹¹⁶ However, the use of only empirical parameters to describe the features observed does not allow one to explain the essence of the phenomenon. In addition, when extrapolations or even interpolations are made, this can distort the results because empirical 'constants' usually vary as functions of concentrations, temperature, *etc.* Meanwhile, the influence of very small amounts of inhibitors on the ignition and combustion over the whole range of pressures (including atmospheric and higher) indicates that they affect the competition between the chain branching and chain termination processes. The effect of inhibitors is due to the fact that they react with atoms and radicals to give radicals of a different type unable to regenerate active species.³¹

Some investigators claim (see, for example, Refs 6, 117) that the inhibitory effect can be explained by assuming that the role of chain branching is substantial only up to the instant of ignition and that the inhibitor suppresses only this pre-flame mode, thus preventing heat evolution. However, one can easily make certain that a chain reaction can proceed at a noticeable rate outside the ignition region only in the case where the chain branching rate is a shade lower than the chain termination rate, *i.e.* if f is slightly smaller than g . On heating, the f value increases exponentially together with the rate constant for branching [see expression (8)], whereas the g value, which relates at these pressures to termolecular termination, decreases. Therefore, even when the self-heating is slight and is much smaller than that needed for thermal ignition, f becomes greater than g , *i.e.* condition (12) is met.

Thus, the mixture enters the region of chain ignition and ignites as a result of generation of a chain avalanche. For example, simple calculations carried out using Eqn (13) demonstrate that heating by only several degrees is enough for the ratio of branching to termination rates (f/g) in the $2\text{H}_2 + \text{O}_2$ mixture at 1 atm and 830 K to change from 0.95 (at which the reaction occurs in a steady-state mode and is virtually unnoticeable) to 1.05 and for chain ignition to occur. Note that under this conditions, substantial self-heating prior to ignition is impossible anyway, because the heat has time to dissipate due to the extremely low reaction rate ($f < g$).

Experimental data and the calculation using Eqn (13) demonstrate that, even when a mixture is located only 5% below the ignition region, the increase in the reaction rate becomes extremely low and soon ceases. Self-heating becomes substantial only under conditions of developed chain combustion and enhances the chain avalanche. However, as noted above, for self-heating to become a heat avalanche, fulfillment of condition (3) is also required. This requirement, however, can be not realised until the end of chain combustion (see below).

Analysis of the equation for the length of a branching chain and of the temperature dependences of the chain branching and termination rates has shown^{59, 103} that at any pressure, self-heating in a branching-chain process results first in the fulfillment of condition (12) and, only after that, does chain ignition occur.

The conclusions made in several studies^{59, 103, 104} concerning the predominant role of the BCM in the combustion at atmospheric and higher pressures and the simultaneous action of chain avalanche and self-heating have been verified experimentally.^{89, 105, 118–121} The governing role of the branching-chain mechanism in the combustion of carbon monoxide in air at atmospheric pressure was demonstrated in a study,⁸⁹ in which the main reactions responsible for the promotory and inhibitory influence of admixtures are also presented. As an example, below we consider the results¹¹⁸ dealing with the influence of various additives, inert diluents and chemically active compounds (inhibitors), on the ignition and on the intensity of combustion in the model hydrogen oxidation process. The reactions were carried out in a metallic evacuated closed reactor with a height of 25 cm and a diameter of 8.5 cm. Gas mixtures were prepared in the reactor according to partial pressures of the components with an accuracy of 0.6%. Within some period after the preparation, necessary for intermixing, the mixtures were conflagrated by pulse heating of a nichrome coil. The setup permitted the duration and power of the conflagrating pulse to be controlled. The chemiluminescence and pressure variations accompanying the ignition were detected using a FEU-39 photomultiplier (wavelength range 300–600 nm) and a quick-response pressure sensor, respectively. The signals from the sensors were recorded using a two-channel digital memory oscilloscope. After combustion had been completed, chromatographic analysis was carried out. The initial pressure of the mixture was 1 and 5 atm in various series of experiments.

The results of the measurements showed that the minimum concentration of argon needed to prevent the hydrogen–air mixtures of any composition from ignition, *i.e.*, the so-called peak concentration of the diluent, is higher than 85 mol. %. The peak concentrations of inhibitors are much lower: for dibromotetrafluoroethane [chladone (Halon) 114B2] and a complex inhibitor of the AKAM series they do not exceed 16% and 9.5% (Fig. 4). The addition of, for example, 2.5% of the AKAM inhibitor decreases the upper concentration ignition limit (UCIL) from 75% to 45%. Meanwhile, the same amount of argon decreases the UCIL only to 73%. The much higher efficiency of inhibitors compared to that of argon and the dependence of the effect of inhibitors on their chemical properties indicate that small admixtures of inhibitors (unlike argon) influence ignitability through chemical reactions with the chain carriers. Thus, ignition of H_2 , like that of CO , in the presence of hydrogen-containing compounds at the atmospheric pressure (see Fig. 3) follows a chain rather than a 'purely thermal' mechanism.

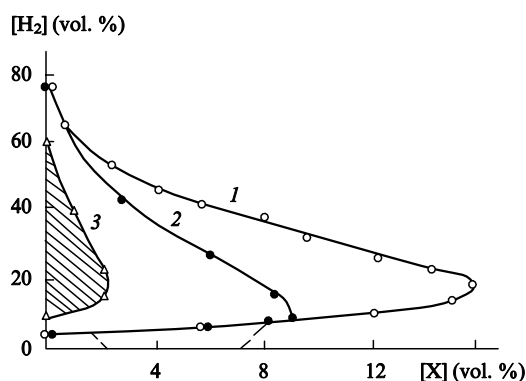
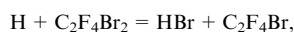


Figure 4. Concentration limits of ignition (1, 2) and boundaries of the chain-thermal explosion region (3) for hydrogen – air mixtures containing various amounts of inhibitors X: halon 114B2 (1) and AKAM-3 (2, 3); dashed lines correspond to ignition with a very high conflagration power in a small reactor.

The inhibitory action is due to fast reactions of the inhibitor with CC. In particular, the effect of the halon 114B2 is mainly determined by the reaction



resulting in the replacement of atomic hydrogen by a haloalkyl radical unable to regenerate chain carriers.

Experimental data obtained in a study¹¹⁸ made it possible to elucidate the role of a chain mechanism in a developed combustion process. Since hydrogen oxidation is accompanied by monotonic decrease in the number of moles of the gas mixture, the increase in the pressure observed during the reaction carried out in a confined space can be due only to rise in the temperature of the reacting gas, *i.e.* its self-heating. Correspondingly, the rate of the pressure increase and the maximum pressure surge characterise the intensity of combustion. The kinetics of the reaction can also be judged from the rate of the growth and the maximum value of the chemiluminescence intensity.

The experiment with variation of the mixture composition made it possible to identify two kinetic modes of combustion. In the absence of inhibitors, the combustion of mixtures of hydrogen with air containing more than 16 vol. % and less than 60 vol. % of H_2 proceeds in a mode characterised by a very sharp pressure increase — to 6–7 atm (the initial pressure being 1 atm). This pressure surge points to an increase in the temperature to at least 2000 K. The process is accompanied by a characteristic bang. The time it takes to reach the maximum pressure and chemiluminescence intensity in these mode is 1–2 ms, *i.e.* it does not exceed the characteristic time of the heat removal from the reactor. This is the explosion mode, the kinetics of which differ substantially from the kinetics of ignition occurring in mixtures with compositions close to the concentration limits, *i.e.*, those containing more than 60 vol. % or less than 16 vol. % of H_2 . The maximum pressures and chemiluminescence intensities and the rates of their growth attained in the ignition of these ‘near-limit’ mixtures are substantially lower. The temperature increases to 1300–1600 K. On smooth variation of the initial composition of the mixture, the transition of the process from one kinetic mode to the other is discontinuous, *i.e.* has a critical nature. Thus, ignition and combustion of hydrogen–air mixtures at atmospheric pressure can occur in two different kinetic modes depending on the initial composition; one mode does not involve thermal explosion, although it is accompanied by substantial self-heating, while the other one occurs as a thermal explosion. The parameters of the reactor used (calibre 3.1) precluded detonation. It is known that thermal combustion (unlike chain combustion) does not involve two different kinetic modes.

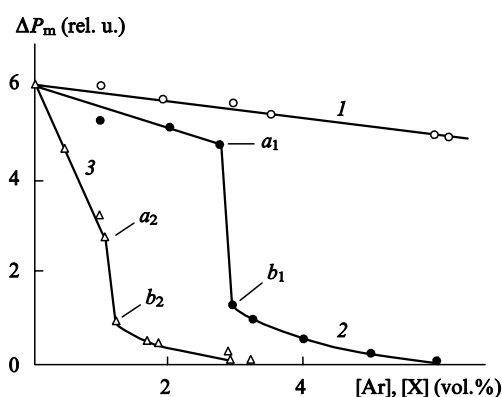


Figure 5. Dependence of ΔP_m on the initial content of admixtures X: argon (1), halon (2), AKAM-3 inhibitor in a mixture of 40% of H_2 with air (3).

To elucidate the role of chain mechanism in the kinetics of developed combustion, argon and inhibitors were admixed (in various amounts) to the initial mixture. The plots for the maximum pressure gain (ΔP_m) vs. the contents of various admixtures — argon and inhibitors (halon and AKAM) — in a mixture of 40% of hydrogen with air, based in the results of several series of experiments, are presented in Fig. 5. The dependence of ΔP_m on the amount of an admixture characterises the efficiency of the influence of this compound on the process. In the absence of additives, ignition and combustion of this mixture switch to the explosion mode described above. It can be seen from the Figure that the inert gas decreases the ΔP_m value only slightly. The explosive character of the process does not change. This influence of argon is due merely to the dilution of the mixture. The dependence of the efficiency of the action of halon and AKAM on the amount added (curves 2 and 3), when this amount is insufficient to dilute the mixture noticeably or to change substantially its heat capacity or heat conductivity, differs qualitatively from that observed for mixtures with an inert diluent. Curve 1 has no turns over the whole range of argon concentrations employed. Conversely, curves 2 and 3 exhibit sharp inflections at points a_1 , b_1 and a_2 , b_2 , respectively. When the concentrations of the admixtures correspond to points b_1 and b_2 , the maximum chemiluminescence intensity (not shown in the Figure) also changes abruptly. In addition, the efficiency of the influence of inhibitors on the combustion intensity is much greater than the efficiency of the influence of argon and depends on their chemical properties (*cf.* curves 1, 2 and 3). When the content of AKAM is greater than 3.4 vol. %, this hydrogen – air mixture does not ignite (no pressure and chemiluminescence growth are observed). At these inhibitor concentrations, the reactants are barely consumed after the source of conflagration has been switched on. The mixture can be ignited only when the content of halon is less than 6% and that of AKAM is less than 3.4%. Thus, a mixture containing 40% of H_2 and 3.4% of the inhibitor AKAM corresponds to the concentration limit of ignition. The same is true for a mixture with 6% of halon.

The smaller the amount of an inhibitor, the more intense the ignition: as the content of an inhibitor in the initial mixture decreases, ΔP_m increases (see Fig. 5). When the reactant mixture contains 3.2% of halon, the final degree of conversion of O_2 during combustion is 40%–50%. When the concentration of AKAM is higher than 1.2% or that of halon is higher than 3.05%, the combustion does not pass to explosion, although the increase in pressure, which accompanies the ignition, points to substantial self-heating. The intensity of combustion increases with a decrease in the concentration of the inhibitor. These facts indicate directly that in this mode, developing combustion is substantially depressed by the inhibitor; hence, the process follows a BCM and its kinetics are mainly determined by the competition between chain branching and chain termination. Thus, chain mechanism

determines the kinetic features of the process not only before ignition and during the induction period, as has been assumed in the consideration of the influence of admixtures on the delay of ignition, but also under conditions of developing combustion after ignition has started.

The absence of signs of explosion in this combustion mode implies that the chain avalanche developing due to fulfillment of condition (12) and accompanied by self-heating owing to fulfillment of relation (2) is the only factor which accounts for the progressive self-acceleration of the reaction. The condition for thermal explosion [inequality (3)] is not met for these mixtures and self-heating only enhances the chain avalanche. This implies that the combustion of mixtures with compositions close to the concentration limits, which occurs without explosion in the absence of inhibitors, is also due only to chain avalanche enhanced by self-heating.

The comparison of the action of inert gas and inhibitor admixtures in the experiment in question¹¹⁸ made it possible to establish the governing role of the branching-chain mechanism in the transition of combustion to explosion and in the explosion itself. When the initial content of the inhibitors decreases, the maximum combustion intensity and the ΔP_m value increase discontinuously (see Fig. 5, regions to the left of points b_1 and b_2). The time it takes to reach these maximum values decreases sharply and the process is accompanied by a click typical of an explosion. Judging by the ΔP_m value, the temperature in this case exceeds 2000°C.

Thus, there are two critical concentrations for each inhibitor, one of them corresponding to the ignition condition and the other (lower) corresponding to the transition of combustion into a chain-thermal explosion (see Fig. 4, curves 2 and 3, respectively).

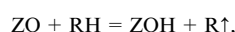
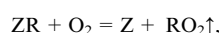
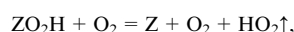
The fact that the slopes of curves 2 and 3 on the left of points a_1 and a_2 in Fig. 5 are much greater than the slope of curve 1 means that in the explosion mode, too, halon and AKAM have a much stronger effect on the combustion than the inert gas. The difference between the slopes of curves 2 and 3 reflects the dissimilar efficiency of the inhibitors, which depends on their chemical properties. Hence, the effect of halon and AKAM on the explosion intensity, unlike that of argon, is due to chemical reactions (inhibition) rather than to dilution. The fact that the slope of curve 3 is greater than that of curve 2 is consistent with the greater inhibiting activity of AKAM compared to that of halon. These data indicate unambiguously that a chain mechanism predominates in the mode of combustion which is realised when conditions (3), (13) and (2) are fulfilled and which has been named¹¹⁹ chain-thermal explosion (CTE).

Experiments in which the initial pressure of the mixtures was 5 atm have given similar results.¹¹⁸

VI. Specific features of heterogeneous reactions determining the dependence of combustion characteristics on the surface properties at high pressures

Dependence of the kinetic parameters and critical conditions on the properties of the surface is an essential feature of BCP at any pressure. In particular, ignition limits include not only critical pressures or concentrations, as has been considered until recently, but also the dependence of these characteristics on the composition and properties of the surface adsorption layer and the ability of adsorbed species to enter into not only recombination reactions but also reactions leading to regeneration of CC. Therefore, to interpret correctly the characteristic features of the process, the reasons for this dependence should be identified and taken into account. In our studies,^{9, 36, 121} we interpreted the dependences of the process kinetics and the P_3 value on the properties of the reactor surface over a broad range of pressures (from a very low to atmospheric pressure), both found experimentally in the same studies and reported in the literature,^{6, 62, 63, 65, 110} within the

framework of the concept of the chain mechanism of ignition and combustion near atmospheric pressure and heterogeneous propagation of the reaction chains.^{9, 54, 122} The hysteresis phenomena mentioned above were also interpreted.[‡] The dependence of the BCP characteristics on the surface properties points unequivocally to an important role of heterogeneous reactions involving CC in the competition between the reaction chain branching and termination. Since the same amounts of reactants are admitted into the reactor in each experiment, the influence of a preceding experiment on the process characteristics is due only to reactions involving the adsorbed intermediate species, which have been formed in the previous experiment and have not been removed completely during evacuation. The atoms and radicals adsorbed on the surface can participate in the propagation of reaction chains. It has been established^{9, 33–36, 54, 122} that in the combustion of, for example, H_2 , heterogeneous chain propagation involves the HO_2 radicals formed in the reactions of adsorbed H atoms with O_2 and also in the gas phase. In this review, we consider those heterogeneous reactions which are significant at high pressures. It has been noted^{9, 122} that, due to high pressures, adsorption of HO_2 from the gas phase is limited by diffusion. Therefore, if each adsorbed HO_2 radical participated in chain termination, no dependence of, for example, P_3 on the properties of the surface would be observed. The presence of this dependence indicates that reactions of some of the adsorbed HO_2 radicals result ultimately in the regeneration of chain carriers, *i.e.*, active species that pass in the gas phase. The following reactions can be cited as examples of regeneration of CC with participation of adsorbed radicals:^{9, 36, 122}



where Z is an adsorption site, R is a radical, the arrow marks the departure of a species into the gas phase. In the first reaction, the H atom passes from an adsorbed HO_2 radical to an O_2 molecule which attacks it from the gas phase.

Since the rates of reactions of adsorbed species depend on the properties of the surface, these properties also influence the fraction of the surface HO_2 species that regenerate the CC. When this fraction (θ) is taken into account, the effective rate constant for the heterogeneous chain termination is

$$k_{het} = k_{het}^0(1 - \theta), \quad (33)$$

where k_{het}^0 is the rate constant for the capture of CC by the surface. Unlike k_{het}^0 , which is determined by the rate of diffusion, the θ value depends on the type of bonding between HO_2 and the surface, *i.e.* on the properties of the surface adsorption layer.³⁶ Therefore, despite high pressures, k_{het} depends on the state of the surface. The surface is subject to the action of the chain reaction products. During evacuation of the reactor, the chemisorbed radicals are removed incompletely, and, after a new portion of the mixture has been admitted, they react with the gas-phase components of the fresh mixture; it is in this way that the 'surface memory' is manifested. The hysteresis phenomenon is also observed in many catalysed oxidation and pyrolysis processes.^{108–111, 123}

It has been shown^{9, 36} that regeneration of atoms and radicals with participation of the CC adsorbed from the gas phase (heterogeneous chain propagation) differs fundamentally from the heterogeneous formation of active species in the reactions involving only initial molecules (heterogeneous initiation). This difference is due to the much higher rates of heterogeneous chain

‡ It is noteworthy that until recently, the majority of researchers have not taken into account heterogeneous chain propagation (see, for example, Refs 92–95, 98).

propagation reactions and to their more important and diversified functional role in BCP. It is this type of reaction rather than chain initiation (which is significant in catalytic reactions according to the generally accepted view) that accounts for the dependence of the process kinetics on the properties of the surface (including hysteresis). Under certain conditions, heterogeneous chain propagation also influences the critical conditions for flame propagation¹²¹ and CTE.¹⁰⁵

VII. The role of chain mechanism in the transition from deflagration combustion to detonation

The branching-chain mechanism plays the governing role in the ignition and combustion at atmospheric pressure; therefore, competition between chain branching and termination also has a crucial influence on the propagation of, for example, a laminar flame, *i.e.* layer-by-layer ignition of a combustible gas. This conclusion was verified experimentally in a study of the influence of inhibitors on the rate of flame propagation¹¹⁸ and in a study dealing with the dependence of the concentration limits of flame propagation on the composition of the adsorption layer on a contacting surface.¹²¹

The influence of inhibitors on the flame propagation velocity was studied in 2-m long horizontal tubes with diameters of 2.4 and 5.4 cm. The ignition was carried out at the end face of the tube and the track of the flame was recorded based on chemiluminescence, the signal of which entered a photoelectric multiplier through three quartz windows, located along the reaction tube, and a branched optical waveguide. It was shown that inhibitors not only narrow down the concentration range of ignition but, at concentrations lower than the first critical concentration (*i.e.* corresponding to the regions confined by curves 1 and 2 in Fig. 4), they also decrease the flame propagation velocity. In addition, if the flame is not stationary and accelerates, inhibitors decrease the acceleration rate. Thus, chain branching also plays the governing role in flame propagation, and this enables one to control both its concentration limits and velocity by using inhibitors. When the inhibitor concentration exceeds a certain value, the flame becomes diminishing.

A correlation between the critical conditions for flame propagation and the chemical properties of the surface contacting with the gas has been elucidated.¹²¹ The study was based on the hysteresis of the upper concentration limit of flame propagation discovered and studied for the combustion of hydrogen in air in a reactor characterised by an especially great surface area-to-volume ratio. When the initial content of H₂ in the mixture was successively increased in each experiment (*i.e.* when the limit was approached from the side of the ignition region), higher values were attained than in the case where the concentration of H₂ decreased and the limit was approached from the side of non-ignitable mixtures. The reactor was evacuated after each experiment; therefore, the dependence of the critical condition of ignition on whether or not combustion had occurred in the previous run was due only to the change in the chemical properties and functions of the adsorption layer of the reactor surface under the influence of intermediate products of combustion, namely, adsorbed CC (see the previous Section). These results are directly related to the filtration and catalytic combustion.

Transition from deflagration to detonation is known to occur as a result of progressive self-acceleration of a flame to velocities higher than the sound velocity (and generation of a shock wave thereupon) at the cost of the energy of a chemical reaction.^{4,6} The fact that inhibitors retard the flame propagation and switch it to a damped regime permitted us to conclude that transition of deflagration to detonation can be prevented by using inhibitors. This was accomplished in another study¹²⁴ for various conditions of combustion at atmospheric pressure. The results of bench testing of an air-feed jet engine are presented in Fig. 6. Suppression of detonation in a hydrogen–air mixture containing 40% of H₂ was also attained in a plexiglass reaction tube of length 600 cm

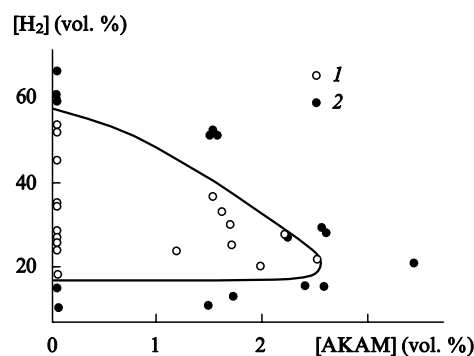
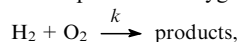


Figure 6. Regions of normal and detonation combustion of hydrogen–air mixtures for the operation of a bench of an air-feed jet engine in the presence of various amounts of the AKAM inhibitor; (1) detonation, (2) normal combustion.

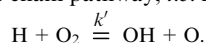
by introducing 2.5% of an inhibitor of the AKAM series.¹⁰³ High-speed filming made it possible to determine exactly the site where detonation arose. It was shown that addition of 0.5% and 1.0% of an inhibitor extends substantially the induction period of detonation and, when the amount is > 2%, detonation does not occur.⁸

It has been shown²¹ that heterogeneous propagation of reaction chains influences the reaction kinetics not only under conditions of developed combustion but also during the induction period (τ). This manifests itself as a decrease in the time τ and as a hysteresis similar to the hysteresis of the upper concentration limit of flame propagation in hydrogen–air mixtures described above.¹²¹ In both cases, the phenomenon is due to the heterogeneous chain propagation reactions involving adsorbed atoms and radicals left on the surface after the previous experiment, because evacuation of the reactor between the experiments does not remove completely the adsorbed species. Heterogeneous chain propagation might influence in a similar way the induction period of detonation in the transition of deflagration combustion to detonation, for example, in shock tubes. This should show as shortening of the pre-detonation period under the influence of detonation of a stoichiometric mixture or a mixture enriched in the combustible component performed in the preceding experiment. Under these conditions, despite the high pressures, the access of gas species to the surface is facilitated by turbulence.

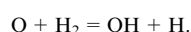
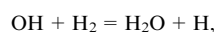
The temperatures typical of a hydrogen detonation wave in air are 2100–2800 K depending on the composition of the mixture.⁴ In addition to the experimental data presented above, the determining role of a chain mechanism at these temperatures and atmospheric pressure is confirmed by comparison of the rate of consumption of dioxygen in the reaction with H₂¹⁰³



which is the rate-determining step of the process occurring by a molecular mechanism, with the rate of dioxygen consumption in the chain pathway, *i.e.* in the reaction with atomic hydrogen



This step determining the rate of the reaction chain is followed by chain continuation steps

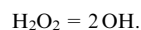
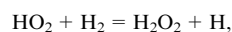
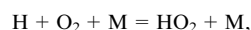


The ratio of the rate constants for these reactions, k and k' found using concentrations of atomic hydrogen in H₂ flames at 2500 K recommended in reference literature^{39,40} and those measured experimentally or calculated^{125,126} is less than

§ The study on the inhibition of detonation was partly performed together with H Gg Wagner.

5×10^{-2} . Thus, more than 95% of O_2 is consumed in the chain process even without allowance for the fact that the primary reaction products are atoms and radicals able to start reaction chains.

At high pressures and temperatures, in addition to the above step, an important channel of branching is provided by the following sequence of reactions (see, for example, Ref. 107):



The above data pointing to the predominant role of the chain mechanism even at about 2500 K also indicate that under conditions where detonation has already occurred, inhibitors are still able to influence the process substantially up to destruction of the detonation wave.

Thus, despite the fact that chain combustion at high pressures is accompanied by intense self-heating of the reaction mixture, which enhances the chain avalanche and, under particular conditions, switches the process to the CTE mode, it is sufficient to weaken the chain avalanche, for example, by adding a small amount of an inhibitor, to diminish appreciably the rate of any mode of the process down to complete suppression of the combustion.^{16, 103, 105, 118, 121, 124} The high sensitivity of the process to the influence of inhibitors is due to the fact that the BCP rate, the temperature dependence of the BCP rate and other important characteristics of the process are largely determined by the difference between the chain branching and termination rates [$f-g$, see Eqns (7) and (20)] rather than by the absolute magnitudes of these rates. Therefore, to suppress combustion, the inhibition rate should not necessarily be close to the branching or termination rates taken separately. It is only required that the inhibition rate be commensurate with the difference between these rates. Note that the difference $f-g$ appears in the exponent of power in the function for the temperature dependence of the BCP rate.

The concentration limits of ignition of hydrocarbons in air are markedly narrower than those for ignition of hydrogen–air mixtures (see, for example Ref. 6), although heats of combustion of hydrocarbons are much greater. This is due to the fact that the combustion is inhibited; the hydrocarbon itself acts as the inhibitor because the chain carriers H, O and OH react with its molecules and are thus replaced by less reactive intermediate species.³¹

To conclude this section, we shall list briefly the characteristic features of gas-phase combustion near atmospheric pressure that cannot be interpreted without taking account of the governing role of the branching-chain mechanism of the process and competition of the reaction chain branching and termination.

1. The substantial influence of inhibitors and promoters on all modes of combustion including ignition, developed combustion, explosion, deflagration flame propagation and transition to detonation.

2. The presence of two different kinetic and, correspondingly, thermal modes of chain combustion; the critical character of transition of the process from one mode to the other.

3. Dependence of the critical ignition conditions, the chain-thermal explosion, flame propagation and the process kinetics on the properties of the contacting surface and on the composition of the adsorption layer even if the access of CC to the surface is limited by diffusion.

4. The unusually strong temperature dependence of the specific rate of the process, which differs fundamentally from the Arrhenius law.

5. The much narrower concentration limits of ignition for hydrocarbons in air compared to those for hydrogen in air, although the molar heats of combustion of hydrocarbons are substantially higher.

Unlike the traditional, ‘purely thermal’ approach, the theory of non-isothermal chain processes developed in a number of studies,^{59, 103, 104, 119, 121} which takes into account not only linear but also non-linear heterogeneous and homogeneous reactions of CC and heterogeneous chain propagation, accounts for all the above-listed and some other features observed. Previously these characteristic features of combustion have not been considered.

VIII. Thermal modes of chain combustion in the low-pressure region

When conditions of chain combustion ensuring self-heating of the system are met and the rate of chain combustion obeys a very strong, non-Arrhenius temperature dependence, which facilitates the fulfillment of condition (13), chain combustion is able to switch to the CTE even at low pressures and temperatures, where processes not occurring by a branching-chain mechanism cannot pass to the chain explosion mode. This has been demonstrated^{16, 105, 125} for the oxidation of H_2 , SiH_4 and GeH_4 . It was shown in these experiments that existence of two different kinetic (and, correspondingly, thermal) modes is peculiar to branching-chain combustion irrespective of whether or not heat and mass transfer, convection, or concentration and temperature gradients are present in the system.

Combustion was performed in temperature-controlled heated quartz reactors, the walls of which had been treated preliminarily with hydrofluoric acid, which ensured small coefficients for the decay of CC on the surface, kinetic control of the heterogeneous chain termination and very low P_1 values. This virtually excluded the presence of CC concentration, process rate, or temperature gradients in the reactor; thus, combustion was uniform throughout the whole bulk. The use of mixtures prepared beforehand ruled out the possibility that the process would be controlled by diffusion. High-speed recording of chemiluminescence in the wavelength range of 200–600 nm and at the pressures of the mixture was carried out from the instant the reaction mixture was admitted into the evacuated reactor until the combustion was over. In experiments with SiH_4 and GeH_4 actual concentrations of these compounds were also recorded based on the intensity of the corresponding absorption bands in the IR spectra. Prior to the measurements, the mixture under study was ignited repeatedly until quantitative reproducibility of the state and properties of the surface was attained.

The ratio of chain branching to termination rates was varied by changing the initial pressure of the mixture, and, hence, the reactant concentrations inside the ignition region. When the pressures P_0 exceeded the first ignition limit, the branching rate for unit concentration of CC, *i.e.* the f value, increased proportionally [see also expression (8)]. Since the role of termolecular reactions near the first ignition limit is insignificant, the g value [see expression (9)] is virtually equal to k_{het} . Upon an increase in P_0 , this constant does not change or even decreases if the rate of capture of chain carriers by the surface is limited by diffusion to the surface. In both cases, in the low-pressure region, an increase in P_0 results in higher f/g ratios and, what is more important, the difference $f-g$ also increases. Correspondingly, the growth of n and W is enhanced [see Eqns (7) and (10)] and heat evolution accelerates. As a consequence, under conditions of developed combustion, self-heating is significant even at pressures slightly exceeding P_1 ; it sharply increases on further increase in P_0 . This pressure dependence of the process characteristics permitted the researchers to vary the kinetics of combustion and, correspondingly, the intensity of heat evolution.

To record correctly self-ignition from its very beginning and to transfer combustion to explosion, a special technique was used which ensured that the delay time of self-ignition was longer than the time it took for the gas mixture to enter a heated reactor and for a stationary pressure to be established. The essence of the method is introduction into the reaction mixture of tenths of percent of ethane as an inhibitor, which delays the ignition, being

partially consumed. The ignition occurs only after the diminishing concentration of the inhibitor reaches a critical value. The remainder of the inhibitor burns during the ignition, and combustion proceeds in the presence of the inhibitor, which is rapidly spent.

As an example, Fig. 7 presents the pressure oscillograms for the combustion of a stoichiometric mixture of H_2 with O_2 in a reactor with a diameter of 5.5 cm.¹⁶ Point *A* corresponds to the beginning of the admission of the combustible mixture to the reactor and point *B* marks the onset of self-ignition. Since the number of moles of the gas mixture steadily decreases during the hydrogen oxidation, the observed increase in pressure during the propagating combustion can be due only to self-heating of the mixture, as in the experiments at high pressures described above. The initial pressures in runs 1 and 2 differed by 2.25%, those in runs 2 and 3 differed by less than 0.5%. Nevertheless, as can be seen from oscillograms, the combustion kinetics in runs 2 and 3 were much more different than those in runs 1 and 2. The maximum self-heating in runs 1 and 2 was 200–250°C (measurements were carried out using a quick-response gas thermometer — a high-sensitivity quartz membrane manometer). Meanwhile, self-heating in runs 3 and 4 was almost an order of magnitude greater. It can be seen that variation of P_0 in the vicinity of a particular value (in this case, 26.7 Torr) resulted in a discontinuous change in the maximum temperature (see Fig. 7*b*). The ignition in runs 3 and 4 and at higher initial pressures was accompanied by a sonic effect — a click. These findings indicate that in runs 3 and 4, condition (3) holds in addition to relation (2). Thus, runs 1 and 2 correspond to non-isothermal chain combustion without explosion, whereas runs 3 and 4 correspond to a CTE realised at very low pressures. Attention is attracted to the low activation energy of the rate-determining step of the process, namely reaction I ($< 70 \text{ kJ mol}^{-1}$).

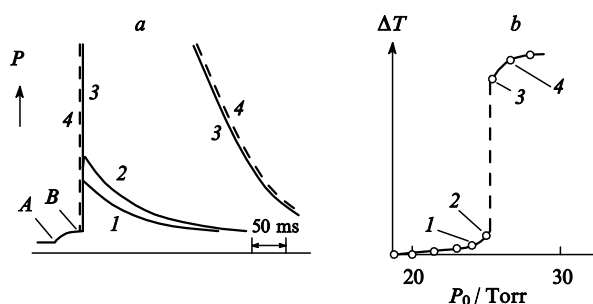


Figure 7. Pressure oscillograms for combustion of a stoichiometric mixture of H_2 with O_2 in a reactor of diameter 5.5 cm at an initial temperature of 728 K (*a*) and change in temperature vs. initial pressure of the reaction mixture in the same experiments (*b*).

P_0/Torr : (1) 26.1, (2) 26.7, (3) 26.8, (4) 27.2.

Figure 8 shows the temperature dependences of P_1 and P_2 (curves I and IV) measured in the same series of experiments as the data of Fig. 7. The region between curves I, II and IV in Fig. 8 is the region of self-ignition and chain combustion without explosion. Oscillograms 1 and 2 in Fig. 7 correspond exactly to this region near curve II. The region above curve II to the right of curve I is the region of CTE. The point marked by the arrow is the limit of CTE found from the data of Fig. 7. It can be seen that the CTE region is confined on the low-temperature side by the second ignition limit at any composition of the mixture; as the region of chain ignition narrows down due to an increase in the content of the inhibitor, the CTE region narrows down in a similar way. Thus, CTE can arise only in the developing chain combustion. The CTE limit (curve II in Fig. 8) is higher than the first chain ignition limit because origination of a CTE requires that the chain combustion rate and the temperature be sufficiently high for the second condition for thermal explosion, relation (3), also to hold.

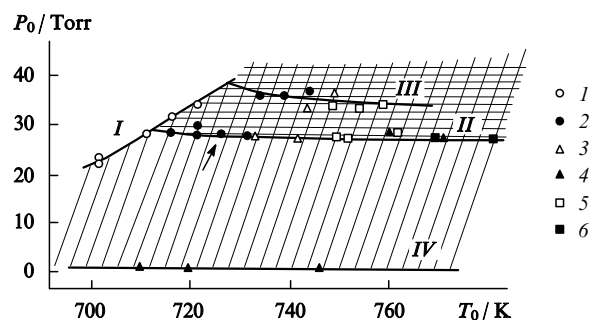


Figure 8. Regions of chain ignition and CTE in a stoichiometric mixture of H_2 and O_2 ;

(I, IV) the second and first limits without an inhibitor; (II, III) the CTE limit in reactors of diameters 5.5 and 3.3 cm, respectively. The content of the inhibitor in the initial mixture (mol. %): (1, 2) 0, (3) 0.2, (4) 0.3, (5) 0.4, (6) 0.7.

The limit itself depends only slightly on the temperature because the critical rate of the chain process at which combustion turns into explosion also depends slightly on the initial temperature.

In the experiments the results of which are presented in Figs. 7 and 8, the pressures P_1 were only 12–13 Pa, depending on the temperature, which is ~ 200 times lower than the CTE limit. Under these conditions, chain termination and the heat evolution which accompanies it in the CTE proceed in the gas phase. It has been verified¹⁰⁵ whether chain combustion could turn into CTE at a lower rate of heat evolution, namely, under conditions of heterogeneous chain termination ensuring virtually complete removal of the energy of recombination of atoms and radicals by the reactor walls. The rate constant for chain branching in the oxidation of monosilane, carried out for this purpose, is much greater than that for the oxidation of H_2 ; therefore, it should be expected that the conditions for CTE — relations (2) and (3) — would be met at even lower pressures and temperatures than in the combustion of H_2 with O_2 . At low pressures, chain termination occurs on the reactor walls; hence, the recombination energy is removed almost entirely from the reaction medium and heat evolution in the reaction bulk substantially decreases. In addition, the activation energy of the rate-determining step of this chain process does not exceed 25 kJ mol^{-1} (see Ref. 129), which is much lower than the values needed for the generation of thermal explosion in non-chain processes.^{3,5}

Chain termination in this reaction system also occurred in the kinetic region. The reaction was carried out under conditions of double self-ignition of SiH_4 in a confined space. The first ignition occurred near the reactor surface, while the second one occurred over the whole bulk (this was established by the kinetic method of separate photometry¹²⁸).

When the initial pressure exceeded a definite critical value by only a few percent, the intensity of combustion in the second outburst increased by a factor of several dozens (Fig. 9). The combustion proceeded dozens of times faster, its duration diminished and became shorter than the characteristic time of heat removal. This points to the switching of the combustion to the CTE mode. The same is indicated by the data obtained upon partial replacement of O_2 by He or Ar. The thermal conductivity of argon differs slightly from that of O_2 . Therefore, replacement of 50% of O_2 by Ar does not change the CTE limit (Fig. 10). In the case where oxygen is replaced by helium, the CTE limit markedly increases, because thermal conductivity of helium is much greater. Thus, in the combustion of SiH_4 , the chain-thermal explosion occurs even at pressures of about 200–300 Pa (see Figs 9, 10), which is an order of magnitude lower than the CTE pressures for the $2H_2 + O_2$ mixture. Nevertheless, the boundary of CTE remains very sharp even in dilute mixtures.

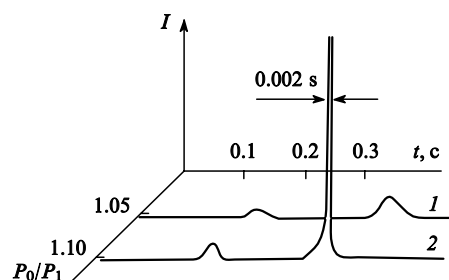


Figure 9. Chemiluminescence oscillograms obtained for ignition of the $0.05 \text{ SiH}_4 + 0.95 \text{ O}_2$ mixture at an initial temperature of 363 K and different P_0/P_1 ; (1, 2) are the numbers of outbursts.

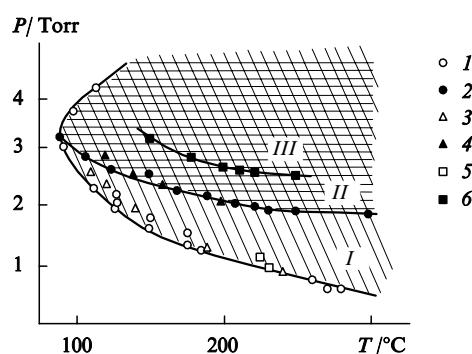


Figure 10. Self-ignition (I) and CTE (II, III) limits for various mixtures; (1, 2) $0.05 \text{ SiH}_4 + 0.95 \text{ O}_2$; (3, 4) $0.05 \text{ SiH}_4 + 0.45 \text{ O}_2 + 0.50 \text{ Ar}$; (5, 6) $0.05 \text{ SiH}_4 + 0.045 \text{ O}_2 + 0.50 \text{ He}$.

When the initial pressure increases, combustion in the first outburst does not pass to the CTE mode because this outburst is located just near the surface, and the heat evolved is quickly removed by the walls (almost 50 times as fast as in the second outburst).

The fact that replacement of some of the O_2 by Ar or He does not change the self-ignition limit implies that the chain termination step occurs in the kinetic region (see Fig. 10, curve I). There are no gradients of CC concentrations or the process rate in this reaction system until combustion passes to the CTE mode; thus, the presence of two different combustion modes is inherent in the reaction kinetics itself.

At low pressures, as at the atmospheric pressure, the process passes to the CTE mode after the critical reaction rate has been attained during the chain combustion. The concentration range of the CTE is much narrower than the concentration range of ignition (similarly to Fig. 4). In the case of mixtures the composition of which does not differ much from the stoichiometric composition, chain combustion at atmospheric pressure switches to the CTE within a very short period of time after chain ignition has started; hence, the process is perceived only as an explosion.

The experimental data on the combustion of H_2 and SiH_4 at low pressures presented here demonstrate that the ignition peninsula is kinetically non-uniform; it is divided by a sharp boundary into a region of chain combustion that does not pass to the explosion mode and the region of CTE, characterised by a markedly greater self-heating and by a more vigorous behaviour of the process. These data also indicate that combustion switches to chain-thermal explosion even when the low pressure and temperature and the efficient heat removal from the reaction system make impossible a thermal explosion by a non-chain mechanism. The activation energies of the limiting steps of a BCP are much lower than the energy needed to bring about an explosion in a non-chain reaction.

A chain-thermal explosion differs from a classic explosion not only by its fundamentally different mechanism and a broader range of initial conditions under which it can occur but by very sharp critical conditions even at low pressures, which is due to the 'double exponent law'. In simple types of reactions, explosion becomes degenerate despite the very high activation energies.^{130, 131} Degeneration of a BCP is possible in processes characterised by rarely branching (although long) chains, for example, in reactions of CO with O_2 in the presence of very small amounts of hydrogen-containing compounds.¹³² The difference between the CTE and a non-chain explosion also shows in the fact that, when heterogeneous reactions play an important role, the course of the CTE depends on the composition and properties of a contacting surface.

Since the kinetics of a chemical reaction determines the macrokinetic features of the process, it should be expected that different kinetic modes of the reaction would be matched by different velocities of flame propagation. Study of the two kinetic modes of chain combustion, one of which is the CTE, elucidation of the differences between these modes, manifested as specific features of the process macrokinetics, and concentration and temperature fields, and determination of the critical conditions for the transition between these modes present considerable interest both for the BCP and combustion theory and for practical purposes (for example, to ensure explosion safety).

The existence of two modes of branching-chain processes in the region of ignition peninsula is indicated by the results of the numerical solution of equations corresponding to the generalised kinetic scheme of a BCP below the second ignition limit under static conditions, together with the equation for the heat balance of the reaction system.^{37, 133–135} The parameter χ , equal to the ratio of the heat evolution rate to the heat removal rate, varied in these calculations. Figure 11 presents the kinetic curves for the variation of the relative concentration of one CC (x) for various χ . As the χ value approaches 1.381, the change in the reaction kinetics becomes more and more pronounced, the transition from 1.381 just to 1.382 inducing an abrupt increase both in the maximum x value and in the rate of its growth.

It is notable that, despite a large number of studies dealing with the numerical solution of equations describing combustion of gases, the CTE phenomenon has not been recognised even after publication of works^{16, 105, 118, 119, 133} in which this mode has been detected both experimentally and theoretically. This may be explained by the fact that the discovery of specific features of

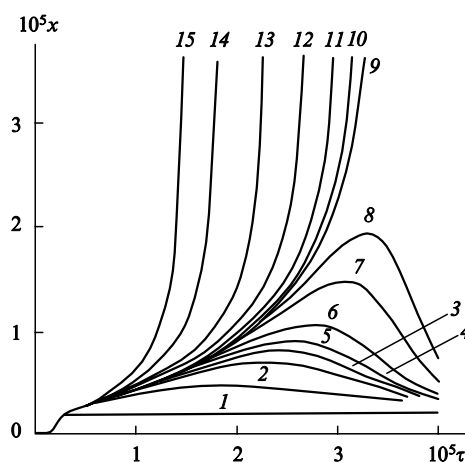


Figure 11. Kinetic curves for the CC at various ratios of the rates of heat evolution and heat removal (the parameter $\chi \times 10^3$) constructed based on a generalised kinetic scheme for a BCP.¹³³ The values $10^3 \chi$: (1) 0, (2) 1.00, (3) 1.20, (4) 1.30, (5) 1.35, (6) 1.37, (7) 1.38, (8) 1.381, (9) 1.382, (10) 1.383, (11) 1.39, (12) 1.41, (13) 1.50, (14) 2.00, (15) 2.50.

combustion inaccessible to a physical experiment has not been the aim of these calculations; they have been usually undertaken in order to describe particular observations or to compare experimental and calculated characteristics of a process (most often, the induction period) using a large number of parameters for calculations. In addition, when the pressure is relatively high, chain combustion rapidly switches to the CTE and, therefore, the whole process is identified with this mode and is regarded as being 'purely thermal'.

It should be noted that in the solution of sets of equations describing non-isothermal combustion of various gas mixtures, the temperature dependence of the heat of reaction is usually neglected. Meanwhile, since the heat capacities and the temperature dependences of the heat capacities of the reactants and products are different, the heat of a non-isothermal reaction changes as the reaction proceeds, this change being quite substantial in many cases. As a consequence, the real rate of heat evolution differs from the value calculated using an invariant heat of the reaction. Correspondingly, the calculated temperature also differs from the real one. Since the rate of a BCP follows an unusually strong temperature dependence and is inversely related to self-heating, it is obvious that errors in the calculation of the temperature result in deviations of the calculated reaction rates and other kinetic characteristics of the process from those observed experimentally. Therefore, the results of calculations of this type are reliable only for qualitative discussions.

IX. Conclusion

The results of experimental and theoretical studies carried out in recent years indicate that branching-chain mechanisms and competition between branching and termination of reaction chains are the governing factors in the gas-phase ignition and combustion of hydrogen-containing and many other compounds not only at very low pressures (tens or hundreds of times lower than the atmospheric pressure) but also at atmospheric and higher pressures. Self-heating becomes substantial only during developing chain combustion and enters a positive feedback with chain avalanche. It has been found that combustion, being a chain process over the whole pressure range studied, can be caused, depending on the initial reactant concentrations, either by the chain avalanche alone, enhanced by self-heating, or by simultaneous action of chain avalanche and avalanche-like accumulation of thermal energy in the reaction system. The second mode can occur only after chain ignition and after a particular rate of chain reaction and, correspondingly, the rate of heat evolution have been attained. The transition between these modes induced by variation of the initial conditions is a critical process. The competition of chain branching and termination throughout the whole range of pressures (both low and high) determines the kinetic features of each combustion mode including ignition, developed combustion, chain-thermal explosion (unknown until recently), flame propagation and its transition to detonation. The branching-chain mechanism also determines the dependence of characteristic features of combustion on the properties of the contacting solid surface under conditions where the access of atoms and radicals to the surface is unhindered (for example, when the ratio of the surface area to the reactor volume is great or in the case of turbulent movement of gases). This relates, for example, to fluid bed and catalytic combustion and to the transition from deflagration to detonation. Thus, the main factor governing the regularities of the gas combustion of hydrogen-containing and many other compounds was actually identified.

Elucidation of the governing role of the branching-chain mechanism in the gas-phase combustion processes at atmospheric and higher pressures and the regularities discovered open up new prospects for the theory of chemical kinetics, first of all, as regards chain processes, and for combustion theory. The data obtained recently would help in the solution of important applied problems. This is confirmed by the above-cited examples, which

demonstrate that the use of proposed and tested highly efficient non-corrosive and inexpensive inhibitors can help in controlling not only ignition but also the intensity of developed combustion and explosion, the velocity of flame propagation and its transition to detonation. The predominant role of a chain mechanism at temperatures typical of detonation creates conditions for controlling also the velocity of a detonation wave, within certain limits, by using inhibitors and promoters. Development of the scientific foundations of the chemical control of all the combustion modes mentioned above by selection and application of appropriate inhibitors and promoters is a topical theoretical and practical task.

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^d — *Russ. J. Chem. Phys. (Engl. Transl.)*

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^f — *Mendeleev Chem. J. (Engl. Transl.)*

^g — *Russ. Chem. Bull. (Engl. Transl.)*

Biosensors for the determination of environmental inhibitors of enzymes

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Abstract. Characteristic features of functioning and practical application of enzyme-based biosensors for the determination of environmental pollutants as enzyme inhibitors are considered with special emphasis on the influence of the methods used for the measurement of the rates of enzymic reactions, of enzyme immobilisation procedure and of the composition of the reaction medium on the analytical characteristics of inhibitor assays. The published data on the development of biosensors for detecting pesticides and heavy metals are surveyed. Special attention is given to the use of cholinesterase-based biosensors in environmental and analytical monitoring. The approaches to the estimation of kinetic parameters of inhibition are reviewed and the factors determining the selectivity and sensitivity of inhibitor assays in environmental objects are analysed. The bibliography includes 195 references.

I. Introduction

Biochemical analytical methods have assumed great importance in the last years. They provide information about qualitative and quantitative composition of a subject under study on the basis of *in vitro* and *in vivo* studies of biochemical processes, which involve enzymes, antibodies, DNA, *etc.* The main advantage of biochemical methods is that the formation of analytical signals simulates the processes occurring in the living beings, which offers a unique possibility for rapid and selective detection of biologically active substances and elucidation of the mechanism of their effects on living organisms.^{1,2}

Enzymic methods of analysis relate to biochemical methods. Enzymes have long attracted the attention of analytical chemists as highly efficient protein catalysts.^{2,3} By virtue of their unique properties, such as high selectivity and sensitivity towards specific substrates and functioning in aqueous media at ambient temperatures,^{4,5} enzymes appear to be ideal analytical reagents for the determination of biologically active substances by diverse kinetic

methods. The development of enzymic methods of analysis was, to a certain extent, stimulated by the increasing demand for clinical and toxicological assays (*e.g.*, determination of major metabolites, diagnostics of various diseases and dysfunctions of discrete organs of an organism on the basis of changes in the composition of biological fluids, *etc.*).

The possibility of usage of enzymes for the determination of specific substrates and effectors has been at the centre of discussion since the late 1940's, *i.e.*, since the beginning of the first systematic *ex vivo* studies of enzyme properties. However, the difficulties connected with the isolation of enzymes, their low stability in solution and high cost of analyses impeded the practical application of novel methods. As a result, until the early 1970's it was thought that enzymic methods ranked below routine physicochemical analyses. The situation changed radically owing to the progress in engineering enzymology and industrial biotechnology (*viz.*, to large-scale production of a great variety of enzyme preparations, which sharply reduced their cost) and to the development of novel methods for stabilisation of enzymes including their fixation (immobilisation) on inert carriers.⁶ Of no less importance for the development of enzymic methods of analysis was the creation of special-purpose measuring devices called biosensors.^{2,3} In those, enzymes are integrated into a single system comprising a device for detecting biochemical signals (a sensor or a transducer) and a reaction medium containing essential stabilisers, effectors and other low-molecular-weight components required for their steady functioning. With the advent of biosensors, the maintenance of optimal experimental conditions and measurement of analytical signals have become routine laboratory procedures available for users having no special biochemical training or skills. It is the manufacture of biosensors that has opened the way for commercial application of enzymes for the determination of biologically active compounds. In 1996, the world's market of biosensors including those designed for clinical assays of glucose, urea, lactic acid and other essential metabolites (~ 70% of the total sales) amounted to US \$ 508 million.⁷

The commercial success of medical biosensors is not exclusively due to their demand and considerable investment into scientific research. At a sufficiently high lower level of metabolite assays of the order of 10^{-4} mol litre⁻¹, high selectivity is the main requirement for the method. Thus, the advantages of enzymes as analytical reagents are especially well realised in biosensors.

The situation with enzymic monitoring of environmental pollutants is different in principle. Only cholinesterase-based biosensors designed for the detection of residual organophos-

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phorus pesticides in water and agricultural products⁸ and immuno-enzymic diagnostica for specific haptens have found commercial application. The reasons preventing practical application of enzymic methods in environmental monitoring are due to specific features of subjects under study and more strict requirements for analytical characteristics of determination of environmental pollutants in comparison with subjects of clinical analysis.⁹

As the requirements for the maximum permissible concentrations of toxic agents become more rigorous, novel procedures are required for the determination of pollutants (*e.g.*, dioxins and pesticides in drinking water and foods, radionuclides, *etc.*) at the level of 10^{-12} mol litre⁻¹ (Ref. 10). Such low concentrations can be detected only in those cases where the pollutant is an effector (*viz.*, an inhibitor or an activator) of the corresponding enzymic reaction rather than its substrate.

Besides, qualitative and quantitative compositions of the main components of those items that subject to environmental and analytical monitoring (*e.g.*, natural and sewage waters, soils, sewage water sediments, *etc.*) are much more diverse than the compositions of biological media analysed with the use of medical biosensors. This imposes additional demands on the selectivity of biochemical signals and the methods used for their measurement. Many compounds, such as salts of alkaline and alkaline-earth metals, biogenic amines, phenols and surfactants, influence not only the rate but also the sensitivity of enzymic reactions with respect to inhibitors. Low temporal stability of specimens, high degree of mineralisation (which is especially apparent in the case of sewage water and silt extracts), the presence of microheterogeneities (suspensions, emulsions), coloured compounds, *etc.*, also restrict potential applications of biosensors. These limitations can be overcome through the use of special methodological approaches, since the use of biosensors for the analysis of environmental subjects differs in principle from their application for medical purposes.¹¹

The present review summarises the published approaches to the development of biosensors designed for the determination of environmental pollutants as enzyme inhibitors and demonstrates the potentials of purposeful control over the selectivity and sensitivity of biosensors used for the assay of toxic substances.

II. Biosensors: general characteristics and functional features

The term biosensors refers to devices which contain a biological element (an enzyme or a cell culture, microorganisms, biological tissues, antibodies, *etc.*) and a means for measurement of the reaction (response) of this element to the alteration of the qualitative composition of the medium.^{3,11} Some authors apply the term 'biosensors' to the supramolecular level of organisation of a biological component and thus separate enzyme-based or immune sensors from microbial and tissue biosensors.¹²

A general scheme of a biosensor assembly is shown in Fig. 1. Irrespective of its application, each biosensor consists of three elements, which determine its operational and analytical characteristics, *viz.*, a sensor, a biological component itself and a reaction medium. In addition to the subject to be assayed (*e.g.*, a substrate or an effector), the latter includes enzyme stabilisers, a supporting electrolyte, screening reagents, buffer components, *etc.*

The choice of a method used for detecting analytical signals determines not only the convenience of operation but also the limit of detection of the substrate. Preference is given to versatile methods and detectors of similar type for measuring the rates of different enzymic reactions. Electrochemical biosensors are represented by Clark's oxygen electrode, amperometric hydrogen peroxide sensors, pH-metric electrodes, field transistors and conductometric cells. In recent years, planar thin- and thick-filmed electrodes prepared from metals and carbonaceous materials which are photolithographed or screen-printed onto plastic or ceramic planar surfaces have received wide acceptance.^{13,14}

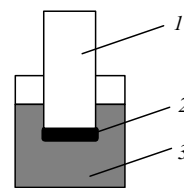


Figure 1. A schematic diagram of a biosensor; (1) sensor (electrode); (2) biological element; (3) working solution, *i.e.*, the reaction medium containing the analysed sample.

The selectivity of signal detection with a biosensor is provided by the selection of operation conditions for the measurement (the electrode potential, the composition of the reaction medium, *etc.*) as well as by optimisation of the biosensor design. Thus the use of electron transfer mediators makes it possible to decrease the working potential of an electrode and to exclude side oxidation (reduction) of electroreactive admixtures present in the specimen.¹⁵ The use of additional membranes diminishes the effect of the buffer capacity of the specimen and the pH of the working solution to the response of pH-metric biosensors.¹⁶

The general requirements for biosensors developed for environmental and analytical monitoring were formulated by the US Environmental Protection Agency (EPA).^{11,17} They are as follows: low cost of assays (US \$1–15 per assay), the possibility of detection of toxic substances at the level of 1 mg litre⁻¹–1 µg litre⁻¹ and within the range of detectable concentrations of not less than two orders of magnitude, duration of analysis of 1–60 min, short-term (1–3 h) training of laboratory personnel, application of zero or minimum supply voltage, specificity with respect to one or a group of related compounds, simplicity of the sampling procedure and portability of the device (which is designed to be easily moved by one man or transported by car).

1. The choice of an enzyme

The choice of biological elements (enzymes) to be incorporated into biosensors is usually made on the basis of a concept about the pathways of biochemical transformations of a particular compound for substrate assays or the mechanism of its toxic effect for inhibitor assays. Obviously, the great diversity of living organisms and well-characterised enzymes makes it possible in principle to detect any biologically active compound in various ways. A combination of several enzymes providing consecutive conversions of the substrate in a biosensor assembly adds new features. In each particular case, the accessibility of an enzyme (simplicity of the isolation procedure or commercial availability), its storage and immobilisation stability, efficiency of measurement procedures, detection limits and ranges of measurable substrate/inhibitor concentration are taken into account. A change in the analytical characteristics of inhibitor assays within the same enzyme–substrate system is attained by varying the sources of the enzyme, the method used for its immobilisation, the measurement conditions and the steps involved in the incubation procedure.

The data concerning the application of enzymes for assaying environmental pollutants as inhibitors [with the exception of cholinesterase (ChE) biosensors, see below] published in 1993–1998 are presented in Table 1. The results obtained in earlier studies are documented in several reviews.^{1,9–11} It should be noted that far from every publication provides analytical characteristics of inhibitor assays, *viz.*, detection limits or the lowest limits of measured concentrations, sensitivity of assays, range of detectable concentrations, *etc.* In many cases, biosensors are used to merely demonstrate the efficiency of an idea of determination of toxic substances with immobilised enzymes (see, *e.g.*, Ref. 41) or for calculation of kinetic parameters of inhibition, usually, with reference to inhibition of free enzymes.

Table 1. Some characteristics of methods used for inhibitor assays in the environment and the experimental parameters, viz., concentration range (c /mol litre⁻¹), limits of detection (LD/mol litre⁻¹) and inhibitor concentrations inducing a 50% decrease in the biosensor response (I_{50} /mol litre⁻¹).

Enzyme	Method	Conditions of measurement and enzyme stabilisation	Inhibitor	Parameters of determination of the inhibitor			Ref.
				<i>c</i>	LD	<i>I</i> ₅₀	
Oxidoreductases							
Cytochrome oxidase (EC 1.9.3.1)	amperometric (cyclic voltamperometry)	the enzyme was incorporated into a carbon paste together with azolectin and cytochrome <i>c</i> from horse heart; phosphate buffer, pH 7.0	cyanides	$(0.5-12) \times 10^{-6}$	—	—	18
	amperometric (linear voltamperometry)	electrochemical polymerisation of pyrrol on a planar gold electrode with subsequent immobilisation with glutaraldehyde; phosphate buffer, pH 7.0	atrazine	—	5×10^{-6} (see ^a) 1×10^{-5} (see ^b)	—	19
	pulse amperometry, chronocoulometry	immobilisation by cross-linking with glutaraldehyde on the surface of a glassy carbon electrode in the presence of a mediator (1,2-naphthoquinone-4-sulfonate); phosphate buffer, pH 7.0	benzoic acid	$1 \times 10^{-5}-5 \times 10^{-4}$	3×10^{-6} (see ^c)	—	20
	UV/visible spectrophotometry	the enzyme, myoglobin and hemoglobin were incorporated into a sol-gel matrix	nitrogen(II) oxide and carbon monoxide	around 10^{-6}	—	—	21
Tyrosinase (EC 1.14.18.1)	amperometric (cyclic voltamperometry)	the enzyme was incorporated into a carbon paste (4%); phosphate buffer, pH 7.0; catechol was used as a substrate	cyanides	—	1×10^{-5}	—	18
	amperometric (Clark's electrode)	sorption on paper with subsequent application of a dialysis membrane; hexane saturated with phosphate buffer, pH 7.0; catechol was used as a substrate	phenylthiourea	—	0.013×10^{-6}	0.80×10^{-6}	22
			<i>N,N</i> -diphenylthiourea	—	0.045×10^{-6}	1.83×10^{-6}	
			ethylphenylthiourea	—	0.078×10^{-6}	3.08×10^{-6}	
			benzylthiourea	—	0.104×10^{-6}	4.58×10^{-6}	
			isopropylthiourea	—	0.137×10^{-6}	5.55×10^{-6}	
			allylthiourea	—	0.181×10^{-6}	6.91×10^{-6}	
	amperometric (linear voltamperometry)	the enzyme was immobilised on the electrode surface; phosphate buffer, pH 7.4; phenol was used as a substrate	benzoic acid, thiourea, propyl gallate	—	—	—	23
	amperometric (by quinone reduction current)	immobilisation in polypyrrol formed on the electrode surface by oxidation of substituted pyrrol; catechol, dopamine, L-DOPA and epinephrine were used as substrates; air-saturated phosphate buffer, pH 6.5	3,4-dichlorophenol	—	0.4×10^{-6}	—	24
			chloroisopropyl phenylcarbamate	—	2×10^{-6}	—	
			3-chloroaniline	—	2×10^{-6}	—	
			atrazine	—	4×10^{-6}	—	
			cyanide	—	0.02×10^{-6}	—	
amperometric (detection of stationary signals)	the enzyme was incorporated into a carbon paste prepared from mineral oil without a cross-linking reagent (immersion or planar electrodes); phenol was used as a substrate; phosphate buffer, pH 7.4	hydrazine	—	—	4.5×10^{-4}	25	
		methylhydrazine	—	—	5.5×10^{-4}		
		dimethylhydrazine	—	—	6.3×10^{-4}		
amperometric (cyclic and pulse amperometry, chronocoulometry)	the enzyme was immobilised on the surface of a glassy carbon electrode by cross-linking with glutaraldehyde without the carrier; phosphate buffer, pH 7.0; potassium ferricyanide is used as a mediator	cyanides	around $10^{-3}-10^{-4}$ (see ^c)	—	—	26	

Table 1 (continued).

Enzyme	Method	Conditions of measurement and enzyme stabilisation	Inhibitor	Parameters of determination of the inhibitor			Ref.
				<i>c</i>	LD	<i>I</i> ₅₀	
Tyrosinase (EC 1.14.18.1)	amperometric (detection of stationary signals)	screen-printed carbon electrodes placed onto a ceramic mount (working area 1 × 5 mm); the enzyme was incorporated into a carbon paste. catechol was used as a substrate; phosphate buffer, pH 7.4	diethyl dithiocarbamate	—	2×10^{-6}	9.2×10^{-5}	27
			benzoic acid	—	5×10^{-6}	1×10^{-4}	
			4,6-dinitro- <i>o</i> -cresol	—	9×10^{-6}	2×10^{-4}	
			thiourea	—	4×10^{-6}	—	
	amperometric (linear voltamperometry)	tyrosinase isolated from meadow mushroom (<i>Agaricus campestris</i>) carposomes was incorporated into a carbon paste; catechol was used as a substrate; phosphate buffer, pH 7.4	2,4-D	—	—	7×10^{-6}	28
			diethyl dithiocarbamate	—	—	4×10^{-5}	
			benzoic acid	—	—	5.8×10^{-5}	
			thiourea	—	—	6.2×10^{-5}	
	the same	the enzyme was incorporated into a hydroxycellulose cryogel; the measurements were performed in chloroform, chlorobenzene and 1,2-dichlorobenzene containing tetraethylammonium perchlorate	benzoic acid,				29
			in chloroform,	$(1-16) \times 10^{-6}$	0.05×10^{-6}	—	
			in chlorobenzene,	$(10-85) \times 10^{-6}$	1×10^{-6}	—	
			in 1,2-dichlorobenzene	$(10-30) \times 10^{-6}$	5×10^{-6}	—	
			thiourea,				
			in chloroform,	$(1-35) \times 10^{-6}$	0.5×10^{-6}	—	
			in chlorobenzene,	$(5-100) \times 10^{-6}$	2×10^{-6}	—	
			in 1,2-dichlorobenzene	$(25-85) \times 10^{-6}$	1×10^{-5}	—	
			2-mercaptoethanol,				
			in chloroform,	$(0.5-70) \times 10^{-6}$	1×10^{-7}	—	
			in chlorobenzene,	$(0.1-35) \times 10^{-6}$	0.05×10^{-6}	—	
			in 1,2-dichlorobenzene	$(0.5-70) \times 10^{-6}$	0.5×10^{-6}	—	
Peroxidase (EC 1.11.1.7)	amperometric, coulometric	tyrosinase was immobilised on the surface of Clark's electrode together with a mediator (1,2-naphthoquinone-4-sulfonate)	diazinon	—	5×10^{-6}	1×10^{-3}	30
			dichlorvos	—	7.5×10^{-8}	2×10^{-5}	
	amperometric, photometric	the enzyme was immobilised by incorporation into a polymeric film (Eastman Kodak 55D) on the surface of a Pt electrode; the measurements were performed in acetonitrile, methanol, acetone and butan-2-ol containing 1.5% of water and butanone peroxide; phenylenediamine was used as a substrate	thiourea,				31–33
			in methanol,	—	—	1.2×10^{-4}	
			in acetone,	—	—	0.5×10^{-4}	
			in butan-2-ol,	—	—	2.1×10^{-4}	
			in acetonitrile	—	—	19.4×10^{-4}	
			ethylenethiourea,				
			in methanol,	—	—	1.3×10^{-4}	
			in acetone,	—	—	0.9×10^{-4}	
			in butan-2-ol,	—	—	4.5×10^{-4}	
			in acetonitrile	—	—	10.4×10^{-4}	
			methyl isocyanate,				
			in methanol,	—	—	1.8×10^{-4}	
			in butan-2-ol	—	—	3.7×10^{-4}	
			2-mercaptoethanol,	—	—	20.2×10^{-4}	
			in acetonitrile				
	amperometric (cyclic voltamperometry)	the enzyme was immobilised by incorporation into a polymeric film (Eastman Kodak 55D) on the surface of a glassy carbon electrode; the measurements were performed in acetonitrile, methanol and acetone containing 1.5% of water, butanone peroxide and dimethylferrocene	thiourea,				34
			in acetonitrile,	—	—	2.4×10^{-4}	
			in methanol,	—	—	18.9×10^{-4}	
			in acetone	—	—	3.5×10^{-4}	

Table 1 (continued).

Enzyme	Method	Conditions of measurement and enzyme stabilisation	Inhibitor	Parameters of determination of the inhibitor			Ref.
				<i>c</i>	LD	<i>I</i> ₅₀	
Peroxidase (EC 1.11.1.7)	amperometric (linear voltamperometry)	the enzyme was incorporated into a methyltriethoxysilane gel on the surface of a glassy carbon electrode modified with an Os-containing polymer; phosphate buffer under argon, pH 5.5, was used	methyl isocyanate ^d	$(4-40) \times 10^{-6}$	5×10^{-7}	—	35
Alcohol oxidase (EC 1.1.3.13)	conductometric (planar Pt microelectrodes)	the enzyme was immobilised on the active surface of a field transistor by vapour of glutaraldehyde into a bovine serum albumin film and dextrin; Tris-buffer, pH 7.5; formaldehyde was used as a substrate	Hg(II)	$(1-100) \times 10^{-6}$	—	—	36
Catalase (EC 1.11.1.6)	amperometric (detection of stationary signals)	the enzyme was immobilised in polyacrylamide gel; the membranes were fixed directly on the teflon membrane of Clark's electrode; the measurements were performed in a flow-injection regime; hydrogen peroxide was used as a substrate; phosphate buffer, pH 7.0	fluorides	10 ^e	1 ^e	—	37
			cyanides	100 ^e	1.5 ^e	—	
Aldehyde dehydrogenase (EC 1.2.1.5) and diaphorase (EC 1.8.1.4)	amperometric (linear voltamperometry)	diaphorase was immobilised on a membrane prepared from a copolymer of styrylpyridine and vinyl alcohol (PVA-SbQ); aldehyde dehydrogenase was immobilised on the same membrane or added to the working solution; phosphate buffer pH 7.5; propionaldehyde was used as a substrate	cineb and maneb	0.15 ^e	—	—	38, 39
			cineb	7.4 ^e , 1.5 ^e	—	—	
Glucose oxidase (EC 1.1.3.4)	potentiometric (pH-sensitive ion-selective field transistor, ISFT)	the enzyme was immobilised on the active surface of a field transistor by vapour of glutaraldehyde into a bovine serum albumin film	Cu(II)	4.0–3.0 ^f	—	—	40, 41
			Co	4.2–3.2 ^f	—	—	
			Sn	3.8–2.0 ^f	—	—	
			Pb	3.5–2.2 ^f	—	—	
			Ni	3.8–2.0 ^f	—	—	
			Cd	2.0–1.5 ^f	—	—	
	the same	the enzyme was immobilised on the active surface of a field transistor by vapour of glutaraldehyde into a bovine serum albumin film and dextrin; Tris-buffer, pH 7.5	Ag(I)	$(1-100) \times 10^{-6}$	—	—	37
β-Glycosidase (EC 3.2.1.21), mandelonitrile lyase (EC 1.11.1.7), peroxidase	"	the three enzymes were co-immobilised on the active surface of a field transistor by vapour of glutaraldehyde into a bovine serum albumin film; citrate buffer, pH 6.0	cyanogenic glycosides (amygdalin)	$(1-30) \times 10^{-5}$	—	—	42

Table 1 (continued).

Enzyme	Method	Conditions of measurement and enzyme stabilisation	Inhibitor	Parameters of determination of the inhibitor			Ref.
				<i>c</i>	LD	<i>I</i> ₅₀	
Miscellaneous oxidoreductases							
L-glycero-phosphate oxidase, pyruvate oxidase, lactate dehydrogenase	amperometric (Clark's electrode)	the enzyme was immobilised on the surface of Clark's electrode; Tris-buffer	HgCl ₂	—	—	20 × 10 ^{−6}	43
			HgCl ₂	—	—	0.05 × 10 ^{−6}	
			HgCl ₂	—	—	1 × 10 ^{−6}	
			AgNO ₃	—	—	0.1 × 10 ^{−6}	
			CdCl ₂	—	—	10 × 10 ^{−6}	
			ZnCl ₂	—	—	10 × 10 ^{−6}	
			Pb(CH ₃ COO) ₂	—	—	50 × 10 ^{−6}	
			CuSO ₄	—	—	25 × 10 ^{−5}	
alcohol oxidase glycerol 3-phosphate oxidase choline oxidase, glutathion oxidase, sarcosine oxidase	amperometric (detection of stationary signals)	the enzymes were immobilised by cross-linking using glutaraldehyde into a bovine serum albumin film or on activated nylon (Immobilon), on the surface of a planar ruthenium-coated (0.5%) carbon-paste electrode; Dulbecco's phosphate-buffered saline was used; incubation for 5 min	Hg(II)	—	0.05 ^g	—	44
			Cu(II)	—	0.05 ^g	—	
			Hg(II)	—	0.5 ^g	—	
			Hg(II)	—	1.0 ^g	—	
			V(V)	—	20 ^g	—	
			Se(IV)	—	0.015 ^g	—	
			Ni	—	0.10 ^g	—	
			Hydrolytic enzymes				
Liver esterase (EC 3.1.1.1)	photometric (by NADH absorption)	esterase and NAD-dependent alcohol dehydrogenase were co-immobilised on glass; the product of enzymic hydrolysis of the substrate (ethyl propionate), <i>i.e.</i> , ethanol oxidised by alcohol dehydrogenase, was assayed in a flow-injection regime	fluorides	(0.8–8) × 10 ^{−6}	—	—	45
Acid phosphatase (EC 3.1.3.2)	amperometric (detection of stationary signals)	the enzyme (tissue sections of potato tubers) was co-immobilised with glucose oxidase on activated nylon in the presence of polyazotidine; glucose 6-phosphate was used as a substrate; phosphate buffer pH 6.6; the measurements were performed in citrate buffer pH 6.0 at 30 °C	pesticides ^h , malathion, methylparathion, paraoxon,	4.4–15 ^e (3.0–2.0) ^e	3 ^e (1.5) ^e	—	46
				0.7–12 ^e (0.7–8.0) ^e	0.5 ^e (0.3) ^e	—	
				6.2–18.3 ^e (3.1–2.0) ^e	5 ^e (1.5) ^e	—	
				46–125 ^e (46–125) ^e	40 ^e (40) ^e	—	
		potentiometric	the enzyme was incorporated into a polyacrylamide gel on a dialysis membrane; 4-nitrophenyl phosphate was used as a substrate	Hg(II)	—	1	—

Table 1 (continued).

Enzyme	Method	Conditions of measurement and enzyme stabilisation	Inhibitor	Parameters of determination of the inhibitor			Ref.
				<i>c</i>	LD	<i>I</i> ₅₀	
Alkaline phosphatase (EC 3.1.3.1)	potentiometric	the enzyme was immobilised by cross-linking using glutaraldehyde into a bovine serum albumin film on the surface of a dialysis membrane; Tris-buffer pH 7.0, 34 °C; α-D-glucose 1-phosphate was used as a substrate	Hg(II)	1	—	—	47
	amperometric (detection of stationary signals)	sorption together with glucose oxidase on the surface of a planar ruthenium-coated carbon electrode; glucose 6-phosphate was used as a substrate; the rate of oxidation of hydrogen peroxide, the product of enzymic oxidation of glucose formed upon substrate hydrolysis, was measured in glycine buffer, pH 9.0; incubation for 10 min	dichlorvos	$10^{-8} - 10^{-5}$ (see ^c)	6×10^{-8} (see ^c)	—	48
Urease (EC 3.5.1.5)	fluorimetric	the enzyme was immobilised on a glass surface; the measurements were performed in a flow-type detector	Hg(II)	$0.5 - 100^g$	—	—	49
	conductometric (planar Pt microelectrodes)	the enzyme was immobilised on the active surface of a field transistor by vapour of glutaraldehyde into a bovine serum albumin film in the presence of a stabilising agent (glycerol); Tris-buffer pH 7.4; urea was used as a substrate; the inhibition was studied in a kinetic regime by the rate of signal alteration after addition of the substrate	Hg(II)	$(1 - 50) \times 10^{-6}$	—	—	50
			Cu(II)	$(2 - 100) \times 10^{-6}$	—	—	
			Cd	$(5 - 200) \times 10^{-6}$	—	—	
			Co(II)	$(1 - 50) \times 10^{-5}$	—	—	
			Pb	$(2 - 500) \times 10^{-5}$	—	—	
			Sr	$(1 - 500) \times 10^{-4}$	—	—	
	potentiometric (pH-ISFT)	sorption on the surface of a field transistor coated with a polymeric film (Nafion); Tris-buffer, pH 7.0; urea was used as a substrate	Ag	—	0.2×10^{-6}	—	51
	the same	the enzyme was immobilised by glutaraldehyde on the active surface of a field transistor into a nitrocellulose film; Tris-buffer, pH 7.4; urea was used as a substrate	Hg(II)	—	1.5×10^{-6}	—	
			Cu(I)	—	3×10^{-6}	—	
			Hg(II)	$8.7 - 3.5^f$	—	—	40
			Cu	$6.7 - 3.3^f$	—	—	
			Co	$5.8 - 2.8^f$	—	—	
			Cd	$5.8 - 2.2^f$	—	—	
			Ni	$5 - 3^f$	—	—	
			Pb	$4.8 - 3.2^f$	—	—	
			Sn	—	—	—	
	"	sorption on the surface of a field transistor coated with a film of poly(4-vinylstyrene); Tris-buffer, pH 7.0; the activity of the enzyme recovered following inhibition with CuCl ₂ was determined; urea was used as a substrate	EDTA	$5 - 500^e$	—	—	52

^a Hydrodynamic method. ^b Flow-through method. ^c Calibration curve. ^d Thiourea, thiocyanates and azides do not interfere with the determination up to concentration 1×10^{-3} mol litre⁻¹. ^e µg litre⁻¹. ^f The values of $p_c = -\log c$ (mol litre⁻¹) are given. ^g mg litre⁻¹. ^h The parameters for the listed pesticides were obtained using bienzyme and hybrid (in parentheses) biosensors.

This complicates comparison of experimental results obtained by different authors.

The majority of publications devoted to the practical application of analytical enzymic methods deal with the studies of biosensors including peroxidase, tyrosinase and urease. Other enzymic systems are described in only a limited number of papers, although their potentials are rather high.

Different organic compounds are determined with horseradish peroxidase, which is resistant to denaturing reagents and elevated temperatures and manifests high specific activity, and is a reliable and sensitive tool for determining the rates of enzymic reactions. The rate of peroxidase-based oxidation of different substrates can be used for determining the concentration of hydrogen peroxide; therefore, this enzyme is a common constituent of two-enzyme biosensors designed for assaying substrates or effectors of oxidoreductases.^{2,3} Tyrosinase (polyphenol oxidase) fulfils similar biochemical functions by oxidising various biogenic phenols.

Peroxidase and tyrosinase inhibitors can block the active sites of enzymes (due to the complex formation with metal cofactors and uncoupling of an electron transfer chain) or manifest non-specific inactivating effects by disturbing the tertiary structures of proteins. For example, the results of Hg(II) and Fe(III) assays which employed peroxidase with photometric detection of signals^{53–55} and phenylthiourea derivatives assays using an electrochemical tyrosinase biosensor²² (both processes were characterised by low detection limits) have made it possible to recommend these methods for direct assays of toxic compounds in environmental objects without sample concentration.

The main advantage of peroxidase and tyrosinase in comparison with other enzymes consists in the possibility of using them as biosensor constituents for measurements in organic or aqueous-organic media,^{56–58} including inhibitor assays.^{22, 29, 31–33, 59, 60} This makes it possible to use biosensors as detectors in liquid chromatography⁶¹ and to carry out inhibitor assays directly on organic extracts. On the whole, the stability of enzymes in organic solvents is lower than in aqueous media, however, definite approaches to their stabilisation do exist.⁶² In the case of inhibitor biosensors able to function in aqueous-organic and non-aqueous media, enzymes are incorporated into hydrophilic polymers based on polyaniline,⁶¹ a hydrophilic vinyl chloride and pyrrole copolymer Eastman AQ^{31–34} and hydrogels based on hydroxycellulose²⁹ and methyltriethoxysilane.³⁵ Electrical conductivity is achieved by adding 1%–20% of a buffer solution or a tetraalkylammonium salt to the organic solvent. Kinetic parameters of both the enzymic reaction and the enzyme–inhibitor interaction depend on the nature of the solvent and the inhibitor. Usually, the presence of polar organic solvents miscible with water decreases the sensitivity of the biosensor to reversible inhibitors of tyrosinase and peroxidase, such as thiourea and dithiocarbamate derivatives. Nonpolar solvents have insignificant effects on the inhibition kinetics.

Urease catalyses the hydrolysis of urea. High substrate specificity of the enzyme and ease of potentiometric or photometric determination of the hydrolysis product, *viz.*, ammonia, provide the practical application of urease for the determination of residual heavy metal salts in environmental objects.

Thus a flow system consisting of 26 glass capillaries with a total volume of 100 μl was developed for the determination of urease inhibitors in natural and sewage waters. Urease was immobilised on the inner surface of the gelatinised capillaries by physical sorption.⁶³ A water sample and a substrate solution were consecutively pumped through the capillary tubes with a peristaltic pump for 15–240 and 20 min, respectively, and the urease activity was measured from the concentration of the ammonia formed using a potentiometric method. The activity of immobilised urease was preserved after continuous pumping of solutions for 8 h. The use of this system made it possible to detect the presence of carbaryl (1×10^{-4} mol litre⁻¹) (4 h) and copper(II) salts (1×10^{-7} and 1×10^{-9} mol litre⁻¹) (1 and 4 h). A similar

indicator system based on a urease reactor (a column filled with glass beads with immobilised urease) was used to evaluate the general contamination of waters with heavy metals.⁶⁴ Ammonia concentration was measured by a photometric (with the Nessler reagent) or a potentiometric method. The detection limits of the majority of heavy metals were $(1–2) \times 10^{-6}$ mol litre⁻¹, those for iron were $10^{-8}–10^{-9}$ mol litre⁻¹. The selectivity of individual metal assays could not be reached. This system was tested in the monitoring of pollution of drinking water sources in the Moscow Region.

Urease biosensors based on pH-sensitive field transistors possess enhanced analytical characteristics for the determination of metal ions. The progress in this area was achieved owing to both the use of ultrathin membranes contacting with the electrode and the coating of biosensors with ion-exchange polymers, which favour the concentration of cations on the electrode surface.^{51, 52}

Microorganisms and sections of biological tissues incorporated into biosensors may sometimes be regarded as sources of the corresponding enzymic activity. This can increase the stability of the response and reduce the cost of biosensors, since the enzymes are in a customary microenvironment in the presence of the necessary stabilising agents and effectors. The cells possess natural mechanisms, which protect enzymes against autooxidation and hydrolysis by proteolytic enzymes. Besides, inactivated enzymes are continuously reproduced owing to catabolic intracellular processes. Some applications of tissue sections of mushroom carposomes as a source of tyrosinase²⁸ and of potato as a source of acid phosphatase⁴⁶ are given in Table 1.

Biosensors based on the use of complete biochemical cycles in which inhibition of a particular biochemical function is measured as an analytical signal offer radically new possibilities. Special mention should first be made of the use of biosensors for the assay of herbicides (algicides) and evaluation of general toxicity in respect of the respiratory activity of microorganisms.

Biosensors designed for measuring concentrations of phytotoxic chemical compounds incorporate chloroplasts as the biological components (as whole cells of unicellular microalgae^{65–67} or within thylakoid membranes isolated from these cells⁶⁸). Illumination of chlorophyll generates a photocurrent measured as the current of oxidation of electron acceptors added to the solution instead of natural acceptors, *viz.*, carbon dioxide. Ferricyanide,⁶⁸ soluble ferrocene derivatives^{65, 66} and diaminodurene⁶⁷ are used as mediators. The reduction of the photocurrent is a measure of the herbicide effect of the toxicants. Thus in the case of *Synechococcus* *sp.* cells, the detection limit of *sym-triazine*-based pesticides is 2 μg litre⁻¹, that in the case of *Chlorella vulgaris* cells is ~ 1 mg litre⁻¹. When thylakoid membranes isolated from spinach cell cultures were used, a 50% reduction of the photocurrent was observed at the following concentrations (mol litre⁻¹): 1×10^{-6} (diuron), 9×10^{-6} (atrazine), 5.5×10^{-4} (sodium nitrite), 1.7×10^{-3} (sodium sulfite), 7.2×10^{-3} [Cu(II) salts], 1×10^{-3} (Pb), 1.8×10^{-3} [Hg(II)], 2×10^{-3} (Zn) and 4×10^{-3} (Cd). These data suggest that biosensors based on chloroplasts and microalgae are promising tools, especially for the determination of residual herbicides. However, these biosensors cannot compete with enzymic ones in terms of sensitivity of metal ion assays (see Table 1).

Biochemical oxygen demand (BOD) is measured with the aid of microbial biosensors designed for detection of toxic substances in aqueous media.^{69–71} The magnitude of BOD can be established within 15–40 min (*cf.* 5–20 days in the titration method) by the rate of oxygen consumption in cells immobilised on the oxygen electrode membrane. The presence of toxic substances decreases the rate of oxygen consumption. In toxicity studies, a sample is introduced simultaneously with the nutrient (determination of respiratory activity) or after it (by a characteristic bend on the respiration curve).^{72–74} Commercial systems for monitoring of the toxicity of sewage waters (*e.g.*, Toxiguard,⁷³ RODTOX^{72, 75}) were developed based on some microbial biosensors. Microbial biosensors for toxicity studies allow the detection of different

substances with a broad spectrum of toxic effects ranging from disturbance of transmembrane oxygen transport (surfactants, petroleum products) to uncoupling of oxidative phosphorylation and inhibition of oxidoreductases (phenols, cyanides, heavy metal ions). However, adaptive protective detoxification mechanisms decrease the sensitivity of microbial biosensors to individual groups of toxic agents in comparison with enzyme-based electrodes. Thus the detection limit of Cu(II) ions is $0.2 \text{ mg litre}^{-1}$ with the yeast-based electrode.¹

In addition to respiratory activity, the intensity of luminescence of luciferase microorganisms (a biosensor version of the Microtox test) can serve as the measure of toxicity.⁷⁶ The use of an electrode containing an immobilised revertant strain of *Salmonella* for the screening of chemical compounds possessing mutagenic activity has been described.⁷⁷

2. Effect of enzyme immobilisation

Immobilisation of enzymes usually causes significant alterations in the analytical characteristics of inhibitor assays. The main reasons for the change in the sensitivity of enzymes to inhibitors upon their transition from the native to the immobilised state are as follows:^{3,5} (1) diffusion-dependent retardation of the reagent (substrate, inhibitor, reaction product) transfer to the membrane including steric hindrances in the accessibility of the active site of an enzyme for high-molecular-weight inhibitors and/or substrates (e.g., proteolytic enzymes), (2) changes in the enzyme micro-environment (buffer capacity, dielectric conductivity, ionic composition) and concomitant changes in electrostatic interactions and activity coefficients of the reagents.

There is no unequivocal evidence so far that the change in the enzyme affinity for a substrate or an inhibitor upon immobilisation is due to the changes in the tertiary or quaternary structure of the protein. Physical sorption or covalent cross-linking of protein globules with bifunctional reagents results in modification of very few surface functional groups. Since active and allosteric sites occupy a small part of the protein globule surface, any change in the structure of protein globules upon immobilisation is hardly likely.

Optimisation of the immobilisation procedure is aimed at retaining the activity of immobilised enzymes and implies mild, sparing treatment in order to preserve the microenvironment of the enzyme active site. This allows one to consider the enzyme-containing film on the biosensor surface as a solid solution where the native protein is uniformly distributed and 'fixed' in a homogeneous medium, which is denser and more viscous than water. Despite its obvious arbitrary character, in many cases this model describes adequately the behaviour of biosensors incorporating an immobilised enzyme.

Diffusion-dependent retardation of the reagent transfer is the main reason for discrepancy in the results of inhibitor assays employing native and immobilised enzymes. Depending on the ratio of the rates of transfer of the substrate into the membrane and its enzymic conversions, one can distinguish two regimes of biosensor functioning^{3,78} which differ in stationary distribution of the substrate throughout the membrane.

Kinetic regime. The rates of transfer and diffusion of a substrate from the solution into the membrane and its diffusion into the membrane are higher than the rate of its enzymic conversion. The reactants are uniformly distributed throughout the membrane and the active sites of enzymes are saturated with the substrate. In this case, the rate of the formation of the reaction product (and, consequently, the response of the biosensor) is determined exclusively by the kinetics of the enzymic reaction. This regime is particularly suitable for detection of enzyme effectors. However, any decrease in the enzymic activity caused by desorption, spontaneous inactivation or microbial degradation influences the biosensor response. The kinetic regime is observed in the case of low specific activities of immobilised enzymes, small thickness of the membrane and lack of the substrate transfer retardation at the membrane–solution interface.

Diffusion-dependent regime. If the activity of an enzyme is high, its diffusion-controlled transfer does not fully compensate for the decrease in the substrate concentration in the enzymic reaction. As a result, the membrane incorporating the enzyme is not saturated and part of the enzyme active sites are unoccupied. The electrode response is steady and remains at this level despite the variations in the activity of the immobilised enzyme unless the reaction regime is changed. The diffusion-dependent regime is observed in the case of high specific activity of the enzyme, retardation of the substrate transfer (e.g., when additional covering membranes decreasing the rate of the substrate transfer from the solution into the enzyme-containing layer are used), etc.¹⁶

If the reaction occurs in the diffusion-dependent regime, the sensitivity of inhibitor assays is lower than in the kinetic regime. A decrease in the concentration of active sites of enzymes as a result of their interaction with their inhibitors is partly compensated for by the involvement of free, nonreacted sites in the enzymic reaction which occurs independently of the enzyme–inhibitor interactions. Thus on going from the native to the immobilised enzyme, the limits of detection of Hg(II) with choline oxidase and glycerol 3-phosphate oxidase increase 2- and 2.5-fold, respectively, while the limits of detection of Hg(II) with lactate oxidase and glutamate oxidase, of cadmium with D-amino acid oxidase and of V(V) with alcohol oxidase increase more than 20-fold.⁴⁴ Moreover, many metal ions inhibit native enzymes without influencing the activities of immobilised preparations. The limit of detection of paraoxon for a luminescent biosensor containing ChE, choline oxidase and peroxidase was $0.75 \text{ } \mu\text{g litre}^{-1}$ when ChE was used as a solute and the other two enzymes were immobilised in an acrylate gel and $125 \text{ } \mu\text{g litre}^{-1}$ when all the three enzymes were immobilised.⁷⁹

The diffusion-dependent and kinetic regimes represent extreme functioning regimes for biosensors and are separated by a vast transition region where the biosensor response is determined by both kinetic parameters of the enzymic reaction and the diffusion coefficients of the reagents. A comprehensive mathematical description of responses of amperometric and potentiometric biosensors has been given.^{3,80–84} However, these models do not take account of the pH dependence of the rate of the enzymic reaction, which is a rough approximation, since the change in pH value of an enzyme-containing membrane can vary from 1 to 3 units during the measurements of biosensor responses.

No simulation of the effect of inhibitor on responses of biosensors including stationary and dynamic responses caused by the addition of substrates (dynamic or transition responses) have been carried out thus far. This may be due to significant complication of the mathematical model in comparison with the description of kinetics of reactions of immobilised enzymes. Besides, in the majority of cases kinetic parameters of individual stages of the inhibition reaction essential for simulation are unknown.

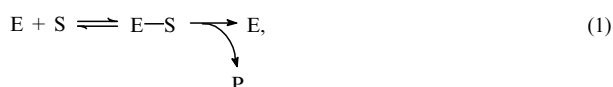
In the simplest case, the effect of an inhibitor can be described in terms of a mathematical model of the biosensor response in the absence of the inhibitor. In the case of uniform distribution of the inhibitor throughout the membrane, a decrease in the biosensor response can be simulated using the dependences of the biosensor response on the substrate concentration calculated for different rates of enzymic reaction. A change in the biosensor response as a result of its contact with the inhibitor will be similar to that observed in the case where a smaller concentration of the enzyme is used for the preparation of the membrane.

This approach does not take into account the effect of enzyme immobilisation on the mechanism of inhibition. In particular, on going from native to immobilised ChE the mechanism of inhibition by *N*-methyl-4-piperidinyl benzylate or tacrine (1,2,3,4-tetrahydro-9-aminoacridine)⁸⁵ is changed, which is associated with steric factors (e.g., limited access of the inhibitor to the membrane or a change in the ratio of substrate/inhibitor concentrations in the membrane in comparison with that in solution) rather than with changes in the mechanism of enzyme–inhibitor

interactions. The necessity of estimating the contribution of the final rate of the inhibitor transfer into the membrane brings about additional problems.

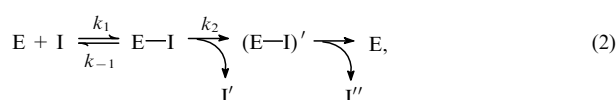
III. Determination of kinetic parameters of inhibition

The choice of methods for quantitative evaluation of effects of inhibitors on immobilised enzymes incorporated into biosensors is determined by the type of interactions in 'enzyme–substrate–inhibitor' systems and the procedure used for measuring of analytical signals implemented in biosensors. Hereinafter it is assumed that the enzymic reaction occurs in accordance with the classical Michaelis–Menten mechanism:^{4, 5}



where E is the enzyme, S is the substrate, ES is the enzyme–substrate complex and P is the enzymic reaction product.

An important feature of the inhibition mechanism is the reversibility of interaction of the inhibitor with the active site of the enzyme. It is necessary to distinguish between reversible and irreversible enzyme inhibition upon its reaction with the inhibitor in the absence of the substrate depending on the type of dissociation of the enzyme–inhibitor complex.



where I is the inhibitor, E–I is the enzyme–inhibitor complex and I' and I'' are the inhibitor decomposition products. If the dissociation of the E–I complex occurs with simultaneous decomposition of the original inhibitor, the inhibition is irreversible ($k_2 \gg k_{-1}$); if the dissociation of the complex into the original molecules prevails ($k_{-1} \gg k_2$), the inhibition is reversible.

The indication to the type of inhibition does not provide any information about the possibility of restoration of enzymic activity after the interaction of the inhibitor with the enzyme. Thus carbamates cause irreversible inhibition of ChE, but spontaneous hydrolysis of carbamoylated ChE occurs very fast and the enzyme activity is completely restored. The reactivation rate constant of carbamoylated acetyl cholinesterase (AChE) from electric eel is 0.012 min^{-1} , while that of phosphorylated AChE is 10^{-5} min^{-1} and the corresponding value for the hydrolysis of the acetylated enzyme formed upon enzymic cleavage of the substrate is $6 \times 10^5 \text{ min}^{-1}$ (see Ref. 86). Inhibition of urease with heavy metal ions is also expected to be reversible; however, the restoration of enzymic activity requires the use of complexones, e.g., EDTA.^{51, 52} Toxic irreversible inhibitors, e.g., contaminants-xenobiotics, are more dangerous to living organisms than reversible inhibitors because of the low rate of spontaneous reactivation and the lack of efficient detoxification mechanisms.

1. Irreversible inhibition

Irreversible inhibition is evaluated quantitatively by the level of enzymic activity before and after the contact of the enzyme with the inhibitor. If the concentration of the inhibitor is much higher than that of the active sites of enzymes, irreversible inhibition will be described by a second-order kinetic equation⁸⁷

$$\ln \frac{v_0}{v_t} = k_{II} c_I \tau, \quad (3)$$

where v_0 and v_t are the initial rates of the enzymic reactions before and after the contact of the enzyme with the inhibitor, respectively, k_{II} is the inhibition bimolecular rate constant, c_I is the

concentration of the inhibitor and τ is the duration of the enzyme–inhibitor interaction (incubation step). The value of k_{II} depends on the nature of the enzyme and the inhibitor as well as on the reaction conditions and rate constants in separate steps of the reaction. In particular, at $\tau \rightarrow 0$:

$$k_{II} \rightarrow \frac{k_1 k_2}{k_{-1} + k_2}.$$

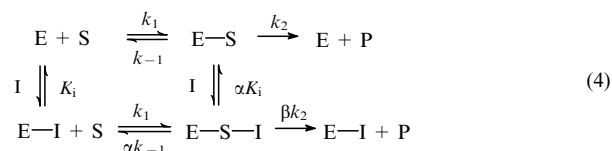
The value of k_{II} describes the inhibitory activity of the toxicant better than I_{50} , since it allows comparison of the results obtained under different experimental conditions, particularly, for different τ .

If the concentrations of the enzyme active sites and the inhibitor are comparable, the dependence of the relative decrease in the rate of the enzymic reaction on the inhibitor concentration for strictly irreversible inhibition is linear. However, this dependence, as applied to biosensors, is not realised, since the specific activity of immobilised enzymes should be rather high in order to provide high accuracy of measurement of the response.

In the case of irreversible inhibition (*i.e.*, at low rate of spontaneous reactivation), the inhibiting effect depends on the time of incubation and the calibration curve for the inhibitor assay is linear in the $c_I - \ln(v_0/v_t)$ coordinates and passes through the origin of the coordinates. Moreover, the relative decrease in the activity of the enzyme (the biosensor response) as a result of incubation does not depend on the concentration of the substrate, which is especially important for optimisation of conditions of inhibitor assays.

2. Reversible inhibition

A kinetic description of reversible inhibition is more complex than that of irreversible one, since the interaction of the enzyme active site with the substrate and the inhibitor may occur in different ways:



Here E–S–I is the enzyme–substrate–inhibitor complex, K_i and αK_i are the equilibrium constants of the enzyme–inhibitor interaction, k_1 , k_{-1} , k_2 , αk_{-1} and βk_2 are the rate constants of the corresponding steps of the enzymic reaction. Usually, for the inhibitors $\alpha > 1$ and $\beta < 1$, but at $\beta \rightarrow 0$ the coefficient α is < 1 . For enzyme activators, the kinetic mechanism of which is described by the same equation, $\alpha < 1$ and $\beta > 1$.

Knowing the dependences of reaction rates on concentrations of the substrate and the inhibitor, one can determine the type of inhibition and the values of K_i and αK_i .^{88, 89} In actual practice, extreme cases may occur. Thus at $\alpha \rightarrow \infty$, complete competitive inhibition takes place. The latter also includes the interaction of the enzyme with an irreversible inhibitor in the presence of the substrate. If $\alpha \rightarrow 0$, the inhibition is referred to as non-competitive. The corresponding constants for the formation of inhibitory complexes, K_i and αK_i , are termed as competitive and non-competitive ones. Mixed type of inhibition is characterised by a combination of competitive and non-competitive inhibition, *i.e.*, in this case the inhibitor binds both to the active centre of the enzyme and the enzyme–substrate complex. Incompetitive inhibition is a particular case of mixed inhibition, if $\alpha = 1$ and $\beta = 0$.

The competitive (K) and incompetitive (K') components of mixed inhibition are calculated from the dependence of relative changes in the rate of the enzymic reaction on the concentrations of the substrate and the inhibitor:

$$\frac{v_0}{v_i} = \frac{K_M(1 + c_I/K) + c_S(1 + c_I/K')}{K_M}, \quad (5)$$

where v_0 and v_i are the reaction rates in the absence and in the presence of the inhibitor and K_M is the Michaelis constant of the enzymic reaction in the absence of the inhibitor.

The total inhibiting effect is described by the reduced inhibition constant

$$\bar{K}_i = \frac{K_i K'_i}{K_i + K'_i}.$$

The constants k_{II} and K_i reflect the sensitivity of the enzyme–substrate system to the inhibitor. Their values can be used for the identification of inhibitors using a set of enzymes differing in their sensitivities to toxic agents. If the experiments are run under identical conditions (incubation time for irreversible inhibitors, substrate concentration for reversible inhibitors), it is sufficient to determine the relative changes in the rate of the enzymic reaction according to the formulae:

irreversible inhibition

$$\frac{(k_{II})_1}{(k_{II})_2} = \left(\ln \frac{v_0}{v_i} \right)_1 / \left(\ln \frac{v_0}{v_i} \right)_2; \quad (6)$$

reversible inhibition

$$\frac{(\bar{K}_i)_1}{(\bar{K}_i)_2} = \left(\frac{v_0}{v_i} \right)_1 / \left(\frac{v_0}{v_i} \right)_2.$$

The indices 1 and 2 refer to the kinetic data obtained in experiments with enzyme preparations differing in the degree of purity, the method of isolation, the source, *etc.*⁹⁰

The relative sensitivity of enzymes to a definite group of inhibitors is established in a similar way. By illustration, the sensitivity of ChE isolated from different sources can be characterised by the relative value:

$$\exp \left(\sum_n \frac{\ln(k_{II}^i/k_{II}^0)}{n} \right),$$

where the index i relates to the enzyme the relative sensitivity of which is being calculated, the index 0 relates to the reference enzyme and n designates the number of inhibitors. The ratio of inhibition constants, k_{II} , is established for each insecticide and is then summated for all the pesticides under study.⁹¹

Estimation of inhibition parameters of immobilised enzymes including those incorporated into biosensors can also be used in the case of kinetic regimes. Biosensors in which the enzyme is immobilised on the electrode surface (without any carrier) or in a thin hydrophilic layer which has no substantial effect on the diffusion coefficients of the substrate and the inhibitor are best suited for this purpose. Albumin, polysiloxanes, silicates, hydrophilic polymers of the Eastman AQ 55D type, *etc.*, are used as carriers.

The feasibility of formal equations for Michaelis–Menten kinetics provides indirect evidence for the lack of diffusional limitations. In particular, for tyrosinase- or peroxidase-based biosensors the current (I) of the reduction of the reaction product (quinone) or of the oxidised form of the mediator can be used as a measure of the rate of the enzymic reaction. The calibration curve for the substrate is linearised in double reciprocal coordinates $I^{-1} - c_S^{-1}$, whereas the segment intercepted on the abscissa gives the value of K_M^{-1} as well as the Lineweaver–Burk equation. Other kinds of anamorphoses of kinetic curves known in homogenous enzymic reaction kinetics can also be used for this purpose. Thus a calibration curve for determining reversible competitive or uncompetitive inhibitors at a constant concentration of the substrate is linearised in the coordinates $I^{-1} - c_I^{-1}$; the inhibition constant, K_i , is determined from the segment intercepted on the abscissa.²⁴

In some cases, it is more preferable to use the degree of inhibition of the enzyme (Y) instead of the biosensor response. This offers a possibility of using the data obtained for different

experimental conditions for calculation. For example, the value of Y relates to the response of an amperometric biosensor:

$$Y = \frac{c_{E-I}}{c_{E-I} + c_E} = \frac{c_I}{c_I + K_i} = \frac{\Delta I}{I_0}, \quad (7)$$

where c_{E-I} , c_E and c_I are the concentrations of the enzyme–inhibitor complex, of the free centres of the enzyme and of the inhibitor, respectively, ΔI is the change in the biosensor response upon inhibition and I_0 is the biosensor response before the contact of the enzyme with the inhibitor.^{29, 31–34} Derivation of Eqn (7) *a priori* entails a fully competitive type of inhibition, since it is in this particular case that the decline of the response will be proportional to the concentration of the enzyme–inhibitor complex.

For practical purposes, the ratio (7) is linearised in the $Y/c_I - Y$ coordinates (the Scatchard equation) to determine K_i :³¹

$$\frac{Y}{c_I} = -\frac{Y}{K_i} + \frac{I_0}{K_i} \quad (8)$$

or in the $Y/(1-Y) - c_I$ coordinates (the Hill equation):⁹²

$$\frac{Y}{1-Y} = \frac{I}{I_0 - I} = \left(\frac{c_I}{K_i} \right)^x = \left(\frac{c_I}{I_{50}} \right)^x, \quad (9)$$

where x is the empirical Hill coefficient; $x = 1$ in the case of the Michaelis–Menten mechanism, the value x for organic solvents increases to 3–4.^{18, 22, 29} The Hill coefficient serves as a criterion of efficiency of the catalysis I_0/K'_M (K'_M is the experimental value of the Michaelis constant) and the effect of the solvent on the kinetics of the enzymic reaction.

Equations (7)–(9) were obtained assuming that the response of the biosensor is proportional to the rate of the enzymic reaction. On the whole, the dependence $v - I$ is sigmoidal and is approximated by a linear dependence in a narrow range of substrate or inhibitor concentrations.

In the case of irreversible inhibition, the inhibition bimolecular constant is calculated from Eqn (3). By expressing v_0/v_i through the degree of inhibition Y , we obtain the following ratio:

$$k_{II} = -\frac{\ln(1-Y)}{c_I \tau}. \quad (10)$$

The plots are linearised in the $\ln(1-Y) - c_I$ coordinates or, if the degree of inhibition is expressed on a percentage basis, $\ln(100-Y) - c_I$.⁹³

If the kinetic parameters k_{II} and K_i are used for comparative characterisation of the enzyme–inhibitor interaction, it should be remembered that they do not provide any direct information about the analytical characteristics of inhibitor assays, such as limits of detection or a concentration range.

IV. Optimisation of operating conditions for inhibitor assays

1. Concentration of the substrate

A crucial role in the choice of experimental conditions belongs to the choice of working concentrations of the substrate. In irreversible inhibition, the relative decrease in the rate of enzymic reactions does not depend on the measurement conditions. If a change in the rate of an enzymic reaction by 15%–25% is taken as a statistically significant quantity, the limit of detection estimated by Eqn (3) is $(0.13 - 0.22)/k_{II}\tau$. In particular, the calculated values of the limit of detection of organophosphorus pesticides ($\tau = 2 - 30$ min, $k_{II} = 10^5 - 10^7$ mol⁻¹ litre min⁻¹), are in the range of $10^{-9} - 10^{-7}$ mol litre⁻¹, which is consistent with the published data for enzymic assays of pesticides with free ChE.^{8, 86, 94}

The value of v_0/v_t can be determined by analysis of any characteristics of the system which are proportional to the reagents concentration, *e.g.*, the time needed for reaching a definite (normally, not more than 30%) level of substrate conversion:

$$\frac{v_0}{v_t} = \frac{t_i}{t_0},$$

where t_0 and t_i are the times of the enzymic reactions before and after the interaction of the enzyme with the inhibitor, respectively.

The choice of small initial concentrations of substrates ($c_S \ll K_M$) has a number of advantages. If a substrate participates in several enzymic reactions (the presence of enzymes with low substrate specificity in the original preparation, significant differences in the kinetic parameters of isoenzymes) or if several substrates interact with the same enzyme, the general view of the equation describing the rate of the target enzymic reaction will be complicated:

$$v_0^1 = \frac{v_{\max}^1 c_S^1}{\left[1 + \sum_{i=2}^{i=n} \frac{c_S^i}{K_M^i}\right] K_M^1 + c_S^1}, \quad (11)$$

where $v_{\max}^1$ is the maximum rate of the enzymic reaction; the index 1 relates to the target enzymic reaction the rate of which is being determined and the index i relates to reactions between competing substrates/enzymes which occur in parallel. If the initial rate of the substrate c_S^1 is sufficiently small ($c_S^1 \ll K_M^1$), the equation is simplified:

$$v_0^1 = \frac{v_{\max}^1}{K_M^1} c_S^1,$$

and the effect of simultaneously occurring reactions can be neglected.⁹⁵

For competitive and mixed-competitive ($\alpha > 1$) inhibition, the limit of detection of the inhibitor decreases with an increase in the substrate concentration. At $c_S \ll K_M$, the limit of detection of environmental pollutants ($K_i = 10^{-4} - 10^{-6}$ mol litre⁻¹) by the most common methods is $(0.15 - 0.25)K_i$ or in the range of $10^{-5} - 10^{-7}$ mol litre⁻¹.

At $c_S \gg K_M$, the limit of detection of non-competitive inhibitors ($\alpha = 1$) does not depend on the substrate concentration. For uncompetitive and mixed-non-competitive inhibition ($\alpha < 1$), the limit of detection of inhibitors decreases with an increase in the substrate concentration. In other cases, any increase in the substrate concentration will increase the limit of detection of the inhibitor.

While estimating limits of detection, one should remember that inhibitory effects are established on the basis of results of two response measurements, *viz.*, before and after the contact of the enzyme with the inhibitor. Therefore, the minimum value of the degree of inhibition is equal to the double measurement accuracy of the biosensor response to the substrate. The metrological characteristics of sensors incorporated into biosensors can be used as a preliminary estimate. Thus the magnitude of steady-state oxidation (or reduction) currents on solid electrodes can be measured with $\sim 1\% - 2\%$ accuracy, while that of the potential of the ion-selective electrode is $\sim 3\%$. Consequently, the minimum significant inhibition corresponds to a decrease in the amperometric and potentiometric responses by not less than $2\% - 4\%$ and $\sim 6\%$, respectively. Even in those cases where the calibration curve for the inhibitor is plotted from the absolute value of the response, it is assumed that the initial response of the biosensor (before its contact with the enzyme) is constant. In other words, the measurement error of the biosensor response after its contact with the inhibitor includes the measurement error of its response to the substrate. Therefore, whilst choosing a detection method (for irreversible, non-competitive, uncompetitive and mixed-non-competitive inhibitors) preference should be given

to the methods which ensure more accurate measurements of the biosensor response rather than the possibility of detection of smaller concentrations of the substrate. In other cases, sensors allowing maximum reduction of working concentrations of the substrate will be the sensors of choice.

2. Enzyme reactivation

The ability of enzymes to regain their activity after measurement of the inhibitory effect is a prerequisite for repeated application of biosensors. In the case of reversible inhibitors, this is achieved by washing of biosensors or enzyme-containing membranes with working buffer solutions which may contain stabilisers or enzyme cofactors preventing its inactivation. In some cases, natural reactivation occurs so slowly that under real experimental conditions it is necessary to use special reagents accelerating the dissociation of enzyme-inhibitor complexes. For example, heavy metal assays make use of complexing or precipitating reagents, such as EDTA, potassium iodide, sulfur-containing organic compounds (cysteine, dithiothreitol, *etc.*);^{36, 51, 52, 96, 97} while antidotes (*i.e.*, substances that counteract poisons in human beings) are often used as reactivating reagents in the analysis of organic inhibitors. Thus 2-PAM (2-pyridinaldoxime methiodide) or TMB-4 [1,1'-trimethylenebis(4-hydroxyiminomethyl)pyridinium dibromide monohydrate] which accelerate hydrolysis of the phosphorylated active site of ChE are used for reactivation of the enzyme after its interaction with organophosphorus compounds.⁹⁸

The efficiency of enzyme reactivation depends on the nature of the reactivating agent, the degree of enzyme inhibition, the nature of the carrier and the time elapsed between inhibition and reactivation. By illustration, phosphorylated ChE which is reactivated at $\sim 70\%$ inhibition restores up to $95\% - 100\%$ of its initial activity, which makes it possible to use the same immobilised enzyme for 15–20 assays.⁸ When heavy metal salts are used as inhibitors, the reactivation amounts to $70\% - 80\%$ if the enzyme is immobilised on nitrocellulose⁹⁶ and up to 100% if gelatine is used as a carrier.⁹⁷

The effects of reactivating reagents, similar to those of inhibitors, are strictly selective. Therefore, the former can be used for separation of inhibitory effects of individual toxic agents present in the same solution as well as for selective determination of individual inhibitors. Thus it was proposed to determine Fe(III) ions according to their reactivating effects on peroxidase inhibited with cyanides or salicylic acid,⁵³ and to determine EDTA according to its reactivating effect on urease inhibited with Cu(II) ions.⁵² An addition of sodium iodide allows one to separate the inhibitory effects of Ag(I), Hg(II) and other heavy metal ions on urease⁵¹ and ChE.⁹⁸

An excess of reactivating reagents can decrease the enzyme activity down to complete irreversible inhibition as a result of elimination of cofactors from the active site or the formation of more potent inhibitors, *viz.*, the products formed in the reaction of the reactivating reagent with the toxic compound.⁹⁹ However, in some cases, reactivating reagents act as allosteric activators of enzymes.

3. Acidity of the working solution

The activities of enzymes and their sensitivities with respect to inhibitors are strongly pH-dependent; therefore, a crucial role in inhibitor assays is played by the correct choice of buffer solutions and pH.

In the overwhelming majority of studies, the optimisation of the composition of reaction media is aimed at eliciting maximum response of the biosensor with respect to the substrate, but not to the inhibitor. Indeed, in many cases, especially in the case of irreversible and non-competitive reversible inhibition, the pH of the medium corresponding to the maximum inhibitory effect is close to that providing optimum functioning of the enzyme (*e.g.*, in the cyanide assay with cytochrome oxidase,¹⁸ in dithiocarbamate and cyanide assays with tyrosinase and peroxidase^{27, 59} and

in organophosphorus pesticide assays with ChE and tyrosinase).^{8,30} In all those cases where the inhibitors had competitive or irreversible inhibiting action, the maximum sensitivity of the response of amperometric biosensors with respect to inhibitors was determined by the I_0/K_i ratio and the magnitude of the biosensor response to the substrates.

In many cases, the pH of the buffer solution can strongly influence the extent of inhibition. In particular, such effects are observed if the inhibitor is involved in acid–base reactions; it is noteworthy that only one of the equilibrium forms interacts with the enzyme. For example, the pH dependence of the inhibitory effect of metal ions on ChE is due to accumulation in solutions of metal hydroxo complexes MOH^+ , which competitively inhibit the enzyme.¹⁰⁰ As a result, the effects of Cu(II), Ni and Fe(II) ions are manifested in a very narrow range of pH which is limited from the alkaline region by the commencement of precipitation of the corresponding hydroxides. Apparently, the optimum value of pH (5.0) for Hg(II) determination with peroxidase in the presence of thiourea is associated with the hydrolytic stability of the inhibitor.⁵³ Colloidal solutions of heavy metal hydroxides can also inhibit enzymes, at least after long-term incubation. Thus the inhibitory effect of Hg(II) salts on urease was studied at pH 8.9;¹⁰¹ the maximum inhibitory effect of beryllium ions on alkaline phosphatase is manifested at pH 9.8.¹⁰²

Instability of inhibitors is yet another reason for the deviation of the working pH from the optimum values. Some organophosphorus pesticides are spontaneously hydrolysed in alkaline media, which markedly decreases the reproducibility of inhibition of free and immobilised ChE.⁸

Immobilisation of enzymes can significantly alter both the value of pH corresponding to the optimum enzymic activity and the sensitivity of the enzyme to the inhibitor. This is due to a change in ionic equilibrium constants caused by the differences in dielectric conductivity and ionic strength of the microenvironment of the enzyme active site and the solution. Enzyme carriers and ballast proteins being electrolytes can represent ion-exchange materials thereby increasing buffer capacity of the enzyme microenvironment and decreasing the rate of removal of hydrogen ions formed upon enzymic reactions into the solution.^{78,103} Therefore, the results of investigations of free enzymes demand verification when passing to the study of immobilised enzymes. For example, if ChE is immobilised by microencapsulation into cellulose trinitrate, the maxima of the enzymic activity and sensitivity towards organophosphorus pesticides are shifted to the alkaline region (to pH 9–10).¹⁰⁴ The pH maximum is not changed upon immobilisation of ChE on paper (7.5–8), but the sensitivity of the biosensor response to pH decreases in comparison with the corresponding dependence of the free enzyme.⁸

In some cases, a change in the pH dependence of inhibition due to immobilisation extends the range of compounds that can be determined. Thus hydrazinium dialkyl dithiophosphates inhibit microbial carboxyesterase at pH 3.5–4.5 but have no effect on free ChE. On the other hand, these compounds cause reversible inhibition of ChE immobilised on paper with a gently sloping maximum at pH 6.0.¹⁰⁵

When immobilised enzymes are incorporated into biosensors, the working range of pH can be narrowed due to the instability of the material used for the preparation of biosensors. For example, destruction of the electrode material limits the pH value for the operation of a cholinesterase biosensor based on a carbon–epoxide composition:¹⁰⁶ the assays of organophosphorus pesticides were carried out at pH 7.0, although the maximum enzymic activity was observed in the pH range 8.0–9.0. In the case of electron transfer mediators, the response of oxidoreductase biosensors was also pH-dependent, which can be ascribed to the change in the redox potential of the mediator.^{35,107,108}

4. The presence of effectors

The effect of compounds present in solution and affecting the enzymic activity is non-additive. Irreversible inhibitors used in low concentrations represent the only exception.

The presence of both a reversible effector and a substrate reduces the irreversible inhibition owing to the so-called protective effect.¹⁰⁹ In the course of incubation, the active site of the enzyme binds to the reversible effector to form a labile complex, which is inaccessible to an irreversible inhibitor. Following addition of the substrate, the complex dissociates, resulting in partial restoration of enzymic activity. In the majority of cases, the protective effect impairs the analytical characteristics of irreversible inhibitor assays, *viz.*, any effectors present in the sample under study including such widespread compounds as alkali and alkaline-earth metal salts, can increase at definite concentrations the limit of detection of the irreversible inhibitor. Therefore, the maximally permissible concentration of salts in the sample is specified to meet the requirements inherent in the methods of enzymic analysis of environmental pollutants irrespective of whether a free enzyme or a biosensor is used in the assay.

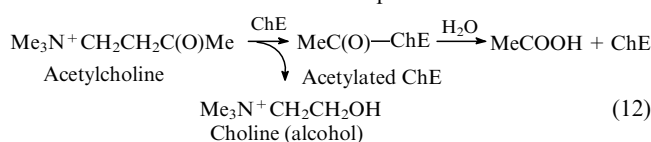
In some cases, enzyme effectors produce a synergistic effect, resulting in a considerable decrease in the limit of detection of the inhibitor or in an increase in the selectivity of measurement. Thus peroxidase ensures a highly sensitive determination of heavy metal salts; the inhibitory effects of Hg(II), Pb, Cd and Bi(III) increase following preincubation of the enzyme with thiourea or with 1,4-dithiothreitol for Bi(III)^{54,55} bringing about nonspecific inactivation of enzymes. With *o*-dianizidine as a substrate, the limit of detection of Hg(II) is 1×10^{-5} mg litre⁻¹, that with 3,3',5,5'-tetramethylbenzidine is 3×10^{-6} mg litre⁻¹. Cadmium and bismuth interfere with the assay when present in a 1000- or 10000-fold excess with respect to mercury. In contrast, organomercurials suppress the inhibitory effects of sulfur-containing compounds (phenylthiourea, 1,4-dithiothreitol). Thus, the selectivity and sensitivity of the method can be varied by changing the duration of incubation, the nature of the substrate and the second effector.

In the presence of magnesium ions, the sensitivity of zinc¹¹⁰ and beryllium¹⁰² ion assays with alkaline phosphatase increases, but the reproducibility of the signal decreases, as a rule. A sharp increase in the sensitivity of ChE to pesticides (chlorofos, 2,4-D, DDT) and heavy metals was observed¹⁰⁴ in alkaline borate buffer in the presence of calcium ions. This effect is manifested within rather narrow ranges of pH and effector concentrations. Interestingly, 2,4-D and DDT do not inhibit free ChE; therefore, in this case either a cooperative effect of calcium ions and pesticide molecules on the active site of the enzyme is manifested or indirect indication of toxic agents, *e.g.*, owing to elimination of the activating effect of calcium ions on ChE upon its incorporation into the enzyme–inhibitor complex or to spatial blockade of the access of hydrophobic pesticide molecules to the enzyme-containing membrane.

V. Cholinesterase-based biosensors

Cholinesterase is being especially widely used and thus deserves special consideration. This enzyme is the subject of up to 60% of publications devoted to biosensors. The interest in ChE of practitioners in environmental and analytical monitoring and toxicology is due to the broad range of inhibitors which involve such widespread toxicants as organophosphorus compounds, heavy metal salts, surfactants, *etc.*^{8,86,94}

Acetylcholinesterase provides hydrolytic cleavage of a natural neurotransmitter, *viz.*, acetylcholine, *i.e.*, it is responsible for the discreteness of transmission of nerve pulses.¹¹¹



Cholinesterases differ in their substrate specificities. Thus acetylcholinesterase (AChE) (EC 3.1.1.7) hydrolyses acetylcholine at the highest rate and does not hydrolyse butyrylcholine. Its activity is inhibited by an excess of a substrate, since deacylation is inhibited by the binding of the second acetylcholine molecule to the anionic site of the acyl-enzyme.¹¹² Butyrylcholinesterase (BChE, EC 3.1.1.8) catalyses hydrolysis of butyrylcholine with the highest efficiency but can also react with acetylcholine. Therefore, this was termed pseudo- or nonspecific cholinesterase, in contrast with the true, specific AChE.

At present, various ChE preparations for biochemical assays including the most popular AChE reagents from electric eel ('Sigma', USA, 'Boehringer', Germany) and BChE from equine blood serum (Joint-Stock Company 'Biomed', Perm, Russia; 'Sigma', USA) are manufactured on an industrial scale. These preparations are available as freeze-dried powders, AChE is also purchased as frozen aqueous solutions containing ammonium sulfate.

Numerous esters of phosphoric, phosphonic and pyrophosphoric acids, carbamates and sulfonic acid esters are irreversible and specific inhibitors of ChE. They bind covalently to the active site of the enzyme to form phosphorylated (carbamoylated, sulfonylated) ChE. Organophosphorus compounds (parathion, diazinon, malathion, *etc.*) are very weak reversible inhibitors of ChE *in vitro*. This is due to the inability of the sulfur atoms to form hydrogen bonds with the hydroxy group of serine-200. In the organism of insects, thionophosphorus pesticides are oxidised by nonspecific oxidases to oxygen analogues. Thus parathion gives paraoxon, malathion gives malaoxon, *etc.*¹¹³ As a result, the inhibitory effect of pesticides increases 10 000-fold and even more. Metabolic activation of the insecticide as a result of the so-called lethal synthesis decreases the hazard of acute poisoning of humans with simultaneous preservation of high insectoacaricidal activity of the preparations. Prior to determination of thionophosphorus pesticides with ChE, they were oxidised to the corresponding oxygen analogues with bromine water¹¹⁴ or 50% nitric acid.¹¹⁵ An effective procedure has been also developed for the oxidation of thionophosphates with chlorine or bromine generated *in situ* by galvanostatic electrolysis.¹¹⁶

Quaternary ammonium salts, acridine derivatives and metal ions are also known as reversible inhibitors of ChE. The activity of ChE decreases also in the presence of polar organic solvents miscible with water.¹¹⁷

Cholinesterase is widely used for the determination of residual organophosphorus and carbamate-type pesticides in water, aqueous and aqueous-organic extracts from plants, soil, food products, *etc.* The published data (1993–1998) concerning cholinesterase biosensors designed for pesticide assays are listed in Table 2.

Enzyme–inhibitor specificity. The analytical parameters of determination of ChE inhibitors strongly depend on the source of the enzyme. Cholinesterases from insects manifest the highest sensitivity with respect to organophosphorus pesticides.^{91, 150, 151} Thus the inhibition constant, k_{II} , of dimethyl dichlorovinyl phosphate (DDVP) is $5 \times 10^5 \text{ mol}^{-1} \text{ litre min}^{-1}$ for AChE from *Drosophila melanogaster*, while that for AChE from bovine erythrocytes is $< 10^3 \text{ mol}^{-1} \text{ litre min}^{-1}$ (see Ref. 91). Cholinesterase from cockroach allows one to determine DDVP at a concentration of $8 \times 10^{-9} \text{ mol litre}^{-1}$, whereas in the case of mammalian enzymes the limits of detection are 10–100 times as high.¹⁵⁰ Insect ChEs are also sensitive to organochloric pesticides (2,3-D, DDT, *etc.*), which seem to be reversible inhibitors.

These enzymes are difficult to isolate in sufficiently large amounts, which restricts their practical application. In future, the situation may change owing to the progress in gene engineering. The preparation of AChE from *Drosophila melanogaster* by incorporation of a mutant gene responsible for AChE synthesis into the genetic apparatus of microorganisms has been described. The yield of AChE was several milligrams per litre of the cultural fluid. This preparation is characterised by high sensitivity to

organophosphorus and carbamate-type pesticides despite its low activity in comparison with the natural AChE from the same source.⁹¹

Cholinesterases from blood serum¹⁵² and brain¹⁵³ of various fish and avian¹⁵⁴ species as well as from the squid optical ganglion¹⁵⁵ are promising for analytical determination of inhibitors. The problems of low stability can be partly solved by immobilisation of the enzymes in gelatine or agar.

The majority of cholinesterase biosensors utilise only three commercial preparations of ChE, *viz.*, AChE from the electric organ of eel *Electrophorus electricus*, bovine erythrocytes and BChE from equine blood serum. Comparison of analytical characteristics (see Table 2) demonstrates difficulties in establishing enzyme–inhibitor specificities for different biosensors. Thus the reported limits of detection of paraoxone using inhibition of AChE from electric eel vary from 10^{-7} (Refs 47 and 134) to $4 \times 10^{-11} \text{ mol litre}^{-1}$ (Ref. 136); for chlorofos (trichlorofon) and its active principle (DDVP), the scatter in the limits of detection amounts to five orders of magnitude, *viz.*, from 10^{-11} (Ref. 104) to $10^{-6} \text{ mol litre}^{-1}$ (Ref. 134).

The experimental value of k_{II} for AChE from electric eel ($< 10^3$ – $4 \times 10^4 \text{ mol litre}^{-1} \text{ min}^{-1}$) is smaller than that for BChE from equine blood serum (8×10^4 – $2 \times 10^5 \text{ mol litre}^{-1} \text{ min}^{-1}$) according to different authors (Refs 86, 91 and 156). It should be mentioned that the sensitivity of chlorofos detection with AChE-based biosensors is higher and the limit of detection is lower than the corresponding analytical characteristics of butyrylcholinesterase-based biosensors. The reason, as in the case of many other similar discrepancies, may be due to diffusion-dependent inhibition of the biosensor response. Commercial preparations of AChE from electric eel normally have high specific activity, which exceeds manyfold (sometimes, hundreds times) that of BChE from equine blood serum. The latter enzyme forms denser films upon immobilisation than the immobilised AChE with high content of the ballast protein. As a result, the biosensors operate in a diffusional-kinetic regime, and the inhibitory effect of the pesticide is reduced.

Special mention should be made of early studies aimed at determining thionophosphorus pesticides without preliminary oxidation. Thus the limits of detection of malathion (carbofos) without preliminary oxidation were 0.1 (Ref. 122) and even 1.6–4.6 mg litre^{-1} (Refs 157 and 158), whereas that after oxidation with bromine water was of the order of $10^{-4} \text{ mg litre}^{-1}$ (Ref. 159).

From the standpoint of toxicology, it is the inhibition of AChE that presents special interest. The calculated values of inhibition constants of AChE (k_{II}) correlate with the mean lethal concentrations (LC_{50}) for mice and rats as well as with hygiene and sanitary MPC standards for natural water reservoirs.^{86, 113, 134} Nevertheless, the use of BChE incorporated into biosensors gives in general comparable limits of detection of pesticides which differ not more than 100-fold in both directions (see Table 2). In order to extend the range of compounds that can be determined by this method, some investigators deliberately decrease the selectivity of the biosensor response through simultaneous use of several ChE isolated from different sources.^{115, 160} Tissue homogenates or biological fluids possessing esterase activity (blood, liver homogenates, *etc.*) are used for the same purpose.^{161–163} By selecting substrates of different specificity, one can vary the set of esterases the activity of which is to be monitored. Thus the use of indophenyl acetate makes it possible to record the overall response of BChE and carboxylesterases. Acetyl(thio)choline is used to detect the responses of AChE and BChE, while butyryl(thio)choline is used for the BChE signal. This extends the potentialities of identification of toxic agents.

Immobilisation (stabilisation) of ChE sometimes plays a crucial role. Immobilisation decreases (or rarely increases) the sensitivity of biosensors with respect to inhibitors in comparison with the free enzyme. Covalent immobilisation by cross-linking of ChE on the electrode surface or an appropriate carrier using glutar-

Table 2. Some characteristics of methods used for the determination of pesticides with ChE-based biosensors and experimental parameters, *viz.*, concentration range ($c/\text{mol litre}^{-1}$) and limits of detection ($\text{LD}/\text{mol litre}^{-1}$).

Enzyme source, substrate	Immobilisation / stabilisation	Method	Conditions	Pesticides	Parameters of inhibitor assay		Note	Ref.
					<i>c</i>	LD		
Potentiometric biosensors								
AChE from electric eel, BChE from equine blood serum, acetyl- and butyrylcholine	cross-linking with albumin by vapour of glutaraldehyde	pH-ISFT; conductometric (Pt electrodes)	phosphate buffer, 2.5×10^{-3} mol litre ⁻¹ , pH 7.4, $c_S = 8 \times 10^{-3}$ mol litre ⁻¹ , incubation for 10 min	trichlorfon	—	10^{-7}	AChE	118—
						10^{-6}	BChE	120
				paraoxon- methyl	—	10^{-7}	AChE	
						10^{-6}	BChE	
AChE from electric eel, acetylthiocholine	on the electrode surface, poly- ethyleneimine and glutaraldehyde	glassy carbon electrode, by a redox mediator potential	citrate buffer, 0.1 mol litre ⁻¹ + + MgCl ₂ , pH 7.2, $c_S = 1 \times 10^{-3}$ mol litre ⁻¹ , incubation for 10 min	DDVP	—	2×10^{-7}	flow-injection regime	121
					—	2×10^{-6}		
AChE from electric eel, acetylcholine	sorption on activated nylon (biodin and immunodin)	pH-ISFT	phosphate buffer, pH 7.0 and 9.0, $c_S = 2 \times 10^{-2}$ mol litre ⁻¹	malathion	—	0.1 ^a	incubation for 1 h	122
BChE from equine blood serum, butyrylcholine	cross-linking with peroxidase and choline oxidase by poly- ethyleneimine on carbon electrodes	glassy carbon electrode	phosphate buffer, pH 7.5, $c_S = 1 \times 10^{-2}$ mol litre ⁻¹ , incubation for 10 min	trichlorfon	$10^{-9} - 10^{-5}$	—	native BChE	123
					—	2×10^{-13}	immobilised BChE	
	cross-linking by glutaraldehyde on paper, in gelatine and nitrocellulose (NC)	glass pH-ISE	phosphate buffer, pH 7.9, $c_S = 2 \times 10^{-2}$ mol litre ⁻¹ , incubation for 10 min	diazinon	0.003–0.3 ^a	—	paper, gelatine	93,
					0.002–0.3 ^a	—	NC	124
				zolone	0.001–0.4 ^a	—	paper	
					0.004–0.4 ^a	—	gelatine	
					0.004–0.7 ^a	—	NC	
					DDVP	0.5–5.0 ^a	—	paper
		0.2–1.0 ^a	—	gelatine				
		0.1–2.0 ^a	—	NC				
	cross-linking by glutaraldehyde on paper, nylon and nitrocellulose	the same	the same	diazinon in the presence of surfactants	—	around 10^{-9}		125
cross-linking with albumin by glutaraldehyde on cellulose acetate	pH-ISFT	phosphate buffer, pH 7.4, incubation for 10 min	DDVP	6.7–3.5 ^b	—		40	
			zolone	7.5–5 ^b	—			
Amperometric biosensors								
	BChE in a working buffer solution	choline oxidase sensor based on a Pt–H ₂ O ₂ sensor	phosphate buffer, pH 7.0, BChE, 0.4 U ml ⁻¹ , 30 °C, $c_S = 3 \times 10^{-4}$ mol litre ⁻¹	paraoxon	—	0.5 ^c	incubation	126
					—	0.2 ^c	for 30 min incubation for 1 h	
AChE from electric eel, acetylthiocholine	incorporation into a carbon paste with an epoxide resin	carbon-paste electrode	phosphate buffer, pH 7.0, $c_S = 1 \times 10^{-4}$ mol litre ⁻¹	carbofuran	—	2.2 ^c	without incubation	106
				carbaryl	—	20 ^c		
				paraoxon	—	2.7 ^c		
				DDVP	—	22 ^c		

Table 2 (continued).

Enzyme source, substrate	Immobilisation / stabilisation	Method	Conditions	Pesticides	Parameters of inhibitor assay		Note	Ref.
					<i>c</i>	LD		
AChE from bovine erythrocytes, acetylthiocholine	cross-linking by carbodiimide on glassy carbon electrodes	rotating disk electrode	universal buffer, pH 8.0	trichlorfon	—	—	$K_i = 5.7 \times 10^{-7}$ (see ^e) $pI_{50} = 4.37^e$	127, 128
AChE from electric eel, 4-aminophenyl acetate	cross-linking with albumin by glutaraldehyde on nylon	Pt electrode	phosphate buffer, pH 8.0, $c_S = 1.2 \times 10^{-2}$ mol litre ⁻¹ , incubation for 5 min	carbaryl paraoxon	$5 \times 10^{-7} - 5 \times 10^{-5}$ $5 \times 10^{-5} - 1 \times 10^{-5}$	1×10^{-7} 1×10^{-7}		129, 130
AChE from electric eel, acetylcholine	cross-linking by glutaraldehyde	choline oxidase sensor based on a Pt-H ₂ O ₂ electrode	phosphate buffer + 0.1% NaN ₃ , pH 7.0, $c_S = 5 \times 10^{-4}$ mol litre ⁻¹ , incubation for 30 min	paraoxon	1.5–15 ^b	1.3 ^b		131
AChE from electric eel, acetylthiocholine	incorporation into a photo-polymerised gel PVA-SbQ (8%)	Pt electrode	phosphate buffer, pH 8.0, $c_S = 1.2 \times 10^{-3}$ mol litre ⁻¹ , 30 °C, incubation for 30 min	paraoxon	$10^{-10} - 10^{-5}$	—	flow-injection regime	132
AChE from bovine erythrocytes, acetylthiocholine	cross-linking by glutaraldehyde on a magnetic carrier	the same	phosphate buffer, pH 8.0	carbofuran	—	3 ^b	$k_{II} = 2.6 \times 10^{-5}$ (see ^d)	133
				paraoxon-ethyl	—	3 ^b	$k_{II} = 2.1 \times 10^{-5}$ (see ^d)	
				paraoxon-methyl	—	7 ^b	$k_{II} = 1.8 \times 10^{-5}$ (see ^d)	
				malaoxon	—	7 ^b	$k_{II} = 1.4 \times 10^{-5}$ (see ^d)	
AChE from electric eel, BChE from equine blood serum, acetylthiocholine	cross-linking of two enzymes with albumin by glutaraldehyde	carbon-paste electrode with cobalt phthalocyanine	phosphate buffer, pH 7.0, $c_S = 5 \times 10^{-4}$ mol litre ⁻¹ , 30 °C	carbaryl DDVP paraoxon	5×10^{-6} 1×10^{-6} 1×10^{-7}		without incubation	134
AChE from electric eel, acetylthiocholine	cross-linking by carbodiimide on the electrode surface	the same	phosphate buffer, pH 7.0, $c_S = 1 \times 10^{-3}$ mol litre ⁻¹ , 37 °C, incubation for 5 min	paraoxon	—	3×10^{-8}	extraction with heptane	135
	the same	"	phosphate buffer, pH 7.0, $c_S = 1 \times 10^{-3}$ mol litre ⁻¹ , 37 °C, incubation for 20 min	DDVP paraoxon	— —	6×10^{-9} 4×10^{-11}		136
AChE from bovine (be), human (he) and electric eel (ee) erythrocytes, BChE from equine blood serum (eu), acetyl- and butyrylthiocholine	cross-linking with albumin by glutaraldehyde	Pt microplanar electrode	phosphate buffer, pH 7.0, $c_S = 1 \times 10^{-3}$ mol litre ⁻¹ , incubation for 10 min		—	430, ^c 190, ^c 3200, ^c 630 ^c	for AChE (be), AChE (ee), BChE (he), BChE (eu), respectively	137, 138
					—		the same	
				carbaryl	—	30, ^c 0.092, ^c 1300, > 10^4 (see ^c)		
				carbofuran	—	3.1, ^c 0.08, ^c 150, ^c 360 ^c	"	
				methomil	—	39, ^c 0.19, ^c 0.88, ^c 1.9 ^c	"	
				propoxur	—	1.5, ^c 0.68, ^c > 10^4 , 11000 ^c	"	
					—			

Table 2 (continued).

Enzyme source, substrate	Immobilisation / stabilisation	Method	Conditions	Pesticides	Parameters of inhibitor assay		Note	Ref.
					<i>c</i>	LD		
AChE from electric eel, acetylcholine	covalent immobilisation by carbodiimide on an affinity membrane UltraBind	choline oxidase sensor based on a Pt Clark's electrode	phosphate buffer, 0.01 mol litre ⁻¹ , pH 7.0, $c_S = 1 \times 10^{-2}$ mol litre ⁻¹ , 30 °C, incubation for 10 min	paraoxon	—	1×10^{-8}	native AChE, buffer native AChE, 0.05% acetone or 5% cyclohexane immobilised AChE, buffer or 1% acetone immobilised AChE, 1% cyclohexane	139
					—	1×10^{-8}		
					—	1×10^{-6}		
					$5 \times 10^{-7} - 1 \times 10^{-5}$	5×10^{-7}		
AChE from bovine and electric eel erythrocytes, BChE from equine blood serum, acetyl- and butyrylthiocholine	incorporation of enzymes immobilised on aminated silica gel into a carbon paste	Pt electrode combined with an enzyme column	phosphate and Tris-, borate buffers, pH 6.0–10.0, $c_S = 1 \times 10^{-4}$ mol litre ⁻¹	carbofuran	—	2.2 ^c	AChE	140
						22.1 ^c	BChE	
				carbaryl	—	2.0 ^c	AChE	
				paraoxon	—	2.8 ^c	AChE	
				chlorofe- vinphos	—	3.6 ^c	BChE	
AChE from electric eel, acetylthiocholine	incorporation into photo- polymerised gel PVA-SbQ (8%)	Pt electrode	phosphate buffer, pH 8.0, $c_S = 1.2 \times 10^{-3}$ mol litre ⁻¹ , 30 °C	dipterex	—	5.6×10^{-6}		141
AChE from electric eel, acetylcholine	incorporation with choline oxidase into a Langmuir–Blodgett film	Pt microelectrode	phosphate buffer, pH 7.5, $c_S = 1 \times 10^{-3}$ mol litre ⁻¹	trichlorfon	—	around 10^{-6}		142
	cross-linking by carbodiimide in an agarose gel in the pores of a carbon electrode	porous carbon electrode	phosphate buffer, pH 7.0, Meldola Blue mediator, $c_S = 4 \times 10^{-4}$ mol litre ⁻¹ , flow-injection regime	paraoxon		1.4 ^c		143
BChE from equine blood serum, butyrylcholine	incorporation into a carrageenan gel with choline oxidase	Clark's electrode	hexane : chloroform mixture (1 : 1) saturated with water, $c_S = 2 \times 10^{-3}$ mol litre ⁻¹ , incubation for 5–20 min	paraoxon	9.4–56.4	4.5 ^c		144
				malathion	10.0–40.0	4.5 ^c		
				ethylparathion	1.0–10.0	0.5 ^c		
				aldicarb	10.0–60.0	4.5 ^c		
				carbaryl	1.0–10.0	0.5 ^c		
	cross-linking with albumin by glutaraldehyde on nylon, nitrocellulose and paper	carbon-paste electrode	phosphate buffer, pH 7.9, $c_S = 6 \times 10^{-5}$ mol litre ⁻¹ , flow-injection regime	diazinon	8.2–6.3 ^b	—		145

Table 2 (continued).

Enzyme source, substrate	Immobilisation / stabilisation	Method	Conditions	Pesticides	Parameters of inhibitor assay		Note	Ref.
					<i>c</i>	LD		
Miscellaneous methods								
AChE from electric eel, BChE from equine blood serum, acetyl- and butyrylcholine	cross-linking with albumin by glutaraldehyde	conductometric, microplanar Pt electrodes	phosphate buffer, pH 7.5, $c_S = 8 \times 10^{-3}$ mol litre ^{−1} , incubation for 10–60 min	paraoxon- methyl	5×10^{-7}	—	lower assay limit	146
				paraoxon	1×10^{-8}	—		
				trichlorfon	5×10^{-7}	—	incubation for 10 min	
					5×10^{-11}	—		
ChE, indoxyl acetate	sol-gel immobilisation in tetramethyl orthosilicate	fuorescent optode	phosphate buffer, pH 7.5, $c_S = 1.63 \times 10^{-4}$ mol litre ^{−1}	phenitrothion	—	17.8 ^b		147
				azinphos-ethyl	—	17.9 ^b		
				methidathion	—	37.6 ^b		
				naled	—	0.36 ^b		
				mecarbam	—	13.9 ^b		
AChE from electric eel, acetylcholine	covalent immobilisation by isothiocyanate on glass	fibre-optic sensor, change in the colouring of Bromothymol Blue	Tris-buffer, pH 7.5, $c_S = 1 \times 10^{-1}$ mol litre ^{−1}	paraoxon	$5 \times 10^{-7} - 5 \times 10^{-6}$	1.1×10^{-7}		148
				carbofuran	$5 \times 10^{-8} - 5 \times 10^{-7}$	1.5×10^{-8}		
AChE from electric eel, indolyl-3-acetate	cross-linking by vapour of glutaraldehyde	piezocrystal sensor	phosphate buffer, incubation for 5 min	paraoxon	—	5×10^{-8}		149
				carbaryl	—	1×10^{-7}		
Note. The following abbreviation were used: pH-ISE is pH-sensitive ion-selective electrode; DDVP is dimethyl (2,2-dichlorovinyl) phosphate; ^a mg litre ^{−1} ; ^b the values of $p_c = -\log c/\text{mol litre}^{-1}$ are listed; ^c µg litre ^{−1} ; ^d mol ^{−1} litre min ^{−1} ; ^e mol litre ^{−1} .								

Note. The following abbreviations were used: pH-ISE is pH-sensitive ion-selective electrode; DDVP is dimethyl (2,2-dichlorovinyl) phosphate; ^a mg litre⁻¹; ^b the values of $p_c = -\log c/\text{mol litre}^{-1}$ are listed; ^c µg litre⁻¹; ^d mol⁻¹ litre min⁻¹; ^e mol litre⁻¹.

aldehyde (in vapour or as an aqueous solution) ^{118–120, 129, 130, 133, 134, 137, 138, 149} or carbodiimide ^{127, 128, 135, 136, 140} are conventionally used. A decrease in enzymic activity as a result of covalent immobilisation depends on the concentration of the cross-linking reagent, the duration of treatment, the initial activity of the enzyme and the nature of the carrier. The losses are minimal (20%–40% of the initial enzyme activity) when protein films are prepared from albumin and gelatine, which are also cross-linked, and in the immobilisation of ChE on aminated carriers of the Immobilon or Biotin type. Highly reactive enzyme-containing membranes are prepared by incorporating enzymes into hydrophilic gels based on acrylamide, ^{79, 159} a *N*-vinylpyridinium–vinyl chloride copolymer, ^{132, 142} polyethyleneimine, ^{121, 123} tetramethyl orthosilicate ¹⁴⁷ and polyurethane. ¹⁶⁴ Biosensors prepared with such membranes are characterised by a rapid response to the substrate; however, the lifetime of immobilised enzymes is much less than that of enzymes obtained by covalent immobilisation on inert carriers.

Under field conditions, it is especially convenient to use biosensors with disposable membranes which can easily be replaced in the case of enzyme inactivation. Disposable membranes are prepared on the basis of inert carriers, such as nylon, ^{122, 125, 145, 165, 166} paper and various cellulose derivatives, ^{40, 93, 96, 104, 105, 124, 167, 168} aluminium hydroxide, ^{164, 169} industrially manufactured membranes (for dialysis and immunoblotting) or carriers for affinity chromatography. ^{122, 140, 141}

The largest losses (up to 99% of the original ChE activity) were observed upon cross-linking of enzyme globules with aqueous solutions of glutaraldehyde on inert carriers, which do not react with the cross-linking reagent, ¹²⁴ such as cellulose trinitrate or paper. Such considerable losses are compensated for by high storage stability of the membranes (up to 6 months at room temperature) and operation lifetime (for over two weeks in a buffer solution within the biosensor).

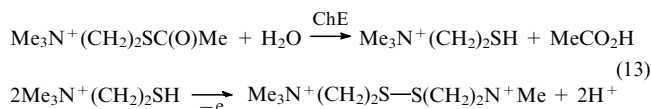
As a rule, immobilisation of ChE does not envisage the use of additional water-soluble stabilisers. However, in some cases 0.1%–3% glycerol, glycine, non-ionogenic synthetic surfactants, 0.01%–0.05% gelatine, magnesium and calcium salts (in the case of AChE) are used to stabilise the activity of the free enzyme.

Stabilisers are necessary when ChE is used in aqueous solutions for analytical purposes, since the stability of even freshly prepared solutions is low. Thus ChEs from insects are completely inactivated within several hours, ¹⁷⁰ AChE from electric eel is stable in a concentrated ammonium sulfate solution. Stabilisers increase the storage stability of enzymes. They form films in which the enzyme is in a solid solution. Such preparations are readily soluble and yield stable solutions the activity of which is not changed during the measurement of the inhibitory effect. In other cases, stabilisers are added directly to the enzyme solution for the same purpose. The addition of stabilisers also decreases the losses of enzymic activity in the course of immobilisation. ¹³⁶ Cellulose and dextran derivatives, other polyalcohols and some non-ionogenic surfactants are used as ChE stabilisers. Probably, they inhibit nonspecific sorption of the protein on glass or a plastic, integrate inhibitors (especially, transition metal ions) into inert complexes or stabilise the tertiary structure of the protein. Incorporation of ChE into tregalose ¹⁶⁹ and *N*-phthalylchitosane ^{73, 116, 155, 171} films for the development of colorimetric indicator devices designed for the determination of ChE inhibitors has been described. Stabilisers suppress the interfering effects of metal ions but do not change the kinetic characteristics of irreversible inhibition of ChE by organophosphorus pesticides.

With a decrease in the diffusion-dependent limitations of biosensor responses, *i.e.*, in the case of thinner membranes and lower specific activity of enzymes, the results of inhibitor assays obtained with free and immobilised enzymes are close. Therefore, amperometric biosensors based on membranes with lower enzy-

mic activities than those used in potentiometric biosensors acquire certain advantage due to higher sensitivity of substrate assays.

On the other hand, comparison of efficiencies of potentiometric and amperometric biosensors under identical conditions shows that the advantages of amperometric detection are not so obvious. ⁹⁴ Thus in experiments with disposable membranes with ChE immobilised on nylon, nitrocellulose or in gelatine, potentiometric biosensors manifested lower limits of detection of paraxon and DDVP. ^{93, 172} This may be due to the interfering Faraday effects, particularly, to additional generation of hydrogen ions upon thiocholine oxidation on the electrode.



Calculation of inhibition bimolecular constants from calibration curves of pesticide assays utilising a potentiometric biosensor with disposable membranes according to Eqn (10) gave overestimated values in comparison with inhibition of the free enzyme under identical conditions. One of possible reasons for increased sensitivity of pesticide assays in the case of immobilised ChE is adsorptive accumulation of pesticides on inert carriers. In particular, this can be confirmed by the fact that non-ionogenic surfactants used in concentrations which do not influence the activity of native ChE, produce differentiating effects on the response of cholinesterase-based biosensors to various inhibitors, *viz.*, the irreversible inhibition effect of pesticides is increased, while the reversible inhibition effect of fluorides or heavy metal ions is decreased. Small concentrations of surfactants also suppress the protective effects of reversible inhibitors in organophosphoric pesticide assays. ¹²⁵ This effect is due to sorption of surfactants on the membrane surface, which facilitates the transfer of hydrophobic organic pesticide molecules to the membrane, while the transfer of small hydrophilic ions (reversible ChE inhibitors) is impeded. The effect of surfactants is a maximum for hydrophilic carriers (paper, nylon) and a minimum for nitrocellulose membranes. The difference between inhibition bimolecular constants for free and immobilised enzymes changes in the same series. For hydrophobic nitrocellulose, the difference is a maximum, while that for hydrophilic paper and gelatine is virtually absent. ^{173, 174}

Increased sensitivity of inhibitor assays upon enzyme immobilisation is observed not only for ChE. The limit of detection of heavy metals with oxidoreductases immobilised in albumin films decreases in the following order (mg litre⁻¹): from 0.25 to 0.05 for Hg(II), from 1.00 to 0.05 for Cu(II) (alcohol oxidase), from 1.00 to 0.10 for Ni (sarcosine oxidase) and from 0.50 to 0.015 for Se(IV) (glutathione oxidase). ⁴⁴ Obviously, electrostatic interactions of metal ions with charged carriers play an important role in these processes along with nonspecific sorption.

Monitoring of environmental objects. Virtually, all the data listed in Table 2 relate to model solutions containing only one ChE inhibitor. The use of cholinesterase-based biosensors for the analysis of real objects is complicated, firstly, because of the presence of considerable amounts of natural enzyme effectors (alkaline-earth metal ions, biogenic amines, *etc.*) in analysed samples and secondly, due to simultaneous presence of several inhibitors with different mechanisms of action. This fact significantly complicates the interpretation of experimental results: one has either to confine oneself to qualitative detection of anti-acetylcholinesterase compounds in analysed samples or to have recourse to their preliminary separation at the expense of simplicity and rapidity, which are the main advantages of enzymic assays.

Commercial production of test systems based on ChE and designed for monitoring residual organophosphorus and carbamate-type pesticides in environmental objects and foodstuff has already been set up. These systems, which represent indicator kits with colorimetric indication are manufactured by 'Boehringer

Mannheim' (Germany)¹⁷⁵ and 'Ohmicron Environmental Diagnostic Inc.' (USA)¹⁷⁶ and ensure qualitative detection of organophosphorus pesticides with limits of detection ranging from 0.05 to 30 $\mu\text{g litre}^{-1}$.

In the 1970's, the manufacturing company 'Midwest Research Institute' (USA) produced a family of automated indicator systems CAM-1,2 (Continuous Alarm Monitor), which represent alarm devices for detecting toxic war gases of neuromuscular action and are adapted to civil needs.¹⁶⁴ These systems are supplied with pumps and aspirators and operate in a semi-automatic regime. The minimum concentrations of pesticides detectable in air and water are as follows (mg litre^{-1}): paraoxon, 0.1; DDVP, 0.2; diazinon, 0.2; dursban, 4.3; difonate, 10; malathion, 17–70 (depending on the brand); temic, 0.5; furadan, 0.75; mesuron, 12 and sevin, 20. Their service cycle includes automated substitution of enzyme-containing polyurethane reactors and electrochemical purification of electrodes, they are supplied with an acoustic signal device of contamination.

A potentiometric biosensor containing AChE immobilised in gelatine on the surface of a pH-metric glass electrode was used to control the quality of waters in the river Seine (France).^{177, 178} The limits of detection of pesticides with this biosensor were as follows (mg litre^{-1}): 0.003 (ethylparaoxon), 0.005 (methylparaoxon) and 0.014 (malathion, ethyl- and methylparathion). Some countries including Russia have begun the commercial production of indicator tubes which contain ChE and chromogenic substrates and are designed for standard aspirators used in air sampling.¹⁷⁹

At present, the possibility to use ChE for environmental and analytical monitoring is chiefly associated with the creation of a market of cheap electrochemical sensors which can form the basis for mass-scale production of disposable cholinesterase-based biosensors that are compatible with standard measuring devices (voltamperographs, ionometers, *etc.*). Such sensors can be manufactured by photolithographic methods. Because of High-Tech production, small size (several square millimetres) and low enzyme expenditure (~ 0.1 unit per electrode), the cost of such biosensors does not exceed US \$1–5. The production of pH-sensitive field transistors and microplanar conductometric devices is currently under way.^{118–120} A technology for the production of screen-printed metal-coated and carbon-paste electrodes with plastic mounts has been developed.¹⁸⁰ The cost of equipment needed for their production amounts to US \$30 000, which is comparable with the cost of a general-purpose voltamperograph. At present, screen-printed electrodes are manufactured in the Czech Republic,¹³³ Italy^{180, 181} and Germany.¹⁸² All of them represent a combination of a working, auxiliary electrode and a reference electrode (Ag/AgCl), which have various geometries, are arranged into a single block (sometimes, in pairs) and operate in a differential regime.

The progress in the design of biosensor elements demands adequate solution of methodological problems. As expected, the effect of the matrix of the analysed subject does not seem to be of crucial importance.¹¹⁵ Biosensors are used for the determination of residual organophosphorus and carbamate-type pesticides in vegetables, fruits, juices,^{137, 138, 183} soils and silt sediments.^{134, 184} The only limitation in the analysis of surface waters is their mineralisation, which should not exceed $0.1 \text{ mol litre}^{-1}$ (Refs 122 and 177). It has to be specified, however, that the accuracy of pesticide assays with biosensors was checked using a method of additives rather than independent methods. Chromatographic methods were used for the estimation of the correctness of measurements only in the case of carbamate-type pesticide assays in vegetables,¹³⁸ of organophosphorus and carbamate-type pesticide assays in fruits and vegetables¹⁸³ and of organophosphorus pesticide assays in natural waters (freezing and subsequent thawing of standard samples).¹²⁸ The divergence of experimental results was $\sim 30\%$, which was accepted to be satisfactory.

A number of simplified sampling techniques have been developed which help elimination of laborious procedures connected with the removal of organic solvents. Thus, a 10-minute

extraction with acetone followed by 10-fold dilution of extracts allows reliable determination of up to 0.1 mg kg^{-1} of pesticides (diazinon, chlorofos, tetraethyl monothiopyrophosphate) in wheat grains and combined fodders.¹⁷² However, in this method the level of extraction is 60%–80%, which means that it is only possible to detect hazardous contamination of the products with pesticides.

If the information about the nature of toxic agents is absent, a reduced biosensor response should not necessarily be related to the concentration of the compound under study. The difference in inhibition bimolecular constants does not allow one to regard the degree of inhibition as a measure of net (molar or mass) content of pesticides even in the absence of interfering factors (diffusion-dependent inhibition of biosensor responses, protective action of effectors, *etc.*). A concept of a standard toxicant has been proposed according to which the net content of pesticides is expressed in units of concentrations of the pesticide used as a standard judging from the inhibitory effects they produce. DDVP,¹⁶⁴ paraoxon,¹³² parathion¹¹⁵ and carbaryl^{180, 181} were recommended as candidates for such standards. The inhibiting effects of other pesticides are calculated with the help of relative toxicity coefficients. The latter are determined in model pesticide solutions of equal concentration by estimating the degree of inhibition of ChE (*i.e.*, a relative decrease in the biosensor response). Undeniably, these coefficients are not equal to the ratio of inhibition constants and depend on experimental parameters including the choice of pesticide concentrations. Similar limitations are typical of calculations of pesticide concentrations expressed as factors of excess over MPC.

Simultaneous use of several biosensors including enzyme-based ones affords additional possibilities for differentiation of biosensor responses. In contrast with the above-described determination of the ratio of inhibition constants ($k_{\text{H}1}/(k_{\text{H}2})$, in this case the result is obtained instantaneously, which makes it possible to use a set of biosensors^{47, 63, 185} (or a multichannel multisensor^{40, 41}) for on-line or even flow measurements.

Hydrolytic enzymes, *e.g.*, urease,^{40, 41} acid and alkaline phosphatases^{47, 185} and glucose oxidase^{40, 41} can also be used for this purpose together with ChE. Unfortunately, enzyme–inhibitor specificity of these enzymes does not allow simultaneous qualitative and quantitative determination of inhibitors. In the best case, adequate interpretation of experimental results can be achieved through the use of chemometric methods, *e.g.*, by estimating individual contributions of Hg(II) ions and the overall effect of all pesticides.¹⁸⁵ However, in this case, too, the mutual effect of solution (sample) components is questionable, since the information about the relative sensitivity of biosensor responses is obtained for single-component solutions. Even with the use of experimental planning methods for the choice of conditions for detecting inhibitor signals, the possibility to separate the contributions of individual inhibitors was established for sufficiently high concentrations (1 mg litre^{-1}), which exceeded the existing hygiene and sanitary standards a thousand-fold.

To some extent, the selectivity of effects produced by reacting reagents can assist in interpretation of experimental results. Thus the anti-cholinesterase effect of metal ions can be suppressed by EDTA and sodium iodide, which allows manifestation of the toxic effect of pesticides.^{1, 97} Contrariwise, ChE added to analysed samples can bind trace amounts of anti-cholinesterase pesticides and then the toxic effects of other pollutants can be determined with other enzymes or indicator organisms.¹

In another approach, the very fact of ChE inhibition is considered as a proof of contamination without regard for the qualitative and quantitative composition of the analysed sample.¹⁸⁶ This approach is widely used in toxicological studies which make use of a special term, 'anti-cholinesterase activity' for a substance or tested subject.^{187, 188} The activity of AChE from blood or brain serves as a measure of chronic poisoning of living organisms with sublethal concentrations of pesticides.^{189, 190} The

total inhibitory effect of toxic agents (*i.e.*, the anti-cholinesterase activity of the medium) can also be used for detection of hazardous poisoning levels and for outlining the main tendencies in their variability. Studies of inhibitory effects of silt sediments in the rivers of the Morava Basin which employed biosensors based on AChE from electric eel revealed a relationship between biosensor signals (the inhibition was studied by following relative changes in the dynamic responses) and agricultural impact on the given territory.¹³⁴ The biotesting conducted by the methods accepted in biological monitoring of surface and sewage waters established a correlation between the degree of inhibition of BChE immobilised on paper or nitrocellulose and the death rate or retardation of growth of hydrobionts of the Cladocera family (crayfish *Daphnia magna* Straus) and the protococcal alga (*Chlorella vulgaris* Beyer).^{191, 192} In the first place, this correlation was established for specific inhibitors of ChE. An analysis of real environmental objects revealed a certain divergence of results obtained by different methods. For example, studies of more than 200 samples of sewage waters from industrial and agricultural enterprises with the aid of potentiometric cholinesterase-based biosensors and acute toxicity tests of waters for the presence of Infusoria (*Paramecium caudatum*) have made it possible to classify all sewage waters into three groups according to the contamination source, *viz.*, (1) sewage waters from machine-building plants which are predominantly contaminated with heavy metals (high death rate among *Paramecium caudatum* with moderate levels of ChE inhibition); (2) sewage waters from petrochemical plants and enterprises of food industry which are contaminated with petroleum products, fats and other high-molecular-weight organic compounds (high death rate among *Paramecium caudatum* in the absence of ChE inhibition) and (3) sewage waters from agricultural enterprises and surface run-off wastes from rural areas (lack of toxicity for Infusoria, low and medium levels of ChE inhibition).¹⁹³

The methods which combine biological and biochemical parameters of water quality (and, in prospect, other generalised hydrochemical parameters) seem to hold especially great promise, primarily due to the possibility to extend the range of potential toxic agents present in environmental objects.

VI. Conclusion

The explosive development of enzymic methods for monitoring of environmental objects has become possible because of a combination of fundamental and applied investigations at the boundaries between biochemistry, biotechnology, toxicology, analytical chemistry and environmental monitoring. With the advent of biosensors, purely laboratorial complex biochemical methods have been transformed into easy-to-handle measuring tools, which are comprehensible for the untrained personnel and are suitable for field use.

This does not mean, however, that the design of biosensors is exclusively confined to the selection of appropriate detectors and immobilisation of enzymes. Investigators are faced with the necessity to solve complicated problems connected with functional features of enzymes to be incorporated into biosensor membranes as well as with optimisation of measurement conditions and effects of template components. A transition from a free enzyme to a biosensor results in the narrowing of the range of experimental facilities used in the study of biologically active substances. Thus the minimum concentrations of substrates and the specific activity of enzymes are limited, while biosensors sometimes require *a priori* non-optimal conditions for their functioning, which are restricted by detectability parameters or specific applications. Optimisation of the biosensor design and the choice of service conditions always involve a compromise between the requirements for the accuracy of response detection, the sensitivity of inhibitor (substrate) assays and the limitations imposed by actual conditions of field tests.

Realisation of specific functioning of biosensors designed for evaluation of toxic effects of environmental pollutants has stimulated the research carried out for commercial purposes. In the first place, this relates to disposable biosensors based on screen-printed and solid-state sensors as well as to the simplest indicating devices with visual indication of signals. Their practical application is still limited due to complexity of interpretation of experimental results and inadequacy of the standardising basis, which bans the use of the data obtained by biochemical monitoring methods for ecological expertise. For this reason, only cholinesterase-based biosensors have found application in environmental and analytical monitoring, although biosensors allow the detection of virtually all priority-driven toxic agents with the exception of dioxins and radioactive compounds.

Nevertheless, the development of biosensors for the determination of environmental pollutants is a very promising trend, primarily because they meet demand. The methods based on the use of biosensors compete favourably with modern methods of toxicological and biological monitoring. To their obvious advantages one may relate small dimensions, ease of signal detection, possibility of integration of biosensors into automated control systems and, last but not least, possibility of quantification of toxicological effects. In our opinion, further developments in this field will proceed along three main lines.

1. Further development of the principal elements aimed at improving the metrological and operational characteristics of transducers and transition to polyenzyme sensors (*e.g.*, multi-sensors, sensor arrays), which help establish not only the presence of inhibitors in analysed subjects but also their nature.

2. Further extension of the range of tested compounds, mostly through optimisation of service conditions for measurement and sampling rather than by increasing of the number of enzymes; further improvement and application of biosensors designed for use in organic solvents, particularly those used as detectors in flow-injection analyses and liquid chromatography.

3. Further development of methodical and methodological aspects of applicability of biosensors in environmental and analytical monitoring; design of expert systems for estimation of biological (physiological) activity of chemical compounds, toxic effects of solid industrial and vital activity wastes; combination of biosensors with conventional methods of biological monitoring and, as a consequence, increasing the information content of biochemical monitoring; large-scale application of methods for chemometric treatment of experimental results.

The integration of different methods and approaches to environmental and toxicological monitoring of environmental objects is still in progress. Recent developments in the field of biosensors are not confined to routine application of enzymes as analytical reagents. Biosensors are used as biochemical models of living organisms and the approaches used therein are related to toxicology and biotesting.¹⁹³ First attempts have been undertaken to direct alteration of the enzyme structure with a view to changing its inhibiting specificity.⁹¹ This approach makes use of 'artificial enzymes' (*i.e.*, oligonucleotides or polymers); their synthesis and selection were performed using molecular recognition of specific toxic agents.¹⁹⁴

And, finally, the vast experience gained in the study of biosensors has served as a basis for the design of entirely new devices, *viz.*, DNA-sensors allowing direct control over mutagenic and genotoxic properties of environmental pollutants.¹⁹⁵ The specificity of their functioning goes far beyond the scope of this review, although their role in the development of new methods of monitoring of environmental objects is now apparent.

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